



Influenza virus infections in humans October 2018

This note is provided in order to clarify the differences among seasonal influenza, pandemic influenza, and zoonotic or variant influenza.

Seasonal influenza

Seasonal influenza viruses circulate and cause disease in humans every year. In temperate climates, disease tends to occur seasonally in the winter months, spreading from person-to-person through sneezing, coughing, or touching contaminated surfaces. Seasonal influenza viruses can cause mild to severe illness and even death, particularly in some high-risk individuals. Persons at increased risk for severe disease include pregnant women, the very young and very old, immune-compromised people, and people with chronic underlying medical conditions. Seasonal influenza viruses evolve continuously, which means that people can get infected multiple times throughout their lives. Therefore the components of seasonal influenza vaccines are reviewed frequently (currently biannually) and updated periodically to ensure continued effectiveness of the vaccines.

There are three large groupings or types of seasonal influenza viruses, labeled A, B, and C. Type A influenza viruses are further divided into subtypes according to the specific variety and combinations of two proteins that occur on the surface of the virus, the hemagglutinin or "H" protein and the neuraminidase or "N" protein. Currently, influenza A(H1N1) and A(H3N2) are the circulating seasonal influenza A virus subtypes. This seasonal A(H1N1) virus is the same virus that caused the 2009 influenza pandemic, as it is now circulating seasonally. In addition, there are two type B viruses that are also circulating as seasonal influenza viruses, which are named after the areas where they were first identified, Victoria lineage and Yamagata lineage. Type C influenza causes milder infections and is associated with sporadic cases and minor localized outbreaks. As influenza C poses much less of a disease burden than influenza A and B, only the latter two are included in seasonal influenza vaccines.

Pandemic influenza

A pandemic occurs when an influenza virus which was not previously circulating among humans and to which most people don't have immunity emerges and transmits among humans. These viruses may emerge, circulate and cause large outbreaks outside of the normal influenza season. As the majority of the population has no immunity to these viruses, the proportion of persons in a population getting infected may be quite large. Some pandemics may result in large numbers of severe infections while others will result in large numbers of milder infections, but the reasons behind these differences are not completely understood. The most notorious

pandemic for which data are available was the “Spanish Flu” in 1918-1919 which caused an estimated 20-50 million deaths worldwide. Subsequent pandemics in 1957 and 1968 resulted in many fewer deaths in spite of large portions of the world’s population being susceptible to infection.

In 2009, a strain of influenza A(H1N1) virus which had not ever been seen before, emerged, spread across the world and caused the 2009 H1N1 pandemic. This pandemic A(H1N1)2009 virus has been widely circulating across the globe since 2009, and is now established in human populations as a seasonal influenza virus, as described above. Currently there is no longer a pandemic virus circulating in the world.

Zoonotic or variant influenza

Humans can also be infected with influenza viruses that are routinely circulating in animals, such as avian influenza virus subtypes A(H5N1) and A(H9N2) and swine influenza virus subtypes A(H1N1) and (H3N2). Other species including horses and dogs also have their own varieties of influenza viruses. Even though these viruses may be named as the same subtype as viruses found in humans, all of these animal viruses are distinct from human influenza viruses and do not easily transmit between humans. Some may occasionally infect humans, however, and may cause disease ranging from mild conjunctivitis to severe pneumonia and even death. Usually these human infections of zoonotic influenza are acquired through direct contact with infected animals or contaminated environments, and do not spread very far among humans. If such a virus acquired the capacity to spread easily among people either through adaptation or acquisition of certain genes from human viruses, it could start an epidemic or a pandemic.

Over the past decades, there have been multiple instances of sporadic transmission of influenza viruses between animals and humans. When viruses of subtype A(H3N2) circulating in swine, began to infect people in the USA in 2011, they were labeled “variant” (with a “v” placed after the name of the virus) in order to distinguish them from human viruses of the same subtype¹. The variant terminology is also used for other non-seasonal influenza viruses of a subtype shared with human seasonal influenza viruses, particularly viruses of the H1 and H3 subtypes circulating in swine, when these viruses are detected in humans¹. For example, a non-seasonal influenza A(H1N1) virus detected in a human would be denoted as A(H1N1)v and a non-seasonal influenza A(H1N2) virus detected in humans would be denoted as A(H1N2)v. The current number of human infections with these variant viruses can be accessed on the Center for Disease Control web site at <https://www.cdc.gov/flu/swineflu/variant-cases-us.htm#table-infections>. Other animal viruses, e.g. avian influenza A(H5N1), A(H7N7), A(H7N9), and A(H9N2), infecting people are simply called “avian influenza”² or “zoonotic influenza” viruses.

When animal influenza viruses infect their natural animal host, they are named for that host, as in avian influenza viruses, swine influenza viruses, equine influenza viruses, etc. As such, the term “swine flu” refers to swine influenza viruses infecting swine, and is never used when such viruses infect people.

¹ http://www.who.int/influenza/gisrs_laboratory/terminology_variant/en/index.html

² http://www.who.int/entity/influenza/human_animal_interface/influenza_h7n9/H7N9VirusNaming_16Apr13.pdf

Efficacy and Safety of Oseltamivir in Children: Systematic Review and Individual Patient Data Meta-analysis of Randomized Controlled Trials

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(See the Editorial Commentary by Uyeki on pages 1501–3.)

Background. Oseltamivir has been used to treat children with influenza for nearly 2 decades, with treatment currently approved for infants aged ≥ 2 weeks. However, efficacy and safety remain controversial. Newer randomized, placebo-controlled trials (RCTs), not included in previous meta-analyses, can add to the evidence base.

Methods. We conducted a systematic review to identify RCTs of oseltamivir therapy in children. We obtained individual patient data and examined protocol-defined outcomes. We then conducted a 2-stage, random-effects meta-analysis to determine the efficacy of treatment in reducing the duration of illness, estimated using differences in restricted mean survival time (RMST) by treatment group. We also examined complications and safety.

Results. We identified 5 trials that included 2561 patients in the intention-to-treat (ITT) and 1598 in the intention-to-treat infected (ITTI) populations. Overall, oseltamivir treatment significantly reduced the duration of illness in the ITTI population (RMST difference, -17.6 hours; 95% confidence interval [CI], -34.7 to -0.62 hours). In trials that enrolled patients without asthma, the difference was larger (-29.9 hours; 95% CI, -53.9 to -5.8 hours). Risk of otitis media was 34% lower in the ITTI population. Vomiting was the only adverse event with a significantly higher risk in the treatment group.

Conclusions. Despite substantial heterogeneity in pediatric trials, we found that treatment with oseltamivir significantly reduced the duration of illness in those with influenza and lowered the risk of developing otitis media. Alternative endpoints may be required to evaluate the efficacy of oseltamivir in pediatric patients with asthma.

Keywords. influenza; oseltamivir; children; meta-analysis.

Globally, influenza is an important contributing cause of hospitalization and mortality in children aged < 5 years [1]. Vaccines, though only moderately effective, remain the most effective way to prevent illnesses [2–4]. Thus, prevention strategies must be coupled with treatment of influenza virus infections to minimize the burden of disease.

Two neuraminidase inhibitors, inhaled zanamivir and oral oseltamivir, were licensed by the US Food and Drug Administration in 1999 for treatment of uncomplicated influenza. The results of the pivotal licensure studies [5–7] were remarkably similar, even though the 2 drugs were dissimilar in their mode of administration and metabolism. In the nearly 2 decades since, zanamivir has had only limited use, leaving oseltamivir as the principal option for the treatment of uncomplicated seasonal influenza and for stockpiling and use during

pandemics [8]. Following the experience with severe disease in young children during the 2009 pandemic, oseltamivir is now licensed for children as young as 2 weeks [9].

Large observational studies have documented evidence of effectiveness and safety of oseltamivir use [10–12]. Significant reductions of severe outcomes were found among hospitalized adults, but these effects were attenuated and not significant among children [13]. Oseltamivir remains controversial in some quarters for several reasons, including safety concerns [14–16]. This controversy has focused on randomized, placebo-controlled trials (RCTs) that were the basis for licensure, mainly due to the potential for bias in analysis and the availability of data from unpublished studies [8, 17, 18]. A recent meta-analysis, using individual-level data from all RCTs of timely (≤ 48 hours from symptom onset) oseltamivir treatment in outpatients with uncomplicated influenza, confirmed significant reductions in duration of illness and complications in those randomized and infected, but not among the uninfected [19]. To avoid complexities due to heterogeneity in pediatric trials, the analysis was limited to adults.

Here, we extend the previous work to RCTs in children aged < 18 years. Following a systematic review that identified 2 recently published trials, we estimated the efficacy of timely oseltamivir

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treatment for uncomplicated influenza by comparing children treated in the outpatient setting to those who received placebo.

METHODS

Systematic Review

We searched PubMed, MEDLINE, Embase, and the Cochrane Library for clinical trials published between 1 January 1997 and 1 May 2016 using medical subject heading terms to identify oseltamivir studies in children with influenza virus infection. Unique titles and abstracts were reviewed for eligibility using prespecified Population, Intervention, Comparator, Outcome, Study design (PICOS) criteria (Figure 1). Nonprimary literature that included reviews, meta-analyses, or secondary analyses were excluded. We reviewed reference lists of systematic reviews and previous meta-analyses and contacted investigators to identify additional trials. Data were obtained from Roche via the Multiparty Group for Advice on Science for 2 published (WV15758 and WV15759/WV15871) and 1 unpublished trial (NV16871); data from 2 additional trials (NCT00707941 and NCT00593502) were obtained directly from investigators (Supplementary Table S1). The risk of bias was evaluated using the Cochrane tool to describe the data quality from each trial (Supplementary Table S2). The protocol for this

systematic review was registered with PROSPERO (14 July 2016; 42016038982) prior to initiation of the review.

Meta-analysis

We conducted a 2-stage, individual participant data meta-analysis of the efficacy of timely oseltamivir treatment in reducing the duration of influenza-associated acute respiratory illness [20]. Kaplan-Meier plots of duration of illness were initially assessed by treatment group for individual trials and for all trials pooled (Supplementary Figures S1 and S2). Treatment effect estimates (time ratio) by trial were obtained from an accelerated failure time model with a generalized F distribution due to violation of the proportional hazard assumption in some trials [21]. The difference in restricted mean survival time (RMST) for duration of illness by treatment group and 95% confidence intervals (CIs) were also estimated for each trial individually [22]. We then conducted a random-effects meta-analysis with a maximum likelihood approach to estimate heterogeneity between trials. All analyses were performed using R version 3.3.2.

Efficacy analyses were first restricted to patients who received at least 1 dose of study drug and who had laboratory-confirmed influenza virus infection (intention-to-treat infected [ITTI] population) and repeated for the intention-to-treat (ITT) population, which included both children with and without influenza virus infection, all of whom were randomized to receive treatment or

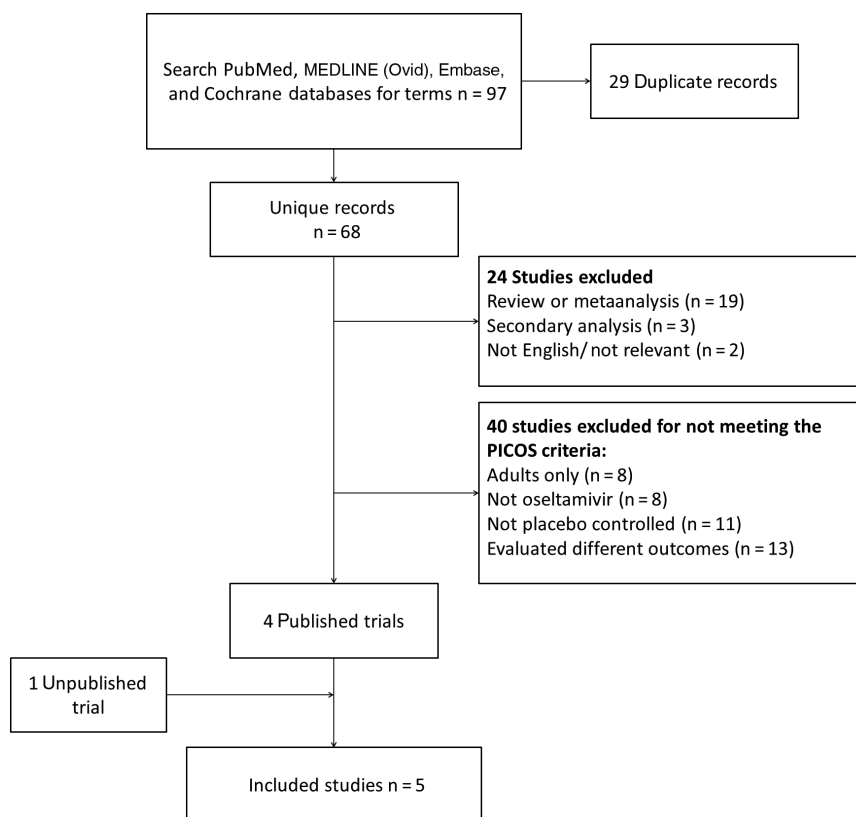


Figure 1. Results of the systematic review. Abbreviation: PICOS, Population, Intervention, Comparator, Outcome, Study design.

placebo. We also conducted a meta-regression to evaluate trial characteristics (inclusion of only patients with asthma, inclusion of adolescents, treatment within 24 hours, and outcome definition) that were hypothesized to confound the overall treatment effect. We then conducted meta-analyses for additional outcomes including complications due to influenza and adverse events.

Main Outcome

The primary endpoint for this meta-analysis, duration of illness in hours, was comprised of the following study-specific endpoints: 3 trials (WV15759/WV15871, WV15758, and NCT0059302) used the phrase “resolution of illness” to describe the time from the start of treatment to when the following conditions were met for at least 24 hours: child was afebrile, cough or rhinitis were either absent or mild, and child had returned to normal activities. In the remaining trials, duration of illness was defined as the time from the start of treatment to resolution of influenza symptoms (NV16871) or resolution of major signs and symptoms (eg, fever, tachypnea, difficult/noisy breathing, cough, and any danger sign; NCT00707941).

Complications and Adverse Events

Binary outcomes (eg, complications, adverse events) were also analyzed using a 2-stage meta-analysis; risk ratios and standard errors for these outcomes were estimated for individual trials using log-binomial regression models [23]. Trials with zero events in both arms were excluded from those specific analyses.

We evaluated the efficacy of oseltamivir treatment in reducing the risk of the following complications: lower respiratory tract complication (LRTC), otitis media, and hospitalization >48 hours after first study drug intake. Patients who took antibiotics at randomization were excluded from these secondary analyses. Complications were determined by clinician diagnosis, as defined in individual study protocols.

Safety outcomes included serious adverse events (SAEs) and nausea, vomiting, and diarrhea. Adverse events were analyzed for “on-treatment” periods only. An adverse event was “on treatment” if it occurred between first study drug intake and up to 48 hours after last dose of study drug.

Pooled Analyses

We also estimated the efficacy of oseltamivir treatment in pooled analyses stratified by subgroups of interest. We estimated the time ratio and RMST difference among those who received treatment early (ie, within 24 hours of onset), by age group (<6 years, 6–11 years, 12–17 years), among individuals with and without asthma, and among those with and without laboratory-confirmed influenza virus infection, adjusted for trial.

RESULTS

Search Results

Our search terms (Supplementary Materials) identified 97 citations. After excluding duplicates, we obtained the full text of 68

unique studies. Twenty-four studies were excluded because they were not primary literature, and 40 were excluded for not meeting all of the PICOS criteria (Figure 1). Four published studies met all inclusion criteria. We identified 1 additional unpublished trial; thus 5 trials were included in the final analysis.

Description of Trials and Participant Characteristics

Three trials (WV15758 [24], WV15759/WV15871 [25], and NV16871 [26]) were performed between 1998 and 2004 (Table 1). Children were eligible if they were enrolled within 48 hours of symptom onset, had fever $\geq 37.8^{\circ}\text{C}$, and had at least 1 respiratory symptom (cough or coryza). Trial NCT00707941, conducted by the International Center for Diarrhoeal Diseases, Bangladesh (icddr,b), from May 2008 through December 2010, included participants only if they presented at the study clinic with a rapid test positive for influenza [27]. A trial of early treatment (NCT00593502) was conducted during the 2007–2008 and 2008–2009 seasons and included only participants aged <4 years who presented at the study clinic within 24 hours of symptom onset [28]. Of note, there was variation between trials in the definition and terminology used to describe the duration of illness (Table 1). This outcome was alternatively referred to as alleviation of symptoms or resolution of illness.

We examined participant characteristics by treatment group overall and by trial (Table 2). In total, the ITT population consisted of 2561 participants randomized within 48 hours of symptom onset to receive either oseltamivir ($n = 1281$) or placebo ($n = 1280$). NCT00707941 enrolled 1190 participants, 796 of whom were included in this meta-analysis because they were randomized within 48 hours of symptom onset. A total of 394 were randomized >48 hours after onset and, therefore, did not meet our inclusion criteria. Two trials (NV16871 and WV15789/15871) were restricted to children with asthma. The pooled ITTI population consisted of 1598 (62%) individuals, 770 (48%) of whom received timely oseltamivir treatment. We found no significant differences in the proportion treated by any of the characteristics examined (Table 2). Overall, 46 (1.8%) children were missing data on duration of illness; 26 from WV15758, 3 from WV15759/15871, and 17 from NCT00593502; missing data did not differ by treatment status.

Meta-analysis

Overall, there was a significant reduction in the duration of illness among those who received timely oseltamivir treatment (RMST difference, -17.6 hours; 95% CI, -34.5 to -0.7 hours; Figure 2). An indicator for enrolling only asthma patients was significant in the meta-regression for the ITTI population ($P = .03$), indicating heterogeneity between asthma-only and combined populations. Thus, we stratified the meta-analysis based on trial inclusion criteria in regard to asthma status. The effect of treatment was larger in trials that enrolled children regardless of asthma status (RMST difference -29.9 hours;

Table 1. Description of Randomized Controlled Trials of Efficacy of Oseltamivir in Pediatric Populations

Trial	WV15758 [24]	WV15759/WV15871 [25]	NV16871 [26]	NCT00707941 [27]	NCT00593502 [28]
Description	Otherwise healthy children (1–12 y) <48 h of symptom onset	Children with asthma (≥ 6 y– ≤ 12 y) <48 h of symptom onset	Children with asthma (≥ 6 y– ≤ 17 y) <48 h of symptom onset	Age +1 y, no upper age limit (89% <18 y, ~80% ≤ 10 y) within 5 days symptom onset	Children (1–3 y), early treatment (≤ 24 h of symptom onset)
Location	United States, Canada	Europe, Israel, United States, Canada, Argentina, Australia, Chile, China, New Zealand, South Africa	Europe, Israel	Bangladesh	Finland
Numbers of intention-to-treat patients	695 (planned = 680)	334 (planned = 500)	329 (planned = 392)	796 (<48 h from onset) ^a	408 (planned = 308)
Number (%) intention-to-treat infected patients	452 (65%) (planned = 340) -217 oseltamivir -235 placebo	179 (54%) (planned = 250) -84 oseltamivir -95 placebo	94 (29%) (planned = 196) -43 oseltamivir -51 placebo	796 (<48 h from onset) ^a -398 oseltamivir -396 placebo	98 (24%) (planned = 154) -37 oseltamivir -61 placebo
Randomization	1:1 Stratified by presence/absence of acute otitis media (baseline clinical diagnosis)	1:1 Stratified by class of asthma (mild or moderate/severe).	1:1 Stratified by class of asthma (mild or moderate/severe) and time from onset of influenza symptoms to treatment start	1:1 Stratified by <48 h and 48+ h since symptom onset; permuted blocks with variable length between 2 and 8	1:1 Randomized in blocks of 4; randomization, labeling and packaging of study drugs performed by Roche
Laboratory assays for detection of influenza	Virus culture, serology	Virus culture, serology	Virus culture, serology	RT-PCR, virus isolation	Virus culture, time-resolved fluoroimmunoassay, RT-PCR
Duration of illness definition	Time from illness onset to presence of mild or no cough, nasal congestion/runny nose, afebrile, return to normal activity	Time from illness onset to presence of mild or no cough, nasal congestion/runny nose, afebrile, return to normal activity	Time from illness onset to resolution of influenza symptoms	Time from illness onset to resolution of major symptoms (fever, tachypnea, difficult/noisy breathing, cough, and any danger sign)	Time from illness onset to presence of mild or absent cough and rhinitis, afebrile, return to normal activities

Abbreviation: RT-PCR, real-time polymerase chain reaction.

Overall 1190 patients enrolled and randomized, 796 patients randomized <48 hours from onset eligible for inclusion in meta-analysis. Separate randomization for those enrolled >48 hours from onset.

95% CI, –53.9 to –5.8 hours). For trials that enrolled only patients with asthma, there was no effect of treatment (Figure 2). Reductions in the duration of illness were attenuated in the ITT population (Supplementary Figure S2) but remained significant (RMST difference, 8.4 hours; 95% CI, –16.7 to –0.01 hours; Supplementary Figure S3).

Complications

In the ITTI population ($n = 1598$) there were fewer cases of LRTC >48 hours after first study drug intake in the oseltamivir group compared to the placebo group (29/770 [4%] vs 38/828 [5%]; relative risk [RR], 0.75; 95% CI, 0.37, 1.52), but the difference was not statistically significant (Figure 3). There was evidence of a 34% reduction in risk of developing otitis media in the ITTI population (RR, 0.66; 95% CI, 0.47–0.95). In the ITT population with complete data on complications ($n = 2458$), the effect of treatment on developing otitis media was attenuated and no longer significant (RR, 0.98; 95% CI, 0.77, 1.26). There were too few hospitalizations to reach meaningful conclusions (ITTI 4/770 [0.5%] oseltamivir compared to 3/825 [0.3%] placebo).

Safety

We found an increased RR of vomiting in the treatment group (RR, 1.63; 95% CI, 1.30, 2.04), but no evidence of an increased risk of nausea, diarrhea, or SAEs among 2558 patients in the safety population (Table 3). SAEs were very rare in both the oseltamivir (11/1074 [1%]) and placebo (4/1078 [0.4%]) groups. In the trials that recorded data, there was also no difference in withdrawal from treatment (26/676 [4%] oseltamivir vs 27/682 [4%] placebo; $P = .93$) and withdrawal due to an adverse event (8/676 [1%] vs 8/682 [1%]; $P = .99$) by treatment group.

Pooled Analysis

Finally, we conducted a pooled analysis, combining data across trials, to examine subgroups of interest. In stratified analyses adjusting for trial, we observed a larger difference in RMST for individuals who received early treatment (<24 hours) compared to those who received treatment 24–48 hours after onset (–22.8 hours, 95% CI, –29.4 to –16.2 hours vs –4.4 hours, 95% CI, –15.5 to 6.5 hours). We observed the largest reduction

Table 2. Characteristics of Trial Participants by Treatment and Trial

Trial	WV15758		WV15759/WV15871		NV16871	
	Placebo	Oseltamivir	Placebo	Oseltamivir	Placebo	Oseltamivir
ITT population	351	344	164	165	164	170
ITTI population (%)	225 (64.1)	209 (60.8)	51 (31.1)	43 (26.1)	95 (57.9)	84 (49.4)
Age category, y (%)						
≤ 5	197 (56.1)	193 (56.1)	0 (0.0)	0 (0.0)	2 (1.2)	4 (2.4)
6–11	138 (39.3)	139 (40.4)	90 (54.9)	93 (56.4)	151 (92.1)	145 (85.3)
12–17	16 (4.6)	12 (3.5)	74 (45.1)	72 (43.6)	11 (6.7)	21 (12.4)
≥18	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Male (%)	179 (51.0)	171 (49.7)	108 (65.9)	107 (64.8)	101 (61.6)	111 (65.3)
Influenza vaccine current season (%)	10 (2.8)	11 (3.2)	–	–	34 (20.7)	31 (18.2)
Influenza vaccine prior season (%)	13 (3.7)	21 (6.1)	–	–	37 (22.6)	39 (22.9)
Asthma (%)	0 (0.0)	0 (0.0)	164 (100.0)	165 (100.0)	164 (100.0)	170 (100.0)

Trial	NCT00707941		NCT00593502		Overall		p value
	Placebo	Oseltamivir	Placebo	Oseltamivir	Placebo	Oseltamivir	
ITT population	396	398	205	204	1280	1281	
ITTI population	396 (100.0)	398 (100.0)	61 (29.8)	37 (18.1)	828 (65.5)	770 (60.8)	
Age category, y (%)							
≤ 5	222 (56.1)	213 (53.5)	205 (100.0)	204 (100.0)	626 (48.9)	614 (47.9)	0.927
6–11	98 (24.7)	102 (25.6)	0 (0.0)	0 (0.0)	477 (37.3)	479 (37.4)	
12–17	28 (7.1)	31 (7.8)	0 (0.0)	0 (0.0)	129 (10.1)	136 (10.6)	
≥18	48 (12.1)	52 (13.1)	0 (0.0)	0 (0.0)	48 (3.8)	52 (4.1)	
Male (%)	208 (52.5)	218 (54.8)	123 (60.0)	106 (52.0)	719 (56.2)	713 (55.7)	
Influenza vaccine current season (%)	–	–	51 (24.9)	52 (25.5)	95 (8.5)	94 (8.4)	0.825
Influenza vaccine prior season (%)	0 (0.0)	0 (0.0)	–	–	50 (4.5)	60 (5.4)	1.00
Asthma (%)	–	–	6 (2.9)	7 (3.4)	334 (37.8)	342 (38.7)	0.379

Abbreviations: ITT, intention-to-treat; ITTI, intention-to-treat infected.

in duration of illness among adolescents (aged 12–17 years), though CIs of age stratified estimates overlapped (Figure 4). We found no effect of treatment in children with asthma but a large difference in those without asthma (–34.9 hours; 95% CI, –46.4

to –23.4 hours). We also found no effect of treatment compared to placebo among uninfected participants (3.1 hours; 95% CI, –5.9 to 12.1 hours), while among infected individuals there was a significant reduction in duration of illness consistent with

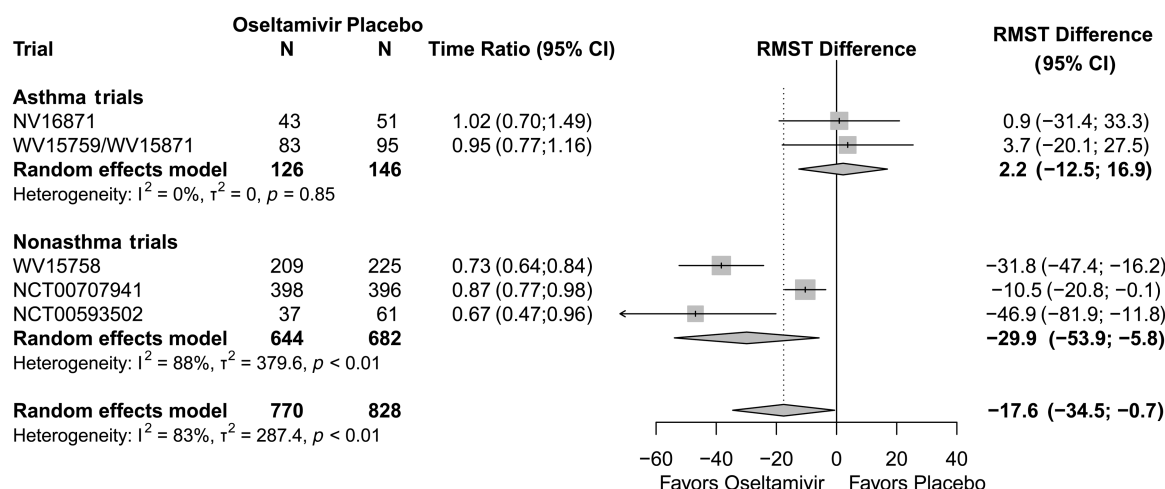


Figure 2. Forest plot, random-effects meta-analysis of the efficacy of oseltamivir treatment in reducing duration of illness as measured by the difference in restricted mean survival time and time ratio from accelerated failure time models in the intent-to-treat infected population. Abbreviations: CI, confidence interval; RMST, restricted mean survival time.

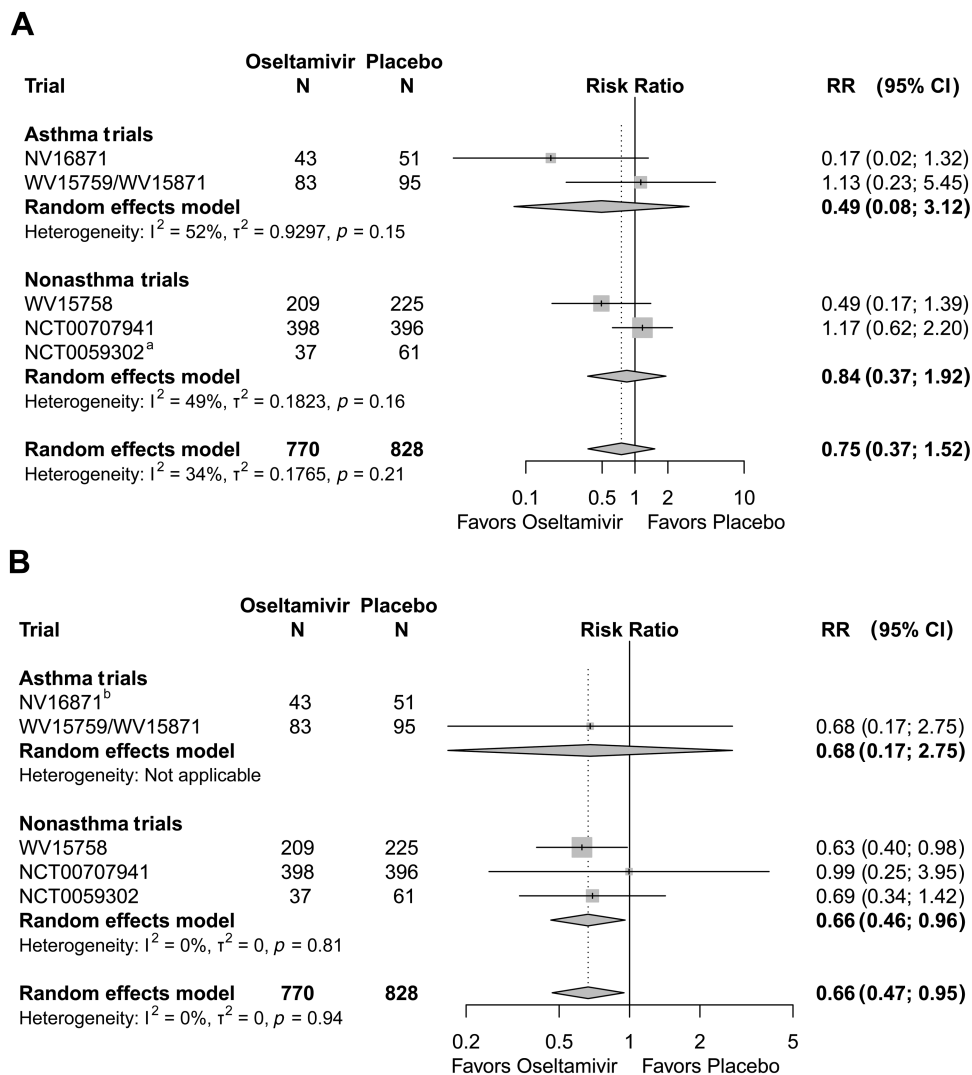


Figure 3. Forest plot, random-effects meta-analysis of the relative risk of developing complications in the intent-to-treat infected population. (A) Lower respiratory tract complications and (B) otitis media. Relative risk estimated from log-binomial regression models. Abbreviations: CI, confidence interval; RR, relative risk.

the pooled effect from the meta-analysis (−17.5 hours; 95% CI, −23.2 to −11.8 hours). Results of pooled analyses, adjusting for potential confounders, were similar to the meta-analyses described above for both complications (Supplementary Table S3) and safety outcomes (Supplementary Table S4).

DISCUSSION

In the current analysis, we demonstrated a reduction in the duration of illness of approximately 18 hours among children who received timely oseltamivir treatment compared to placebo. In addition, we found that treatment reduced the risk of otitis media

Table 3. Meta-analysis of Adverse Event Outcomes

Study	Placebo N	Oseltamivir N	Relative Risk ^a (95% Confidence Interval)			
			Vomiting	Nausea	Diarrhea	Severe adverse events
WV15758	351	344	1.67 (1.08–2.56)	0.96 (0.45–2.02)	0.83 (0.52–1.31)	1.53 (0.26–11.70)
WV15759/WV15871	164	170	1.45 (0.83–2.53)	0.48 (0.13–1.50)	0.80 (0.36–1.81)	2.41 (0.53–16.68)
NV16871	164	165	3.23 (1.08–9.70)	1.21 (0.37–4.12)	–	–
NCT00707941	396	398	1.71 (0.90–3.25)	6.96 (0.86–56.35)	0.80 (0.53–1.21)	–
NCT0593502	202	207	1.54 (1.07–2.20)	–	0.96 (0.74–1.25)	–
Overall	1281	1277	1.63 (1.30–2.04)	1.10 (0.45–2.71)	0.89 (0.74–1.08)	1.98 (0.59–6.52)

^aRelative risk estimated from log-binomial regression models.

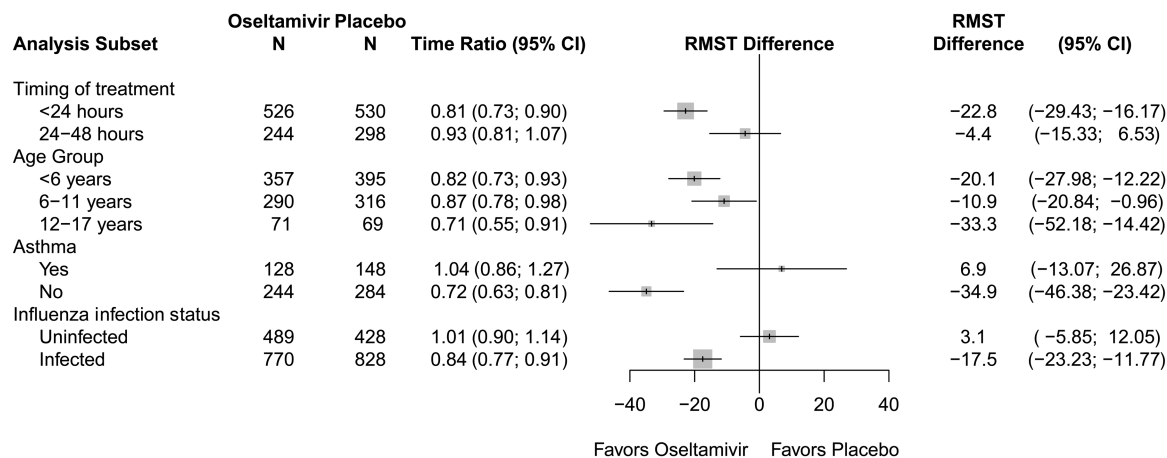


Figure 4. Forest plot, pooled analysis estimating the time ratio from accelerated failure time models with generalized F distribution and restricted mean survival time difference and 95% confidence interval for patients who received oseltamivir compared to placebo stratified by subgroups of interest and controlling for trial. Abbreviations: CI, confidence interval; RMST, restricted mean survival time.

and that there was little evidence of safety issues, except for vomiting. A recent meta-analysis of all adult RCTs found a reduction in duration of illness in the ITT population of 25 hours [19]. The identified adult trials, including published and unpublished works, were all conducted around the time of licensure. The study populations varied in some trials (eg, older adults or those with underlying conditions), but all trials used a similar endpoint, referred to as “alleviation of illness.” This endpoint was defined as absence of fever, but other symptoms could be either mild or absent. In contrast, there was much more variation in both study population and endpoints in the pediatric studies included in this analysis. The largest pediatric trial, for example, was conducted 10 years after licensure, in urban Bangladesh. This setting was chosen to estimate the efficacy of oseltamivir under conditions with high levels of crowding and poor sanitation. The primary outcome, duration of clinical illness, was defined by no sign of illness, including fever, danger signs, or other indications that would require clinical referral [27]. Two other trials included only children with asthma, one limited to children aged >6 years, and each used a different primary endpoint. To address this heterogeneity, we performed a random-effects meta-analysis and used the outcome that was as close as possible to the definition of alleviation from the adult trials. We also examined the sensitivity of our overall estimate to each trial by systematically excluding trials and repeating the analysis (Supplementary Table S5). When the Bangladesh trial was removed, the estimated reduction in duration increased to 20 hours. It is perhaps not surprising, given the potential for effect modification by crowding and other factors, that the estimated reduction when the Bangladesh trial was included was lower.

We also found that the overall estimate was attenuated in the per-protocol (ITT) population, a result of no significant difference in duration of illness among those not infected with influenza viruses. This confirms a similar finding from the meta-analysis of adult trials and suggests that the reduction in

illness duration is attributable to a specific antiviral effect and not generalized antiinflammatory activity, as has been posited [14]. That the reduction detected was a result of antiviral effect is confirmed by the greater reduction in duration when oseltamivir was given within 24 hours of onset [29]. It is also clear that the definition of infection did not affect the results (Supplementary Figure S4).

The major outliers in this analysis were the trials that included only children with asthma. The pooled estimate for the 3 trials that did not specifically enroll asthma patients was a reduction in illness duration of 29.9 hours, which is closer to that found in the adult meta-analysis [19]. There is no clear reason to hypothesize a different antiviral effect in asthmatic children compared to healthy children. Rather the difference in efficacy may be explained by the difficulty in recognizing clinical illness endpoints in those with underlying respiratory conditions. Alternate endpoints such as improvement in pulmonary function or the duration of viral shedding may be more relevant in future studies of asthmatic children. Molecular methods to determine respiratory viral load have become standard since the original trials and may help separate the role of viral replication and symptoms in these children [30, 31].

We found no evidence of an increase in the risk of nausea or SAEs but did detect an increase in the risk of vomiting in those who received oseltamivir. These results are consistent with previous analyses [16, 19, 32]. While the ITT population was relatively large, it might not be large enough to detect more infrequent adverse events. For that purpose, it is useful to look at the evaluations conducted in the course of the pediatric studies, which resulted in approval in the United States for children aged as young as 2 weeks [9, 33]. In these studies, vomiting was also the only adverse effect seen more often with oseltamivir compared with placebo [9]. Approval was an explicit recognition of the need for an antiviral to treat influenza virus infections in this vulnerable population.

Reduction in complications is a major rationale for antiviral treatment of influenza virus infection in adults and the basis for policy recommendations. Not surprisingly, lower respiratory complications were infrequent in the current analysis, which mainly included children without serious underlying conditions. Overall, there were fewer complications in the treated group, but the difference was not statistically significant. Importantly, we did find a significant reduction of 34% in the risk of developing otitis media in those who received oseltamivir treatment. Similar reductions have been found in individual studies [24, 28] and in the pivotal evaluations of live attenuated influenza vaccine in children aged <6 years [34, 35]. These observations further confirm the role of influenza as an etiologic agent of otitis media and the role of both prophylaxis and treatment in its prevention.

During the 2009 pandemic, the need for antiviral treatment of young children with influenza was reinforced as they were particularly vulnerable to severe illness [36–38]. A meta-analysis of individual patient data from observational studies conducted during that period showed a highly significant effect of oseltamivir in preventing mortality among hospitalized adults but not among children [13]. Our analysis is reassuring in that, for uncomplicated influenza, oseltamivir appears to be as safe and effective in children as in adults. With the appropriate dose now established, there does not appear to be any scientific reason why it should be of lower efficacy, even in cases of severe disease. Of particular importance is the evidence for the prevention of otitis media, as this is a relatively frequent complication of influenza virus infection with the potential for long-term consequences on language development and learning. Our findings support current policy [39] and the position of the American Academy of Pediatrics [40] and reinforce the recommendation that treatment is most useful when started early after illness onset.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. R. J. W. reports receipt of fees as a board member of Gilead Sciences. A. S. M. reports receipt of consulting fees from Roche related to the submitted work and from Seqirus outside the submitted work. All remaining authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Neuraminidase inhibitors during pregnancy and risk of adverse neonatal outcomes and congenital malformations: population based European register study

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ABSTRACT OBJECTIVE

To evaluate the possible effects of exposure to neuraminidase inhibitors during embryo-fetal life with respect to adverse neonatal outcomes and congenital malformations.

DESIGN

Population based multinational observational cohort study and meta-analysis.

SETTING

National registers covering information on maternal healthcare, births, and prescriptions in Denmark, Norway, and Sweden and the EFEMERIS database from the Haute-Garonne district in France.

PARTICIPANTS

All women together with their singleton infants born between 1 January 2008 and 31 December 2010. Only infants born at 154 days of gestation or later were included. Infants were defined as exposed if the women filled a prescription during pregnancy for either of the two neuraminidase inhibitors oseltamivir or zanamivir.

MAIN OUTCOMES

Low birth weight, low Apgar score, preterm birth, small for gestational age birth, stillbirth, neonatal mortality, neonatal morbidity, and congenital malformations. Crude and adjusted hazard ratios of preterm birth were estimated using Cox regression models. Crude and adjusted odds ratios for other outcomes were estimated by logistic regression models.

RESULTS

The study included 5824 (0.8%) exposed women and their infants and 692 232 who were not exposed.

Exposure to neuraminidase inhibitors in utero was not associated with increased risks of any of the investigated neonatal outcomes, including low birth weight (adjusted odds ratio 0.77, 95% confidence interval 0.65 to 0.91), low Apgar score (adjusted odds ratio 0.87, 0.67 to 1.14), preterm birth (adjusted hazard ratio 0.97, 0.86 to 1.10), small for gestational age birth (adjusted odds ratio 0.72, 0.59 to 0.87), stillbirth (adjusted odds ratio 0.81, 0.51 to 1.30), neonatal mortality (adjusted odds ratio 1.13, 0.56 to 2.28), and neonatal morbidity (adjusted odds ratio 0.92, 0.86 to 1.00). No increased risk of congenital malformations overall associated with maternal exposure was observed during the first trimester (adjusted odds ratio 1.06, 0.77 to 1.48). Similarly, no significantly increased risks of any of the outcomes were observed in an analysis restricted to oseltamivir alone.

CONCLUSIONS

This large multinational register study found no increased risks of adverse neonatal outcomes or congenital malformations associated with exposure to neuraminidase inhibitors during embryo-fetal life. The results support previously reported findings that the use of neuraminidase inhibitors is not associated with increased risks of adverse fetal or neonatal outcomes.

Introduction

Pregnant women are at increased risk of severe disease and death secondary to influenza infection. In addition, influenza and fever may increase the risk of adverse pregnancy outcomes.¹⁻⁴ Despite limited knowledge on the safety and effectiveness of neuraminidase inhibitors in pregnancy, the regulatory agencies in Europe and the US recommended treatment and post-exposure prophylaxis in patients at high risk, such as pregnant women, during the 2009-10 influenza A/H1N1 pandemic.⁵

In Europe, where our study took place, oseltamivir, taken orally, and zanamivir, which is inhaled, are the two approved neuraminidase inhibitors. Early treatment of influenza with oseltamivir has been associated with a reduced risk of severe infection and of admission to intensive care units for pregnant women.¹⁶ Because of the 2009 H1N1 pandemic and the regulatory agencies' recommendations, the number of women exposed to neuraminidase inhibitors during pregnancy increased markedly during the 2009-10 influenza pandemic compared with previous years.⁷⁸ Accordingly, in the next virulent seasonal influenza pandemic, a large number of women may be targeted for post-exposure prophylaxis and treatment globally.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Seasonal influenza occurs yearly, and millions of pregnant women risk severe illness during seasons with a more aggressive strain

European and American health authorities have recommended treatment and post-exposure prophylaxis with neuraminidase inhibitors for pregnant women

Despite the recommendations, information on possible adverse effects on infants exposed to neuraminidase inhibitors during embryo-fetal life is limited

WHAT THIS STUDY ADDS

This is the largest study on the topic to date and includes almost 6000 infants exposed to neuraminidase inhibitors and around 700 000 unexposed infants

No increased risks of adverse neonatal outcomes including neonatal morbidity or mortality, poor fetal growth, low Apgar score, or congenital malformations were seen in exposed infants

The study supports previously reported findings that the use of neuraminidase inhibitors is not associated with increased risks of adverse fetal or neonatal outcomes

No randomised controlled trials on use of neuraminidase inhibitors during pregnancy have been conducted. To date, seven observational studies including data from a total of approximately 2500 women who used oseltamivir during pregnancy found no increased risks of congenital malformations or other adverse pregnancy outcomes.⁵⁻⁹⁻¹⁴ The largest study so far was from Canada and included around 1200 exposed women. This study, which apparently had no information on timing of drug exposure, found a significantly lower risk (adjusted odds ratio 0.77) of having a moderately growth restricted infant (<10th centile) with oseltamivir.¹⁰ For congenital malformations, exposure during the first trimester is of relevance, and four of the other studies included exposure in the first trimester, collectively including approximately 300 women.⁵⁻¹²⁻¹⁴ Their inadequate size and the fact that outcomes such as infant mortality, preterm births, severe intrauterine growth restriction, and congenital malformations occur rarely mean that the previous studies had limited statistical power for more detailed analyses of these outcomes.

Although the influenza pandemic in 2009-10 was relatively mild in most cases, the uncertainty about the aggressiveness of a next pandemic virus outbreak and the possibility of spreading in vulnerable populations, such as pregnant women, mean that preparedness is critical. This study was set up to assess risks of adverse birth outcomes in association with the two major and non-intravenously administered neuraminidase inhibitors, oseltamivir and zanamivir, when used during pregnancy. Its objective was to evaluate possible adverse effects of exposure to neuraminidase inhibitors in utero on outcomes of low birth weight, low Apgar score, preterm birth, small for gestational age birth, stillbirth, neonatal mortality, neonatal morbidity, and congenital malformations.

Methods

We did a multinational population based register study, including all women and their singleton infants born between 1 January 2008 and 31 December 2010 in the Scandinavian countries (Denmark, Norway, and Sweden) and those recorded in the EFEMERIS database in France.¹⁵

Setting and data sources

The Scandinavian countries have population based national registers, which include prospectively collected information for all inhabitants on demographic and health indicators such as births, dispensed drugs, and hospital contacts. The total population in the Scandinavian countries is approximately 20 million inhabitants, and the national parliaments have given informed consent to be included in the registers on behalf of their population.¹⁶ All registers include the civil registration number of each resident, a unique number assigned at birth or immigration, which allows linkage of individual data between registers. From the Scandinavian countries, we obtained data from the medical birth registers, the registers for prescribed drugs, and the patient registers. The Scandinavian medical birth registers include data on maternal characteristics, pregnancy, delivery, and the neonatal period, including information on maternal body mass index and on smoking during pregnancy. For congenital malformations, the data came from either the medical birth registers or the patient registers. All diagnoses and congenital malformations were recorded according to ICD-10 (international classification of diseases, 10th revision).¹⁷ The prescribed drug registers include data on dispensed substances, dispensed dose, package sizes, and formulations according to the Anatomical Therapeutic Chemical (ATC) classification of drugs together with the date of dispensing.¹⁸

From France, we included women recorded in the EFEMERIS database, which is described in detail elsewhere.¹⁴⁻¹⁵ EFEMERIS is a population based database that holds health related data in the Haute-Garonne district, which has 1 million inhabitants. The register contains individual based information on prescribed drugs, pregnancy outcome, and neonatal health from national health insurance system, Mother and Child Protection Service, hospitals, and neonatal clinics. The data are anonymised before transmission to the pharmacology service.

From the various data sources, we constructed two separate databases: one including Scandinavian data (pooling data from the three countries into one database) and one with French data. Figure 1 describes the flow of data into the analysis.

Participants

All women together with their infants born during the study period and included in the Scandinavian birth registers or the EFEMERIS database were eligible for inclusion. Only singleton infants born at 154 days (22 weeks) of gestation or later were included. We excluded all infants (and their mothers) with an ICD-10 code suggesting chromosomal aberrations (Q90-99) or for whom the information on gestational age at delivery was missing. Women who had been admitted to hospital because of influenza or pneumonia (ICD-10 code J09-18) during pregnancy were excluded from the Scandinavian database. In the EFEMERIS database, information on hospital admission during pregnancy was not available so

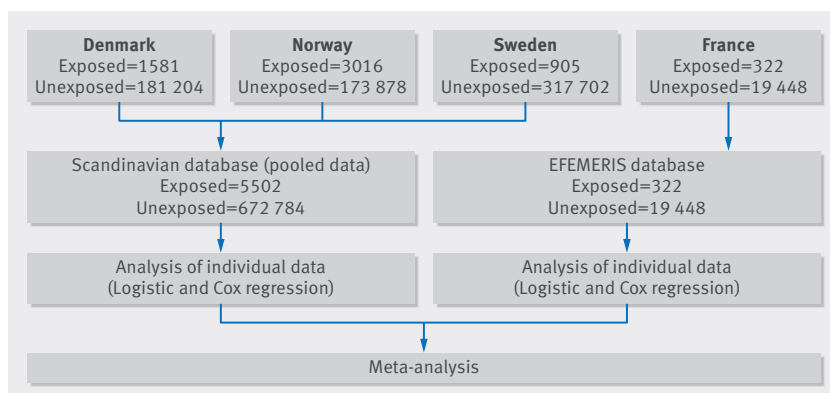


Fig 1 | Data flow in register based study on neuraminidase inhibitors during pregnancy

women admitted with influenza were not excluded in the French data.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Exposure to neuraminidase inhibitors during embryo-fetal life

We defined exposure as having filled a prescription after the date of assumed conception (that is, from 14 days after the first day of the last menstrual period), for either of the two neuraminidase inhibitors—oseltamivir (ATC code J05AH02) or zanamivir (ATC code J05AH01)—as recorded in the prescribed drug registers or the EFEMERIS database. Last menstrual period was based on gestational age calculated at an obstetric ultrasound examination that most of the included women had in the first or second trimester. We defined first trimester as gestational day 0-90, second trimester as gestational day 91-180, and third trimester as gestational day 181 to delivery. For congenital malformations, we evaluated only exposures during the first trimester in the study. We analysed oseltamivir and zanamivir jointly in the study and assessed associations with exposure only to oseltamivir in sub-analyses. Potential confounders included infant's country of birth (Scandinavian countries), infant's year of birth, maternal age, maternal comorbidity, and smoking. We defined maternal comorbidity as having filled at least one prescription for drugs used to treat chronic diseases, such as hypertension or diabetes, within 365 days before the first day of the last menstrual period (Scandinavian data). For the French data, the corresponding period was three months before the last menstrual period. A complete list of the included ATC codes used as proxies for maternal disease is shown in supplementary table A.

Outcome measures

We assessed the following neonatal outcomes: low birth weight, low Apgar score, preterm birth, small for gestational age birth, stillbirth, neonatal mortality, neonatal morbidity, and congenital malformations. We defined low birth weight as weighing less than 2500 g at birth regardless of gestational age, low Apgar as having an Apgar score of 0-6 at 5 minutes of life, preterm birth as birth before 259 gestational days (37 weeks), and small for gestational age birth as weighing 2 standard deviations or less below the corresponding mean birth weight by gestational length and infant sex in Sweden (Scandinavian data) or France (French data).¹⁹ Stillbirth was defined as recorded in the respective national registers or EFEMERIS database, neonatal mortality as death of a liveborn infant within the first 28 days of life, and neonatal morbidity as having one or more recorded ICD-10 codes P00-P99 within the first 28 days of life,

grouped according to the affected organ system (supplementary table B). We defined malformations diagnosed within the first 28 days of life according to ICD-10 codes and the EUROCAT classification system.²⁰ We did not consider minor malformations according to the EUROCAT classification.²⁰

Statistical analysis

The data in each database (Scandinavian countries and France) included information at the individual level, and in a first step we analysed the two databases separately. The Scandinavian database thus encompassed individual data from all three countries. We used logistic regression to estimate crude and adjusted odds ratios together with 95% confidence intervals for low birth weight, low Apgar score, small for gestational age birth, stillbirth, neonatal mortality, and neonatal morbidity. We used exact logistic regression for sparse data—that is, when no cases were reported among the exposed population. We used Cox proportional hazards regression models to estimate the hazards ratios together with 95% confidence intervals for preterm birth, with the gestational length in days as the underlying time variable. For the analyses of preterm birth, we followed women from gestational week 22 until an outcome event or censoring at a gestational age of 259 days (37 weeks). We considered women to be exposed from the day in pregnancy when a neuraminidase inhibitor was dispensed and to remain as such until delivery.

We adjusted all outcomes for country (Scandinavian database only), year of birth, maternal age, maternal comorbidity, and smoking. We excluded women from the adjusted analysis if they had missing data on any of the five covariates. For malformations, we present the adjusted odds ratios only from analyses with more than five births among exposed infants with the specific malformation or organ system event.

To assess the robustness of the logistic regression model and to investigate whether including body mass index in the model affected the results, we did a restricted analysis including only data from Sweden and Denmark, both of which had nearly complete information on this variable. As inclusion of body mass index in the analysis carried out in the subset did not confound the results, we did not consider this variable in further analyses.

To combine the adjusted results from the Scandinavian and the French databases, we did a meta-analysis using the Metan command (version 9) in Stata (version 11.2).^{21,22} We estimated a random effect model. We used the χ^2 test for heterogeneity and the I^2 statistic to assess the heterogeneity between the Scandinavian and French data.

Results

We included a total of 5824 (0.8%) exposed infants and 692 232 unexposed infants in the study—5502 exposed and 672 784 unexposed infants from the Scandinavian countries, and 322 exposed and 19 448 unexposed infants from France (fig 1). Among the exposed

infants, most of the women (4310; 74%) had received oseltamivir and 441 were dispensed a neuraminidase inhibitor more than once during their pregnancy. Among the exposed women, 1220 were exposed in the first trimester, 2408 in the second trimester, and 2196 in the third trimester. Table 1 describes the study participants in more detail. Most of the exposed infants were born in 2010. The exposed women were slightly older and had a higher proportion of maternal comorbidity but a lower body mass index than unexposed women.

Neonatal outcomes

In the entire study population, stillbirth occurred in 4.1 per 1000 births and the neonatal mortality was 1.5 per 1000 live births. Similarly, 38 866 (5.6%) were born preterm, 24 164 (3.5%) had a low birth weight, 17 539 (2.5%) were small for gestational age, and 8503 (1.2%) had a low Apgar score.

Exposure to neuraminidase inhibitors in utero was not associated with increased risks of any of the investigated neonatal outcomes (table 2 and supplementary figure A). Exposure was associated with a decreased risk of being born at a low birth weight (adjusted odds ratio 0.77, 95% confidence interval 0.65 to 0.91) or small

for gestational age (0.72, 0.59 to 0.87). We found no increased risk of being born preterm (adjusted hazard ratio 0.97, 0.86 to 1.10) or for stillbirth (adjusted odds ratio 0.81, 0.51 to 1.30).

The analysis of neonatal morbidity included only Scandinavian data. We found no overall association between exposure to neuraminidase inhibitors and increased neonatal morbidity during the first 28 days of life (adjusted odds ratio 0.92, 0.86 to 1.00) (table 3). In the adjusted analysis, we found a decreased risk of respiratory and cardiovascular disorders specific to the neonatal period among infants exposed to neuraminidase inhibitors during pregnancy (adjusted odds ratio 0.84, 0.75 to 0.95). The estimates of risk for the neonatal outcomes by trimester of exposure and database are shown in supplementary table C.

When we included women exposed to only oseltamivir (supplementary table D), the point estimates and 95% confidence intervals for all the estimated outcomes were similar to those derived from the compound exposure (supplementary tables E-H and supplementary figure B).

Congenital malformations

The analysis of congenital malformations included only Scandinavian data from infants exposed during the first trimester, as no congenital malformations were reported in the 95 infants exposed during the first trimester in the EFEMERIS database. Of the 1125 infants exposed in the first trimester, 44 had at least one congenital malformation diagnosed, yielding a prevalence of 3.9%. In the unexposed group, 19 509 (2.9%) of the 672 784 infants had at least one congenital malformation. Among the exposed infants, three (0.3%) had more than one malformation. The corresponding number for the unexposed infants was 2336 (0.3%). In the adjusted analysis, we found no increased risk of congenital malformations overall in association with exposure in utero (adjusted odds ratio 1.06, 0.77 to 1.48). Although the analysis was limited by small sample size, neuraminidase inhibitor exposure was not associated with increased risk of any of the specific subgroups of congenital malformations according to the EUROCAT classification. Table 4 shows the absolute numbers per organ system and the adjusted odds ratio together with 95% confidence intervals for malformations with more than five exposed births. The adjusted analysis of congenital malformations overall including infants exposed to oseltamivir in utero found an adjusted odds ratio of 1.08 (0.73 to 1.58).

Discussion

In this large multinational population based study including almost 6000 infants exposed to neuraminidase inhibitors in utero, we found no significantly increased risks of adverse neonatal outcomes or congenital malformations. On the contrary, we observed a small decrease in risk of weighing less than 2500 g or being classified as small for gestational age after exposure to neuraminidase inhibitors. The decreased risk remained after adjustment for possible confounders

Table 1 | Maternal and infant characteristics by exposure to neuraminidase inhibitors during pregnancy. Values are numbers (percentages)

	Scandinavian database		EFEMERIS database	
	Exposed (n=5502)	Unexposed (n=672 784)	Exposed (n=322)	Unexposed (n=19 448)
No of infants exposed				
Denmark	1581 (28.7)	181 204 (26.9)	-	-
Norway	3016 (54.8)	173 878 (25.8)	-	-
Sweden	905 (16.4)	317 702 (47.2)	-	-
Sex of infant				
Female	2685 (48.8)	326 785 (48.6)	149 (46.3)	9303 (47.8)
Male	2816 (51.2)	345 853 (51.4)	167 (51.9)	9744 (50.1)
Missing information	1 (0)	146 (0)	6 (1.9)	401 (2.1)
Year of birth				
2008	4 (0.1)	223 989 (33.3)	0 (0)	5308 (27.3)
2009	1489 (27.1)	223 033 (33.2)	67 (20.8)	2794 (14.4)
2010	4009 (72.9)	225 762 (33.6)	255 (79.2)	11 346 (58.3)
Mother's age at delivery				
≤19 years	98 (1.8)	9665 (1.4)	9 (2.8)	306 (1.6)
20-29 years	1943 (35.3)	273 477 (40.6)	136 (42.2)	8442 (43.4)
≥30 years	3461 (62.9)	389 597 (57.9)	177 (55.0)	10 700 (55.0)
Missing information	0	45 (0)	0	0
Smoking during pregnancy				
Yes	560 (10.2)	63 155 (9.4)	21 (6.5)	958 (4.9)
No	4464 (81.1)	574 020 (85.3)	287 (89.1)	16 997 (87.4)
Missing information	478 (8.7)	35 609 (5.3)	14 (4.3)	1493 (7.7)
Maternal body mass index				
≤24	1518 (27.6)	283 713 (42.2)	-	-
25-29	640 (11.6)	127 720 (19.0)	-	-
≥30	340 (6.2)	62 373 (9.3)	-	-
Missing information	3004 (54.6)	198 978 (29.6)	-	-
Maternal comorbidity*				
Yes	1375 (25.0)	125 686 (18.7)	72 (22.4)	3505 (18.0)
No	4127 (75.0)	547 098 (81.3)	250 (77.6)	15 943 (82.0)

*Defined as filled prescription for any drug used for chronic disease (supplementary table A) in one year (Scandinavia) or three month (France) period before last menstrual period.

Table 2 | Neuraminidase inhibitors during pregnancy and risks of neonatal outcomes (birth weight, Apgar score, preterm birth, small for gestational age birth, stillbirth, and neonatal mortality)

	Scandinavian database				EFEMERIS database			
	No (%)		Odds ratio (95% CI)		No (%)		Odds ratio (95% CI)	
	Exposed (n=5502)	Unexposed (n=672 784)	Unadjusted	Adjusted*	Exposed (n=322)	Unexposed (n=19 448)	Unadjusted	Adjusted*
Birth weight								
<2500 g	157 (2.9)	23 137 (3.4)	0.83 (0.70 to 0.97)	0.77 (0.65 to 0.91)	12 (3.7)	858 (4.4)	0.80 (0.45 to 1.44)	0.76 (0.42 to 1.41)
2500-4499 g	5151 (93.6)	624 953 (92.9)	Reference	Reference	293 (91.0)	16 768 (86.2)	Reference	Reference
≥4500 g	183 (3.3)	23 133 (3.4)	0.97 (0.83 to 1.12)	1.00 (0.86 to 1.17)	1 (0.3)	125 (0.6)	0.46 (0.06 to 3.32)	0.46 (0.06 to 3.31)
Missing information	11 (0.2)	1561 (0.2)	-	-	16 (5.0)	1697 (8.7)	-	-
Apgar score								
≤6	61 (1.1)	8345 (1.2)	0.89 (0.69 to 1.15)	0.87 (0.67 to 1.14)	0 (0)	97 (0.5)	0 (0 to 1.81)	0 (0 to 1.55)
≥7	5423 (98.6)	660 649 (98.2)	Reference	Reference	301 (93.5)	17 317 (89.0)	Reference	Reference
Missing information	18 (0.3)	3790 (0.6)	-	-	21 (6.5)	2034 (10.5)	-	-
Preterm birth <37 weeks								
Yes	268 (4.9)	37 145 (5.5)	1.00 (0.89 to 1.13) [†]	0.97 (0.86 to 1.11) [†]	20 (6.2)	1433 (7.4)	1.06 (0.68 to 1.65) [†]	0.97 (0.56 to 1.68) [†]
No	5234 (95.1)	635 639 (94.5)	Reference	Reference	302 (93.8)	18 015 (92.6)	Reference	Reference
Small for gestational age[‡]								
Yes	111 (2.0)	17 046 (2.5)	0.80 (0.66 to 0.96)	0.72 (0.59 to 0.88)	4 (1.2)	378 (1.9)	0.61 (0.23 to 1.64)	0.60 (0.22 to 1.62)
No	5380 (97.8)	654 210 (97.2)	Reference	Reference	300 (93.2)	17 285 (88.9)	Reference	Reference
Missing information	11 (0.2)	1528 (0.2)	-	-	18 (5.6)	1785 (9.2)	-	-
Stillbirth[§]								
Yes	14 (0.3)	2469 (0.4)	0.69 (0.41 to 1.17)	0.73 (0.41 to 1.29)	6 (1.9)	386 (2.0)	0.94 (0.42 to 2.12)	1.02 (0.45 to 2.31)
No	5488 (99.7)	670 315 (99.6)	Reference	Reference	315 (97.8)	19 013 (97.8)	Reference	Reference
Missing information	0 (0)	0 (0)	-	-	1 (0.3)	49 (0.3)	-	-
Neonatal mortality								
Yes	8 (0.1)	979 (0.1)	1.00 (0.50 to 2.00)	1.13 (0.56 to 2.28)	0 (0)	26 (0.1)	0 (0 to 7.39)	0 (0 to 67.49)
No	5480 (99.6)	669 336 (99.5)	Reference	Reference	315 (97.8)	18 987 (97.6)	Reference	Reference
Missing information	14 (0.3)	2469 (0.4)	-	-	7 (2.2)	435 (2.2)	-	-

*Adjusted for country (Scandinavian countries), year of birth, maternal age, maternal comorbidity, and smoking.

†Hazard ratio.

‡Corresponding to birth weight ≤2 standard deviations of national reference curve.

§EFEMERIS data not adjusted for smoking.

such as infant's year and country of birth and maternal age, comorbidity, and smoking during pregnancy. The findings of no increased risks remained when we restricted the analyses to exposure to oseltamivir only.

Comparison with previous studies

The effect of neuraminidase inhibitors during pregnancy on neonatal outcomes and congenital malformations has been assessed previously.^{2,5,9-14,23,24} However,

this study is by far the largest, being almost twice the size of all other studies combined with respect to the number of exposed pregnant women, and our results confirm and expand on the findings in the previous studies of no association between neuraminidase inhibitors and a broad range of adverse neonatal outcomes. The previous studies, including a study from France with data overlapping ours,¹⁴ had limited statistical power to assess specific outcomes such as

Table 3 | Neuraminidase inhibitors during pregnancy and risks of neonatal morbidity by affected organ system in Scandinavian countries

	No (%)		Odds ratio (95% CI)	
	Exposed (n=5502)	Unexposed (n=672 784)	Unadjusted	Adjusted [†]
Neonatal morbidity by organ system*				
Fetus and newborn affected by maternal factors and by complications of pregnancy, labour, and delivery	117 (2.1)	10 940 (1.6)	1.32 (1.09 to 1.58)	0.94 (0.77 to 1.14)
Disorders related to length of gestation and fetal growth	293 (5.3)	35 632 (5.3)	1.01 (0.89 to 1.13)	0.89 (0.79 to 1.01)
Birth trauma	30 (0.5)	3248 (0.5)	1.13 (0.79 to 1.62)	0.85 (0.58 to 1.24)
Respiratory and cardiovascular disorders specific to perinatal period	314 (5.7)	34 630 (5.1)	1.12 (1.00 to 1.25)	0.84 (0.75 to 0.95)
Infections specific to perinatal period	68 (1.2)	8970 (1.3)	0.93 (0.73 to 1.18)	0.78 (0.60 to 1.00)
Haemorrhagic and haematological disorders of fetus and newborn	186 (3.4)	24 450 (3.6)	0.93 (0.80 to 1.07)	0.89 (0.77 to 1.04)
Transitory endocrine and metabolic disorders specific to fetus and newborn	114 (2.1)	13 541 (2.0)	1.03 (0.86 to 1.24)	0.84 (0.70 to 1.02)
Digestive system disorders of fetus and newborn	3 (0.1)	505 (0.1)	0.73 (0.23 to 2.27)	0.87 (0.28 to 2.74)
Conditions involving integument and temperature regulation of fetus and newborn	27 (0.5)	1961 (0.3)	1.69 (1.15 to 2.47)	1.07 (0.71 to 1.63)
Other disorders originating in perinatal period	222 (4.0)	19 753 (2.9)	1.39 (1.22 to 1.59)	0.98 (0.86 to 1.13)
All	912 (16.6)	96 773 (14.4)	1.18 (1.10 to 1.27)	0.92 (0.86 to 1.00)

*Numbers are given by diagnosis. ICD-10 codes (P00-P99) for morbidity per organ system are shown in supplementary table B.

†Adjusted for country, year of birth, maternal age, maternal comorbidity, and smoking.

stillbirth,^{5 13 14} preterm birth,^{2 9-11 13 14 24} low Apgar score,^{10 11} neonatal morbidity,^{9 13 14} mortality,^{9 13} and congenital malformations.^{5 9 12-14}

Previous studies that assessed the outcome of congenital malformations have collectively been based on approximately 300 women exposed in the first trimester and reported a total of 30 exposed cases of malformations.^{5 9 12-14} The 1125 women exposed in the first trimester and included in our study thus add substantially to the body of knowledge on possible adverse effects of neuraminidase inhibitors during pregnancy.

We observed an inverse association between exposure to neuraminidase inhibitors and the risk of low birth weight or intrauterine growth restriction, measured as infants born small for gestational age. A similar finding was reported in a study from Canada, including 1200 exposed women.¹⁰ In the Canadian study, a significant association with small for gestational age birth at less than 10th centile was seen (adjusted odds ratio 0.77, 0.60 to 0.98). Other than being a true association or a finding by chance, the protective effect of neuraminidase inhibitors on fetal growth may imply a “healthy user effect.” Women who filled a prescription for a neuraminidase inhibitor may have been under closer observation by their attending physician than their comparisons, which, at least in theory, could reduce the risk of growth restriction in the neonate. Despite adjusting the analyses for potential confounders related to health condition, such as age, smoking, and co-medication, we cannot preclude residual confounding.

In addition, a fetus may be exposed to several viruses with an adverse effect on fetal growth, and one may therefore speculate as to whether the reduced risk of small for gestational age birth could be partly due to the neuraminidase inhibitors affecting fetal growth in a positive direction through a general antiviral effect.²⁵ Although oseltamivir (which constituted most of the exposure in the study) is converted to its active

metabolite oseltamivir carboxylate, which may be transferred across the placenta, we find this explanation to be less likely.²⁶⁻²⁹

Strengths and limitations of study

Our study was population based and included data from four countries, which suggests good external validity of the results. The Scandinavian population based registers and the EFEMERIS database have previously provided robust data on exposure and outcomes.^{30 31} The large study cohort with almost 6000 exposed women and their infants ensured sufficient statistical power to detect moderately increased risks of low birth weight, low Apgar score, preterm birth, growth restriction, and congenital malformations and to detect large increased risks of rare events such as stillbirth and neonatal mortality. However, with only 1125 women exposed in the first trimester, the study was not sufficiently powered to study specific congenital malformations. The information on exposure was collected prospectively, minimising the risk of recall bias. In contrast to several of the previous studies, we focused on the time period of the most recent influenza pandemic and included women and their infants born in 2008-10. Accordingly, we could ensure a high number of exposed infants in our study cohort, corresponding to almost 1% of the study population. An extended study period would have increased the number of exposed women only marginally, as use of neuraminidase inhibitors declined rapidly at the end of 2010.^{7 8}

We estimated exposure from the day when a prescription for a neuraminidase inhibitor was filled. The possibility exists that some of the women included in the study filled their prescription but did not take the drug or started taking it later than the date it was dispensed. This may lead to a possible bias by misclassification of exposure and a potential underestimation of the risks.

We did not have information on vaccination against H1N1 influenza among the women included in the study. All of the Scandinavian countries and France recommended vaccination for high risk groups, including pregnant women, during the pandemic. The vaccinations were free of charge and made accessible for all pregnant women, and the vaccination rate has been estimated to more than 50% among women in Sweden and Norway, although much lower in Denmark and France.^{4 32-34} Influenza infection is associated with fetal death, and immunisation during pregnancy may have reduced the risk of influenza related fetal death during the pandemic.^{4 35} Accordingly, our results of no association between exposure to neuraminidase inhibitors and fetal death may have been confounded by the vaccination status of the pregnant women, as exposure to neuraminidase inhibitors, presumably, was more prevalent among the non-vaccinated women.

In the studied countries, maternal healthcare is free of charge and widely accepted by the general population. Almost all pregnant women follow the national programmes, and post-exposure prophylaxis with neuraminidase inhibitors was recommended during the influenza epidemic of 2009-10 and was distributed

Table 4 | Neuraminidase inhibitors during first trimester and congenital malformations in Scandinavian countries

Affected organ system*	No Exposed (n=1125)	Unexposed (n=672 784)	Total	Adjusted odds ratio (95% CI)†
Nervous system	0	387	387	-
Eye	0	282	282	-
Ear, face, and neck	1	530	531	-
Heart	9	5360	5369	0.96 (0.48 to 1.93)
Respiratory	0	520	520	-
Cleft palate	3	840	843	-
Digestive organs	12	3118	3130	1.21 (0.62 to 2.33)
Abdominal organs	0	175	175	-
Urinary tract	7	2172	2179	1.31 (0.58 to 2.94)
Limbs	11	6768	6779	0.93 (0.50 to 1.73)
Skeleton	0	101	101	-
Skin	2	480	482	-
Greater arteries	2	1466	1468	-

*Numbers are given by diagnosis. Three exposed infants had malformations in more than one organ system; corresponding number among unexposed infants was 2336.

†Adjusted for country, year of birth, maternal age, maternal comorbidity, and smoking. Adjusted odds ratios with 95% CI are given for outcomes with more than five exposed infants.

free of charge or reimbursed to all pregnant women in Scandinavia and in France. In Norway (in contrast to the other participating countries) post-exposure prophylaxis with neuraminidase inhibitors was allowed to be dispensed by pharmacists to pregnant women without a prescription by a doctor. The dispensed drugs were, however, reported routinely to the Norwegian Prescription Database, and these women are included in our study. The internal validity of the study should be high, considering the absence of barriers to healthcare and access to post-exposure prophylaxis in the study population.

We excluded all women admitted to hospital because of influenza during pregnancy in the Scandinavian database. We did not have information on hospital admission during pregnancy for the French data. Hence, this much smaller cohort in the study may include sicker women than the larger Scandinavian cohort. However, the point estimates for the various outcomes were similar in both databases. The estimates in the meta-analysis show that the risk estimates changed only marginally when we combined the two sets of data. The rationale for the exclusion of women admitted to hospital in the Scandinavian data was to reduce confounding by indication, as we can assume that admitted women are sicker than women who receive outpatient care or post-exposure prophylaxis, as well as to safeguard the classification of exposure, as in-hospital drug use is not included in the prescribed drug registers at the individual level so there was no possibility to investigate whether admitted women had received neuraminidase inhibitors. In addition, we did not have information on the indication for the treatment—that is, whether it was prescribed as post-exposure prophylaxis or treatment for influenza. We assume that most the women were either taking the drug for a relatively non-severe illness or as post-exposure prophylaxis, as women admitted to hospital were excluded. As we excluded women admitted to hospital, our study population may have been healthier than those included in the previous studies.

This study was based on information from a Scandinavian database of almost 700 000 mother and infant pairs and the smaller French database EFEMERIS with almost 20 000 mother and infant pairs. In a previous study that was based on data from the national birth registers and the prescribed drug registers in the five Nordic countries—Scandinavia (Denmark, Norway, and Sweden), Finland, and Iceland—the results of analyses based on pooled data at the individual level were compared with those from an aggregate meta-analysis.³⁶ The authors concluded that, for multi-database studies, the results from the two approaches to analysis would be similar. However, when data are sparse the pooled data are superior to a meta-analysis. We used both approaches in this study, optimising the information by pooling individual data from the Scandinavian countries and, as individual data from the French database could not be provided to the study analyst, doing an aggregate meta-analysis based on the results of the logistic and Cox regression analyses in the two databases.

We found no association between exposure to neuraminidase inhibitors and congenital malformations, although we did not study malformations in pregnancies ending before gestational week 22. If neuraminidase inhibitors cause severe malformations leading to a miscarriage or termination of pregnancy, our results of no increased risks of malformations may have been biased. However, in the French study, which included pregnancies ending before 22 weeks, no cases of termination of pregnancy due to malformation occurred among those exposed to oseltamivir.¹⁴

Conclusion and clinical implications

In this large multinational register study, we found no increased risk of adverse neonatal outcomes or congenital malformations associated with exposure to neuraminidase inhibitors during pregnancy. Our results support previously reported findings that the use of neuraminidase inhibitors is not associated with increased risks of adverse fetal or neonatal outcomes.

Contributors: HK initiated the study and drafted the study aim. TS, ABB, and SG had full access to the data in the study. TS did the analyses in the Scandinavian database and the meta-analysis. ABB did the analyses in the EFEMERIS database. All of the authors contributed to the study design and interpretation of the results. SG and HK drafted the paper. All authors contributed to and approved the manuscript. SG is the guarantor.

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Transparency statement: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

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Supplementary tables and figures

Neuropsychiatric Adverse Events and Oseltamivir for Prophylaxis

We would like to query the numbers of neuropsychiatric adverse events (NPAE) reported by Toovey et al.^[1] who state “in randomized controlled studies, significantly fewer oseltamivir patients (12/1662; 0.7%) reported NPAEs than placebo recipients (20/1128; 1.8%; $p < 0.05$)” referenced to “Data on file, Roche, 2008”.

The text is vague, but the data appear to be from five prophylaxis randomized controlled trials conducted more than 10 years ago as the total number of patients match those reported by Toovey et al.^[1] Three trials were conducted in adults: two in the US (WV15673 and WV15697)^[2] and one in Japan (JV15824).^[3] Two trials were conducted in the elderly: WV15708, in the Southern Hemisphere; and WV15825, in the US and Europe.^[4]

Prophylaxis trials can be particularly useful for determining causality because, unlike treatment trials, adverse events cannot be attributed to the disease (influenza). In Roche oseltamivir treatment trials, events attributed to the disease were not collected as adverse events unless they met the definition of a serious adverse event.

A small proportion of the data from the above prophylaxis studies can be accessed via journal publications^[2–4] and one study appears to be unpublished (WV15708). However, the publications are all brief (7–15 pages) and report little information on adverse events and no information on psychiatric adverse events. This should be compared with the company clinical study reports (CSRs) for the same studies, which are hundreds to thousands of pages in length and were submitted to regulators as part of Roche’s marketing application.^[5] Thus, the majority of clinical data from oseltamivir trials remain unpublished and invisible to researchers, allowing bias and distortion to creep into any research synthesis based on journal publications.

Although Roche failed to honour its promise of providing independent investigators with ‘full study reports’, we requested and received, through a freedom of information request to the European Medicines Agency undertaken in relation to our Cochrane review,^[6] 2359 pages of Roche’s ‘data on file’, including the first two modules of the CSRs for four prophylaxis studies and a synopsis of the fifth (JV15824).^[5] The definition of NPAE is not provided in detail by Toovey et al.,^[1] nor in the CSR protocols. However, the three broad classes of adverse events included in the Toovey et al.^[1] definition are *nervous system disorders*, *psychiatric disorders* and *accidents/injuries*. The reporting of adverse events in the CSRs appears to have been based on a different system of classification where *nervous system disorders* were termed *neurological* and *accidents/injuries* were termed *injury and poisoning*. Table I shows the total numbers of patients with adverse events in the three broad classes by treatment group.

Given that the term neuropsychiatric implies a mental disorder attributable to the nervous system, psychiatric adverse events appear to be the most relevant. However it is possible that particular events classified as neurological or injury could be regarded as neuropsychiatric providing they were likely to have been the result of a nervous system-attributable mental disorder. Overall, the psychiatric (and neurological) adverse event data (table I) show a trend of higher proportion of events in the oseltamivir arm compared with the placebo arm that is consistent with the results of three prospective observational studies of NPAE events in Japanese children.^[7–9] A meta-analysis of these three studies show pooled odds ratio for abnormal behaviours due to oseltamivir exposure

Table I. Number of patients with adverse events reported in clinical study reports of five prophylaxis randomized controlled trials

Adverse event category	Oseltamivir (N = 1662) [n (%)]	Placebo (N = 1128) [n (%)]
Psychiatric	31 (1.9)	13 ^a (1.1)
Neurological	590 (35)	285 (25)
Injury and poisoning	49 (2.9)	32 (2.8)

a This number includes one patient who had concussion but was incorrectly classified as having confusion.

of 1.55 (95% CI 1.21, 1.98; $p=0.0005$) without significant heterogeneity.^[10]

Since NPAEs were not a defined category in the trial protocols, analysing NPAEs requires constructing *post hoc* definitions of which adverse events count as NPAEs (and which do not). This allows the possibility of choosing and selectively reporting adverse events based on the observed data (sometimes referred to as ‘cherry picking’). In addition, the lumping together of adverse events from a number of heterogeneous categories risks swamping any potential signals of importance from being discovered. We request that Toovey et al.^[1] provide further details on what events from the randomized controlled prophylaxis studies were included in their comparison of NPAE, including the list of 98 preferred terms they mention at the end of page 1100. In addition, and perhaps more importantly, they should clearly state which psychiatric adverse events were not included in their comparison.

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Research and Quality, number T32HS019488. He received €1500 from the European Respiratory Society in support of his travel to the 2012 European Respiratory Society annual congress where he gave an invited talk on oseltamivir.

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The Authors’ Reply

We thank Dr Jones and colleagues^[1] for their comments on our review,^[2] and welcome the opportunity to address the points they raise in their correspondence. The reviewers pinpoint a major difficulty in addressing the issue of neuropsychiatric adverse events (NPAEs) when they state that

Assessment of Neuropsychiatric Adverse Events in Influenza Patients Treated with Oseltamivir

A Comprehensive Review

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Abstract

After reports from Japan of neuropsychiatric adverse events (NPAEs) in children taking oseltamivir phosphate (hereafter referred to as oseltamivir [Tamiflu®; F. Hoffmann-La Roche Ltd, Basel, Switzerland]) during and after the 2004–5 influenza season, Roche explored possible reasons for the increase in reporting rate and presented regular updates to the US FDA and other regulatory authorities. This review summarizes the results of a comprehensive assessment of the company's own preclinical and clinical studies, post-marketing spontaneous adverse event reporting, epidemiological investigations utilizing health claims and medical records databases and an extensive review of the literature, with the aim of answering the following questions: (i) what the types and rates of neuropsychiatric abnormalities reported in patients with influenza are, and whether these differ in patients who have received oseltamivir compared with those who have not; (ii) what levels of oseltamivir and its active metabolite, oseltamivir carboxylate are achieved in the CNS; (iii) whether oseltamivir and oseltamivir carboxylate have pharmacological activity in the CNS; and (iv) whether there are genetic differences between Japanese and Caucasian patients that result in different levels of oseltamivir and/or oseltamivir carboxylate in the CNS, differences in their metabolism or differences in their pharmacological activity in the CNS.

In total, 3051 spontaneous reports of NPAEs were received by Roche, involving 2466 patients who received oseltamivir between 1999 and 15 September 2007; 2772 (90.9%) events originated from Japan, 190 (6.2%) from the US and 89 (2.9%) from other countries. During this period, oseltamivir was prescribed to around 48 million people worldwide. Crude NPAE reporting rates (per 1 000 000 prescriptions) in children (aged ≤16 years) and adults, respectively, were 99 and 28 events in Japan and 19 and 8 in the US. NPAEs were more commonly reported in children (2218 events in 1808 children aged ≤16 years vs 833 in 658 adults) and generally occurred within 48 hours of the onset of influenza illness and initiation of treatment. After categorizing the reported events according to *International Classification of Diseases* (9th edition) codes, abnormal behaviour (1160 events, 38.0%) and delusions/perceptual disturbances (661 events, 21.7%) were the largest categories of events, and delirium or delirium-like events (as defined by the American Psychiatric Association) were very common in most categories.

No difference in NPAE reporting rates between oseltamivir and placebo was found in phase III treatment studies (0.5% vs 0.6%). Analyses of US healthcare claims databases showed the risk of NPAEs in oseltamivir-treated patients (n = 159 386) was no higher than those not receiving antivirals (n = 159 386). Analysis of medical records in the UK General Practice Research Database showed that the adjusted relative risk of NPAEs in influenza patients was significantly higher (1.75-fold) than in the general population. Based on literature reports, NPAEs in Japanese and Taiwanese children with influenza have occurred before the initiation of oseltamivir treatment; events were also similar to those occurring after the initiation of oseltamivir therapy.

No clinically relevant differences in plasma pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate were noted between Japanese and Caucasian adults or children. Penetration into the CNS of both oseltamivir and oseltamivir carboxylate was low in Japanese and Caucasian adults (cerebrospinal fluid/plasma maximum concentration and area under the plasma concentra-

tion-time curve ratios of approximately 0.03), and the capacity for converting oseltamivir to oseltamivir carboxylate in rat and human brains was low. In animal autoradiography and pharmacokinetic studies, brain : plasma radioactivity ratios were generally 20% or lower. Animal studies showed no specific CNS/behavioural effects after administration of doses corresponding to ≥ 100 times the clinical dose. Oseltamivir or oseltamivir carboxylate did not interact with human neuraminidases or with 155 known molecular targets in radioligand binding and functional assays. A review of the information published to date on functional variations of genes relevant to oseltamivir pharmacokinetics and pharmacodynamics and simulated gene knock-out scenarios did not identify any plausible genetic explanations for the observed NPAEs.

The available data do not suggest that the incidence of NPAEs in influenza patients receiving oseltamivir is higher than in those who do not, and no mechanism by which oseltamivir or oseltamivir carboxylate could cause or worsen such events could be identified.

Reports from Japan on the safety of oseltamivir phosphate (hereafter referred to as oseltamivir [Tamiflu®; F. Hoffmann-La Roche Ltd, Basel, Switzerland])¹ in children during the 2004–5 influenza season showed that some children had experienced neuropsychiatric adverse events (NPAEs). In the following seasons, ongoing pharmacovigilance by Roche found that the number of NPAEs in Japan had increased. In November 2006, the US FDA provided an update to its Pediatric Advisory Committee, notifying it of 129 NPAEs reported in association with oseltamivir use in children and adults worldwide between 29 August 2005 and 6 July 2006, including three deaths, compared with 126 events in total in the 6 years between approval in October 1999 and 29 August 2005.^[1] Most of the events were in Japan. At the time, the FDA concluded that the relative contribution of oseltamivir to these events was unknown, and indicated this in an update to the product label.^[2]

In assessing these events, Roche explored possible reasons for the increase in the reporting rate and has presented regular updates and analyses to the FDA and other regulatory authorities, most recently a full update to the Pediatric Advisory Committee in November 2007.^[3] Over the influenza seasons in Japan from 2004–5 to 2006–7, disease incidence did

not increase, the characteristics of the circulating virus did not change and no changes took place in drug manufacturing, formulation, dosage or administration of oseltamivir. Notably, the number of prescriptions issued to Japanese children aged ≤ 16 years fell by 33% over the period in question (table I). In 2006, the Japanese Ministry of Health, Labour and Welfare (MHLW) reported survey data showing that the frequency of NPAEs in Japanese influenza patients receiving oseltamivir during the 2005–6 influenza season was the same as in those not receiving the product.^[4] In March 2007, however, the Japanese MHLW warned doctors against prescribing oseltamivir to those aged 10–19 years, after two reports of abnormal behaviour in young patients who had taken the drug resulted in injury and death. Changes were made to the product labelling in Japan to alert prescribers to these events.

Of the 80 countries in which oseltamivir is approved, Japan is the country with the highest usage (see table I), possibly because, unlike most other countries, rapid diagnostic testing for influenza at the point of care is standard medical practice. Rapid test kits are fully reimbursed in Japan, as is antiviral treatment. Antivirals were prescribed to an estimated 60% of clinically diagnosed Japanese influenza patients in 2004–5, compared with about 30% in the

1 The use of trade names is for product identification purposes only.

Table I. Seasonal usage of oseltamivir worldwide (millions of prescriptions)

Influenza season	All patients				Patients aged ≤16 y			
	Japan	USA	RoW	total	Japan	USA	RoW	total
1999–2000	0.00	0.70	0.00	0.70	0.00	0.01	0.00	0.01
2000–1	0.00	0.74	0.00	0.74	0.00	0.11	0.00	0.11
2001–2	2.11	0.66	0.00	2.77	0.62	0.06	0.00	0.68
2002–3	7.21	0.59	0.20	8.00	4.49	0.14	0.03	4.66
2003–4	5.76	1.54	0.16	7.45	2.62	0.35	0.03	2.99
2004–5	9.03	1.72	0.41	11.16	3.81	0.45	0.06	4.32
2005–6	7.18	2.40	0.29	9.87	3.52	0.79	0.03	4.34
2006–7	5.11	1.96	0.24	7.31	2.53	0.95	0.07	3.56
Total	36.40	10.30	1.30	48.00	17.58	2.85	0.22	20.66
% by region	75.8	21.5	2.7	100.0	85.1	13.8	1.1	100.0

RoW = rest of world.

US and ≤1% in France and the UK.^[5] Since the first launch of oseltamivir, 76% of all prescriptions dispensed worldwide were in Japan (see table I), and in patients aged ≤16 years, 85% of cumulative usage was in Japan.

The steps taken by Roche to gain a better understanding of influenza-associated NPAEs and possible mechanisms for them have included a review of the company's own preclinical and clinical studies, analysis of post-marketing spontaneous adverse event reporting, epidemiological investigations utilizing health claims and medical records databases and an extensive review of the literature. This review summarizes the results of this comprehensive assessment, whose aim was to answer the following questions:

1. What are the types and rates of neuropsychiatric abnormalities reported in patients with influenza, and do these differ in patients who have received oseltamivir compared with those who have not?
2. What levels of oseltamivir and its active metabolite, oseltamivir carboxylate are achieved in the CNS?
3. Do oseltamivir and oseltamivir carboxylate have pharmacological activity in the CNS?
4. Are there genetic differences between Japanese and Caucasian patients that result in different levels of oseltamivir and/or oseltamivir carboxylate in the CNS, differences in their metabolism or differences in their pharmacological activity in the CNS?

1. Clinical Safety Assessment

1.1 Post-Marketing Reports of Neuropsychiatric Adverse Events (NPAEs) in the Roche Global Safety Database

Between 1999 and 15 September 2007, oseltamivir was prescribed to around 48 million people worldwide (table I). To estimate the reporting rate of NPAEs in patients given oseltamivir (for treatment or prophylaxis) in Japan, the US and other countries, an analysis was conducted of post-marketing spontaneously reported adverse events (AEs) in the Roche global safety database. All serious AEs (SAEs) from clinical trials, irrespective of the reporter's causality assessment, and all spontaneous reports of AEs from countries where oseltamivir is marketed are coded into the database. This includes all events reported to Chugai Pharmaceuticals, Roche's marketing partner in Japan. Expedited and cumulative single-case reporting to health authorities is then undertaken.

A broad case definition of NPAEs was prospectively defined, encompassing 51 *Medical Dictionary for Regulatory Activities* (MedDRA) high-level terms in three system organ classes (SOCs) [nervous system disorders, psychiatric disorders and accidents/injuries]. A search for these high-level terms from the date of the launch of oseltamivir in each country to 15 September 2007 resulted in the identification of 98 associated preferred terms (MedDRA terminology), each of which were grouped into one

Table II. Summary of post-marketing neuropsychiatric events in children (aged ≤16 y) and adults receiving oseltamivir for influenza treatment or prophylaxis^a

Category	All adverse events			Serious adverse events		
	all	>16 y	≤16 y	all	>16 y	≤16 y
Abnormal behaviour	1160	123	1037	179	28	151
Accident/injury	33	20	13	23	11	12
Cognition disturbance	113	68	45	32	23	9
Convulsions	138	53	85	126	48	78
Delirium	176	35	141	62	18	44
Delusions/perceptual disturbance	661	212	449	111	44	67
Depressed level of consciousness	183	72	111	69	29	40
Encephalitis	11	6	5	11	6	5
Loss of consciousness	108	82	26	48	36	12
Miscellaneous psychiatric	368	117	251	47	18	29
Panic attack	12	6	6	5	3	2
Parasomnia	72	25	47	5	1	4
Suicidal events	16	14	2	14	12	2
Total no. of events	3051	833	2218	732	277	455
Total no. of patients	2466	658	1808	562	212	350

a Medical Dictionary for Regulatory Activities terms and associated preferred terms in three classes (nervous system disorders, psychiatric disorders and accidents/injuries) grouped into 13 categories. Includes all reports made to the Roche global database, including Chugai Pharmaceuticals, Roche's marketing partner in Japan.

of 13 clinically meaningful categories according to *International Classification of Diseases* (ICD) [9th edition] descriptions (see table II for full information). Detailed case review was done for all serious NPAEs.

A total of 3051 NPAEs were spontaneously reported in 2466 patients, of which 2218 (72.7%) were in children ≤16 years (table II). The great majority of NPAEs were in Japanese patients (90.9%), with 6.2% in the US and 2.9% from other countries. In the context of the number of oseltamivir prescriptions dispensed (see table I), NPAEs are generally rare events and are reported more often in Japan than in the US (table III); the numbers in this analysis translated to crude reporting rates (in events per 1 000 000 patients) of 99 in Japan and 19 in the US

in children aged ≤16 years, and 28 events in Japan and 8 in the US in adults.

More male patients (1745) reported events than female patients (1144). Most events (2368 [77.6%]) occurred within the first 2 days of oseltamivir treatment. Most NPAEs (84.9%) improved or resolved; 732 events were classified as SAEs, and although these were most common in Japan (613/2772; 22%), they were relatively more frequent in the US (76/190; 40%). Nineteen NPAEs were associated with fatal outcomes.

The two most common categories for NPAEs were abnormal behaviour (1160) and delusions and perceptual disturbances (661). Although delirium as a category accounted for 176 events, delirium and delirium-like events were associated with many events in other categories; the majority of single or combined events found were consistent with delirium as defined by the American Psychiatric Association (*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition [DSM-IV]). Whereas infection and fever are known to be common causes of delirium in children, particularly those aged 6–12 years, febrile delirium is most common in those aged 1–4 years.^[6]

Table III. Crude reporting rate of post-marketing neuropsychiatric events (events per million oseltamivir prescriptions)^a

Country	Children (aged ≤16 y)	Adults (aged >16 y)
USA	19	8
Japan	99	28
Rest of world	36	56

a Reports made to the Roche global database, including Chugai Pharmaceuticals, Roche's marketing partner in Japan.

1.1.1 Delirium and Delirium-Like Symptoms

Delirium or delirium-like symptoms were associated with NPAEs in 8 of the 13 categories (see table IV and table V for full information), based on DSM-IV definitions; these events and their association with fever, increased motor activity and injury were analysed separately. In all, 2726 such events were found: 2083 in children (94% of all reported NPAEs in children) and 643 in adults (77% of all reported NPAEs in adults). In children, 345 (17%) occurrences of this type of event were classified as SAEs (table IV), the majority (67%) of which started within the first 2 days of the illness; 44% were reported to be associated with fever, although in the vast majority of the remaining cases body temperature was not reported. Increased motor activity was reported in 114 (34%) of the SAEs, most commonly in the categories of abnormal behaviour, delusions and perceptual disturbances and delirium; 26 of the SAEs (8%) were associated with injuries.

In adults, 161 (25%) delirium and delirium-like events were SAEs (table V). Increased motor activity and injuries were reported in association with 28 (17%) and 8 (5%) SAEs, respectively. As the analysis is based on spontaneously reported events for which information is frequently incomplete, information on associated fever was limited. Early onset of delirium and delirium-like SAEs was seen in many adult cases (46% within 2 days of influenza diagnosis and 11.2% within 2 hours of starting oseltamivir treatment); although less prevalent than in children (67% of delirium and delirium-like SAEs within 2 days of influenza diagnosis and 29.8% within 2 hours of starting oseltamivir treatment), this finding suggests a temporal association with the early onset of influenza, which goes in parallel with the start of oseltamivir.

1.1.2 Accidents and Injuries

In all, 33 accidents and injuries were reported as AEs in influenza patients taking oseltamivir, the most frequent cause of which was falls (16 events). Of the 33 events, 23 (70%) were classified as SAEs, 12 of which were falls (see also section 1.1.3). The NPAE most frequently associated with these SAEs was abnormal behaviour; other associated NPAEs

Table IV. Analysis of delirium and delirium-like events in influenza patients aged ≤16 y who received oseltamivir^a

Category	No. of events ^b	No. of patients with SAEs	No. of SAEs/no. of patients with SAEs	No. of patients (%) with SAEs occurring within 2 d of diagnosis	Fever at SAE onset	Increased motor activity associated with SAEs	Injury associated with SAEs	Abnormal motor activity associated with SAEs but restrained by others, e.g. parents
Delirium	140	43/43		29 (67)	15	16	2	3
Delusions and perceptual disturbances	449	67/60		38 (63)	29	17	1	3
Cognition disturbances	45	9/7		4 (57)	1	1	0	1
Parosomnia	47	4/3		2 (66)	0	0	0	0
Abnormal behaviour	1036	151/150		104 (69)	77	62	18	29
Depressed level of consciousness	111	40/40		28 (70)	14	10	4	3
Panic attacks	6	2/2		1 (50)	0	1	0	0
Miscellaneous psychiatric	249	29/27		18 (67)	9	7	1	2
Total	2083	345/332		224 (67)	145	114	26	41

a Reports made to the Roche global database, including Chugai Pharmaceuticals, Roche's marketing partner in Japan.

b Serious and non-serious.

SAE = serious adverse event.

Table V. Analysis of delirium and delirium-like events in adult influenza patients who received oseltamivir

Category	No. of events ^a	No. of SAEs/no. of patients with SAEs/no. of patients with SAEs aged ≥65 y	No. of patients (%) with SAEs occurring within 2 d of diagnosis	Fever at SAE onset	Increased motor activity associated with SAEs	Injury associated with SAEs	Abnormal motor activity associated with SAEs but restrained by others, e.g. carers
Delirium	35	18/18/10	7 (39)	1	5	0	0
Delusions and perceptual disturbances	208	43/35/17	13 (48)	2	2	1	0
Cognition disturbances	66	23/23/10	1 (4)	0	1	0	0
Parosmia	23	1/1/0	1 (100)	0	0	0	0
Abnormal behaviour	120	27/27/4	22 (81)	6	12	5	5
Depressed level of consciousness	72	29/29/6	16 (55)	5	1	2	0
Panic attacks	6	3/3/0	1 (33)	1	1	0	0
Miscellaneous psychiatric	113	17/16/3	9 (56)	1	6	0	1
Total	643	161/152/50	70 (46)	16	28	8	6

^a Serious and non-serious.
SAE = serious adverse event.

were depressed level of consciousness, delusions and perceptual disturbance and hallucinations. The majority of serious accidents and injuries occurred during the first 2 days of illness, many of which were associated with fever.

1.1.3 Suicidal Events

As described earlier, warnings issued by the Japanese MHLW about oseltamivir use in children were prompted by two deaths in 14-year-old children in February 2007, and speculation in the lay press that these were suicides. In fact, of 16 suicidal events reported to be associated with oseltamivir use, only three completed suicides were reported, all in adult men (Japan, 2; Singapore, 1) and all with significant confounding factors. Four deaths in Japanese children, including the two in 14-year-old children mentioned, were related to falls, with no suggestion of suicidal intent, and so categorized under accidents and injuries. The fact that three of the children fell from higher floors of multi-storey buildings probably led to them being reported as suicides. Abnormal behaviour and depressed consciousness (one each) were reported in association with two of these cases; detailed information on the other two cases is not available.

Given that cumulatively, 36.4 million oseltamivir prescriptions have been dispensed in Japan, corresponding to nearly 500 000 patient-years of exposure, and that annual suicide rates in the general population in Japan (per 100 000 people) in 2004 were 35.6 in males and 12.8 in females,^[7] three cases of completed suicide is lower than the expected figure.

1.1.4 NPAEs in Patients Receiving Oseltamivir Prophylaxis

NPAEs were reported in 19 patients who were taking oseltamivir for influenza prophylaxis. Single-case review revealed that 16 of the 19 cases were highly confounded by: underlying medical conditions (6 cases); concomitant medication (2 cases); temporal coincidence of treatment initiation with neuropsychiatric symptoms (2 cases); disqualification as prophylaxis cases with evidence of influenza (1 case) or influenza-like illness (3 cases); for 2

cases there was insufficient information to make a determination.

2. NPAEs in Prospective Clinical Trials of Oseltamivir

To supplement data from post-marketing surveillance, data from prospective phase III clinical studies in the Roche database were analysed, using the same event terms and categories. In all, data from 8000 patients of all ages receiving oseltamivir were analysed, 5384 as treatment and 2616 as prophylaxis. Of these, 3535 and 1662, respectively, took part in randomized, blinded studies.^[5]

‘On-treatment’ neuropsychiatric events (onset during drug administration or within 2 days of the last dose) were recorded in 26 of 5384 (0.5%) patients of all ages receiving oseltamivir as treatment; these were mainly “miscellaneous psychiatric” and loss of consciousness. In randomized, controlled treatment studies,^[5] the reporting rate was very similar to placebo (0.5% and 0.6%, respectively). In 1080 children aged ≤ 16 years receiving oseltamivir as treatment, only three NPAEs were recorded (irritability^[2] and anxiety), the same rate (0.3%) as in 738 placebo recipients.^[5]

Reporting rates in the prophylaxis studies were also low (13 patients, 0.5%); in randomized controlled studies, significantly fewer oseltamivir patients (12/1662; 0.7%) reported NPAEs than placebo recipients (20/1128; 1.8%; $p < 0.05$).^[5]

2.1 Supratherapeutic Doses

No NPAEs were reported in volunteers who received single oseltamivir doses of up to 1000 mg ($n = 6$), which is more than ten times the normal therapeutic dose of 75 mg twice daily, or twice-daily doses of 500 mg ($n = 8$) for 7 days.^[5] In an ECG study of the effects of oseltamivir, 97 and 99 volunteers, respectively, received doses of 225 and 450 mg twice daily for 5 days. One volunteer at each dose level reported anxiety during the first 2 days of dose administration, which resolved within 1 day.^[5]

3. NPAEs in Retrospective Observational Studies

Three retrospective observational studies were recently conducted to investigate the safety and effectiveness of oseltamivir. These utilized health claims data from recognized US databases, UnitedHealthCare (known as the Ingenix Research Data Mart [RDM]) and Thomson Healthcare MarketScan® Commercial Claims and Encounters Database and Medicare Supplemental and Coordination of Benefits Database (known as MedStat).

In the first study, patients in the Ingenix RDM aged >1 year and with a diagnosis of influenza in an outpatient setting between 1 November 1999 and 30 April 2005 were divided into two cohorts: patients dispensed oseltamivir in the 30 days after the diagnosis (60 834) and patients who had no antiviral dispensed (183 786). Propensity-score matching was used to achieve close similarity of the two cohorts.^[8] NPAEs were analysed in three hierarchical categories: all events, major NPAEs (excluding chronic disorders, conditions with stated aetiology, congenital or hereditary disorders and spinal cord disorders) and NPAEs specific to CNS stimulation. The NPAE reporting rate in the 30-day post-diagnosis period related to a medical or similar claim was 3.84% (oseltamivir) and 4.26% (no antiviral), and for major NPAEs, 3.35% and 3.70%, respectively. The reporting rate for CNS stimulation events in the two cohorts was also very similar (both combined and individually). Exposure-adjusted odds ratios (ORs) for NPAE risk in the oseltamivir cohort relative to the no-antiviral cohorts were: 0.89 (95% CI 0.85, 0.94) for all NPAEs, 0.89 (95% CI 0.85, 0.94) for major NPAEs and 0.88 (95% CI 0.83, 0.94) for CNS stimulation events. The use of oseltamivir did not appear to be associated with a higher risk of NPAEs in any of the categories studied.

In the second study, using the MedStat combined databases, patient selection (during influenza seasons 2000–6) was done in a similar way to the Ingenix RDM study, except that the oseltamivir and no-antiviral cohorts ($n = 36\,751$ in each) were propensity matched separately by payer type and influenza season.^[9] Oseltamivir users had a significantly

lower risk of a NPAE or CNS event both in the 14- and 30-day periods after diagnosis (OR of 0.76 [95% CI 0.68, 0.84] and 0.80 [0.74, 0.87], respectively).

Roche performed a third study to re-analyse data from both Ingenix RDM and MedStat databases, but grouped NPAEs into the same categories used to analyse the post-marketing surveillance data (except accident and injury), allowing results to be compared more directly.^[5] Like the other two studies, the study population was individuals diagnosed with influenza in an outpatient setting, but the period studied was from October 2001 to September 2006, and the outcome was claims for NPAEs occurring in the 14 days after diagnosis; in addition, a more detailed propensity-score matching method was used (using 25 strata instead of five). This resulted in 83 307 cases in each cohort from the Ingenix RDM database and 76 079 cases in each from the MedStat databases.

In both databases, logistic regression analysis of all NPAEs showed a significantly lower risk of an event in the oseltamivir cohort: the estimated ORs were 0.65 (95% CI 0.58, 0.72) and 0.74 (0.61, 0.90). Analysis by category showed that in most categories in each database, CIs were wide and the difference in risk was not statistically significant; in the other categories, the difference was significantly lower in the oseltamivir cohort. Separate analysis of the two databases for patients aged ≤ 16 years ($n \approx 26\,000$ – $31\,000$ per cohort) did not show any significant difference in NPAE risk between cohorts. In addition, the absolute reporting rate for all NPAEs in influenza patients of all ages receiving oseltamivir during the seasons in question was very low (Ingenix RDM, 542 events [0.65%]; MedStat, 173 events [0.23%]) and compared favourably with the rate in the no-antiviral cohort (Ingenix RDM, 835 events [1.00%]; MedStat, 233 events [0.31%]).^[5]

The findings of these three retrospective studies suggest that the risk of NPAEs in oseltamivir-treated patients is no greater than in patients not receiving antivirals.

4. Epidemiology Analysis in General Practice

To gain more insight into the incidence of NPAEs in influenza patients *per se*, an analysis of patients in the UK General Practice Research Database (GPRD) was performed. Using the Read^[10] classification of clinical terms and the corresponding MedDRA translation provided by the GPRD, grouping NPAEs as was performed as described in section 1.1, but using 10 rather than 13 categories. For 68 771 patients with a diagnosis of influenza or influenza-like illness between 1 October 2001 and 31 March 2006, the rate of events in the 30 days after diagnosis was compared with the rate in the general database population of 3 012 203 patients. Overall, there was a 75% increased risk for NPAEs in the influenza patients compared with the general GPRD population (relative risk: 1.75 [95% CI 1.54, 1.98]). For individual categories, there was a statistically significant increased risk for delusions, panic attack, depressed level of consciousness, loss of consciousness and cognition disturbances in the influenza patients compared with the general GPRD population. For these events, there was an approximately 1.8- to 2.5-fold increased risk in the influenza patients. Small numbers of children with influenza available in GPRD, coupled with the rarity of NPAEs, do not allow any meaningful comparisons of individual events between the two paediatric groups. However, overall, there was a suggestion of an increased risk in children with influenza. With a relative risk of 1.40 (95% CI 0.79, 2.49) in children, the results were not inconsistent with those for all ages where the estimated overall relative risk of NPAEs comparing influenza patients with the general population was 1.75 (95% CI 1.54, 1.98). As described previously, oseltamivir is used much less frequently in the UK than in Japan and the US. Only 56 of all influenza patients analysed received the drug (seven of those aged ≤ 16 years), none of whom experienced a NPAE.

5. Onset of NPAEs in Influenza Patients and Relationship with Oseltamivir or Other Antiviral Treatment

A literature search was performed to identify reports of NPAEs in patients with influenza and their relationship with oseltamivir or other antiviral treatment. MEDLINE and EMBASE databases were searched on 15 July 2007 for all publications up to this date in English containing the term 'influenza' (and similar constructions such as 'flu') and at least one of roughly 30 terms relating to CNS disorders and symptoms, such as 'encephalitis', 'loss of consciousness' or 'depressed level of consciousness', 'delirium', 'convulsion', 'hallucination' and 'abnormal behaviour'. This identified 338 publications, abstracts of which were screened by two experts to exclude those not relevant to oseltamivir and influenza-associated neurological disorder. The five publications remaining after screening are summarized below.

Two of the five reports were from Japan. In 6121 patients aged <15 years who had received oseltamivir for influenza between January 2004 and March 2006, delirious behaviour was noted in five children before oseltamivir treatment started and in four after treatment had begun.^[11] The delirious behaviour, which was observed ~1 day after the onset of fever, manifested as meaningless speech, disorientation, fearfulness and running around the room. No patient had neurological sequelae and the authors of the report concluded that oseltamivir was not responsible for the delirious behaviour. The same conclusion was reached by the authors of another report on 50 Japanese children aged from 5 months to 15 years old who were hospitalized with influenza during the 2005–6 season.^[12] Abnormal behaviour, manifesting as fright, hallucinations, excitation and unintelligible speech, was reported in 14 cases, 13 of whom had received oseltamivir (two also received zanamivir). The abnormal behaviour preceded initiation of antiviral therapy in six children, and no differences were seen between the behaviours occurring before and after initiation of antiviral therapy.

The remaining three reports were from the Chang Gung Children's Hospital in Taiwan. CNS dysfunction was reported in 26 of 84 children (aged ≤18 years) admitted to the hospital with influenza.^[13] The symptoms were more common in older children (aged ≥6 years), and included 18 with confusion, nine with visual hallucination and four with seizures. No information was presented on what antiviral therapy, if any, was given, but all but one of the 26 recovered fully by the time of discharge. In a second report, 11 of 92 children admitted to the hospital for influenza (aged 1–11 years) were found to have neurological symptoms that occurred mostly within 3 days of illness onset.^[14] Six children presented with either visual or olfactory hallucinations or personality changes such as an unwillingness to speak, and five had seizures. Antiviral therapy was given to only 5 of 92 hospitalized children (two received oseltamivir) but the specific therapy for the 11 with NPAEs is not reported. The third Taiwanese study reported five children with influenza aged 3–5 years who had visual hallucinations and abnormal behaviour such as restlessness and incoherent speech within 3 days of the onset of febrile illness.^[15] All had EEG abnormalities, but were discharged in a stable condition within 8 days. None of the children received any antiviral treatment.

Two additional sources of information on the occurrence of NPAEs in influenza patients receiving antivirals other than oseltamivir were identified. The first was the Japanese MHLW website (<http://www.mhlw.go.jp/>), on which emerging case reports of NPAEs in influenza patients with and without exposure to antivirals were posted. These reports were reviewed to identify patients treated with antivirals other than oseltamivir or no antiviral and then categorized using the same approach employed in the analysis of spontaneously reported NPAEs with oseltamivir. As of 16 June 2007, there were five case reports of NPAEs involving Japanese patients taking amantadine, 12 reports with zanamivir and 25 cases involving no antiviral therapy (table VI). The type and severity of NPAEs reported with non-oseltamivir antivirals or no antiviral were similar to those seen in the oseltamivir post-marketing

Table VI. Neuropsychiatric adverse events (NPAEs) reported to the Japanese Ministry of Health, Labour and Welfare involving influenza patients receiving amantadine, zanamivir or no antiviral (as of 16 June 2007)

NPAE event category	Amantadine (n = 5)	Zanamivir (n = 12)	No antiviral (n = 25)
Abnormal behaviour	1	10	16
Accidental injury	0	0	5
Cognition disturbance	4	1	0
Delirium	0	1	4
Delusions/perceptual disturbance	1	2	2
Decreased level of consciousness	1	0	1
Suicidal events	1	1	0
Miscellaneous psychiatric	3	2	1
Parasomnia	0	0	1
Death	1	0	1

surveillance cases, including delirium with a prominent behavioural abnormality, and death. More cases were reported in males than in females (2 : 1 ratio) and in children than adults.

The second information source was a presentation given to the FDA Pediatric Advisory Committee on 27 November 2007 on the CNS tolerability of zanamivir by representatives of GlaxoSmithKline (GSK), the manufacturer of zanamivir.^[3] This presentation included a review of information from the GSK global safety database identifying spontaneous and post-marketing surveillance reports involving influenza patients with NPAEs who were taking zanamivir during the 2006–7 influenza season. Unblinded SAEs from clinical trials were also included. The review identified 145 cases with one or more events within the ‘nervous system disorders’ or ‘psychiatric disorders’ MedDRA SOCs, all of which were spontaneous reports from Japan that occurred after January 2007. As with the MHLW reports, approximately double the number of cases involved males compared with females, and the vast majority (99%) involved children (aged 6–14 years). GSK also reviewed the database for cases before 30 September 2006, and identified 119 reports with one or more events within the MedDRA SOCs of interest. Although the ratio of male : females was similar to that seen in the 2006–7 reports, these earlier cases differed substantially in other respects. The majority came from the US (41%), and only 12% involved children and adolescents. In both the earlier and later case series, no causal association between the ob-

served NPAEs and zanamivir treatment could be demonstrated.

These findings indicate that NPAEs occurring in influenza patients are similar whether they are exposed to antivirals or not, and that they may occur before treatment initiation.

6. Pharmacokinetic Profile in CNS

6.1 Comparative Systemic Clinical Pharmacokinetics

Oseltamivir, the ingredient in pharmaceutical preparations of Tamiflu®, is an ethyl ester pro-drug that is delivered orally as a phosphate salt; it is hydrolysed in the body by human high-capacity carboxylesterases (HCEs) to the active metabolite oseltamivir carboxylate.^[16,17]

Dose-concentration relationships in healthy adult Japanese and Caucasian volunteers (n = 14 each) were compared in a randomized, placebo-controlled study in which oseltamivir (75 or 150 mg) was administered twice daily for 6 days, plus a single dose on day 7. Individual and mean pharmacokinetics (PK) and exposures to oseltamivir and oseltamivir carboxylate were similar in the two groups (figure 1), with no evidence of ethnic differences in the individual area under the plasma concentration-time curve (AUC)₁₂ values at steady-state.^[18] Although a prospective comparison has not been done in children, data from four separate studies have been pooled to compare oseltamivir with oseltamivir carboxylate plasma concentrations in 141

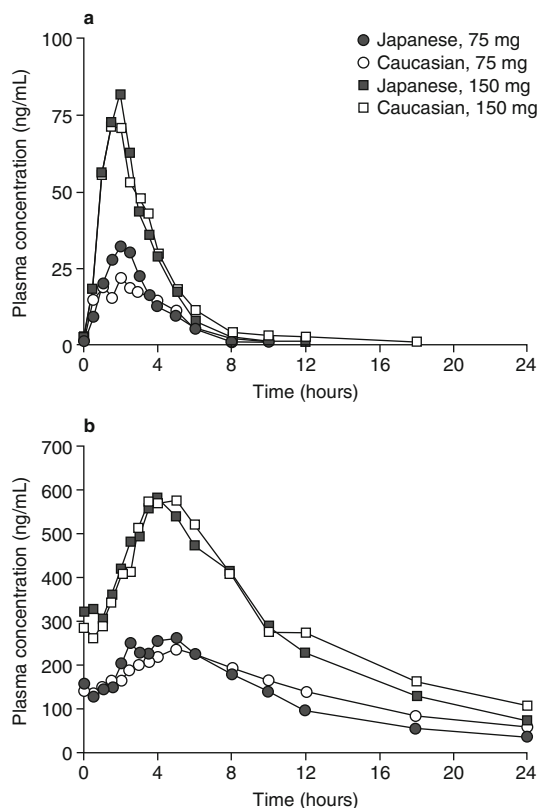


Fig. 1. Plasma concentration-time curves for (a) oseltamivir and (b) oseltamivir carboxylate in Caucasian and Japanese volunteers after doses of 75 and 150 mg twice daily (reprinted from Schentag et al.^[18] by permission of SAGE Publications, Inc.).

Caucasian and 18 Japanese children. After normalization to a 2-mg/kg dose, interquartile ranges for oseltamivir concentration were 3.63–26.75 ng/mL (Caucasian) and 3.95–22.05 ng/mL (Japanese); results for oseltamivir carboxylate were very similar.^[19] The sparse sampling data from this analysis are shown in figure 2.

The results of these studies do not suggest any clinically relevant difference between Japanese and Caucasians in the exposure to oseltamivir and oseltamivir carboxylate after standard doses of oseltamivir – indeed, the data in adult volunteers supports registration of the same oseltamivir dose in Japanese patients as in Caucasians. While no signal for defined PK subpopulations (including across ethnic groups) was observed in the clinical pro-

gramme, it is possible that differences in the systemic PK of oseltamivir and oseltamivir carboxylate between individuals could result at least in part from gene polymorphisms. This possibility is described in section 8 of this article.

6.2 Extent of Oseltamivir and Oseltamivir Carboxylate Penetration into the CNS

Data on CNS penetration in humans are very limited. A recent exploratory study in healthy volunteers (four each of Caucasian and Japanese origin) measured 24-hour cerebrospinal fluid (CSF) and plasma PK profiles of oseltamivir and oseltamivir carboxylate after a single 150-mg dose of oseltamivir. CSF penetration was very limited – mean CSF:plasma ratios in all patients were 2.11%

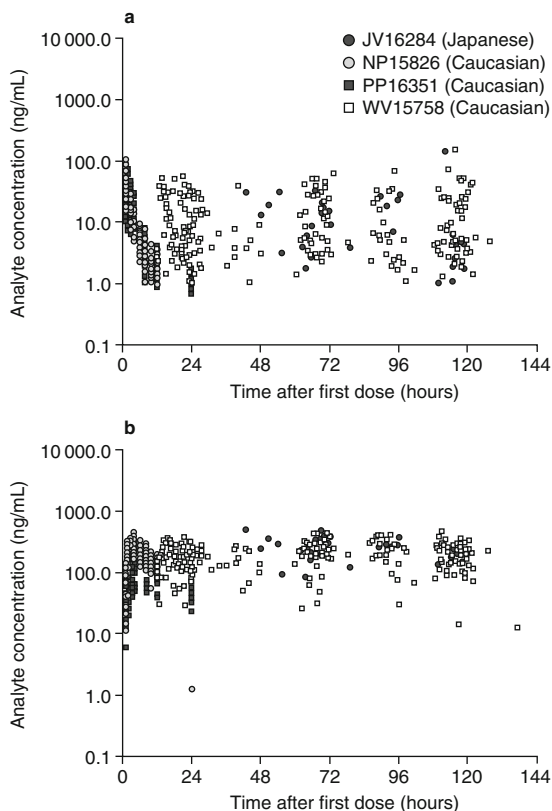


Fig. 2. Plasma concentrations of (a) oseltamivir and (b) oseltamivir carboxylate in Caucasian and Japanese children using sparse sampling of data pooled from four separate studies. Data are normalized to a dose of 2 mg/kg.^[19]

($\pm$ standard deviation [SD] 0.52%) for oseltamivir and 3.47% ($\pm$ 2.94%) for oseltamivir carboxylate (based on maximum concentration [$C_{\max}$] values); the respective ratios based on AUC_{last} were 2.35% ($\pm$ 1.09%) and 2.93% ($\pm$ 4.06%).^[20]

Quantitative whole-body autoradiography in ferrets and rats after oral doses of radiolabelled oseltamivir showed limited distribution of drug to the brain.^[5,16] More specifically, brain concentrations of drug-related radioactive material were generally lower than 20% of those in plasma. After oral treatment, brain : plasma AUC ratios in rats were approximately 0.15 for oseltamivir and 0.01 for oseltamivir carboxylate.^[5] These data are consistent with the low CNS exposure of oseltamivir and oseltamivir carboxylate described in humans.

6.3 Regulation of Oseltamivir Levels in the CNS

The low CNS exposure to oseltamivir and oseltamivir carboxylate can be understood by their physicochemical and PK properties. Because oseltamivir is more lipophilic than oseltamivir carboxylate, it is more likely to cross the blood-brain barrier (BBB) by passive transport, whereas oseltamivir carboxylate penetration into the CNS seems to be very limited.^[5]

Several systems are known to actively transport drugs out of the CNS, for example, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and human multi-drug resistance protein 2 (MRP2).^[21] Oseltamivir is a good substrate for the P-gp system, but not for BCRP and MRP2.^[5] Organic anion transporter 1 (OAT1), for which oseltamivir carboxylate is a weak substrate,^[5] and the homologous transporter OAT3^[22] are expressed in the BBB and could theoretically transport oseltamivir carboxylate out of the brain. However, no evidence for a relevant contribution of such active transport has yet been reported. As oseltamivir is a good substrate for P-gp, impairment or inhibition of this transport system is likely to increase the brain : plasma concentration ratio. The brain : plasma concentration ratio of oseltamivir in P-gp knock-out mice was recently reported to be five to six times that in wild-type mice,^[23]

but an increase of this magnitude is thought to be of limited clinical relevance.

Another possible source of increased oseltamivir carboxylate exposure in the brain is the intracranial cleavage of oseltamivir to oseltamivir carboxylate. In rat and human brains, only low levels of messenger RNA expression of the carboxylesterases HCE1, HCE2 and HCE3 were detected, suggesting that conversion of oseltamivir to oseltamivir carboxylate in the brain is unlikely to be significant.^[5] In addition, the capacity to convert oseltamivir to oseltamivir carboxylate was shown to be very low in studies on rat and human brain homogenates (S9 fractions).^[5]

Generally, the mechanisms regulating the distribution of oseltamivir and oseltamivir carboxylate in the CNS seem to be complex, but clinical and non-clinical data suggest a limited CNS exposure for both compounds.

7. Pharmacodynamic Profile in CNS

7.1 Safety Pharmacology

An extensive safety pharmacology programme was performed in adult mice and rats to establish the CNS safety profile of oseltamivir. Single oral doses as high as 1000 mg/kg were administered to normal healthy mice and rats. In an Irwin test,^[24] a systematic observational method was used to evaluate whether oseltamivir has overt effects on general behaviour and physiology. There were no behavioural or physiological changes on any of the 42 parameters tested.^[5] This was also confirmed in a quantitative assessment addressing spontaneous locomotor activity. Oseltamivir did not exert significant effects on locomotion in mice, whereas diazepam, which was used as a positive control substance, produced its well characterized decrease in locomotor activity.

In a specially designed, safety pharmacology investigation in 7-day-old juvenile rats,^[5] the effects of oseltamivir on behaviour were assessed. In this study, there were either no effects on behaviour or effects at very high plasma exposure levels considered related to non-specific general toxicity. Brain

levels of oseltamivir as compared with plasma were only 2- to 3-fold higher in 7-day-old rats compared with adult rats, and consistent with recalculated values from a previous study in juvenile rats,^[5] and with a published study in juvenile mice.^[22] In all cases, the brain levels were well below those in plasma.

Further studies in adult mice and rats investigated pro- and anti-convulsant activity, effects on hexobarbital-induced sleeping time and effects on nociception, respiration and body temperature. No modulation of any of these parameters was observed, whatever the dose level tested. In these safety pharmacology studies, the highest oral dose of oseltamivir tested, 763 mg/kg, produced mean $C_{\max}$ values for oseltamivir and oseltamivir carboxylate at least 100 times higher than the effective clinical dose^[5] without producing significant behavioural effects in rodents.

7.2 Neuraminidase Inhibition

As human and influenza virus neuraminidases show significant differences, including binding specificity,^[25,26] the probability of oseltamivir carboxylate binding to the human enzyme is low. Although oseltamivir carboxylate is a highly potent inhibitor of viral neuraminidases, with K_i values in the low nanomolar range (0.2–1.7 nM),^[27] no inhibitory activity was observed in mammalian neuraminidases (human liver, mouse liver and mouse uterus) at concentrations up to 1 mM, over 500 times the mean $C_{\max}$ of oseltamivir carboxylate at steady state from a 75-mg twice-daily dose.^[5] As at least two human neuraminidases (NEU1 and NEU4) are expressed in both liver and brain,^[28,29] it seems unlikely that oseltamivir carboxylate would inhibit brain-derived neuraminidases at therapeutic concentrations. In order to fully exclude inhibition of human host neuraminidases by oseltamivir or oseltamivir carboxylate, all four human neuraminidases expressed in recombinant systems, as well as neuraminidase activity in extracts of non-human primate (*Macaca fascicularis*) and rat brains,

were tested for an inhibitory activity of oseltamivir and oseltamivir carboxylate. At concentrations of up to 1 mM, representing concentrations of >100 000- (oseltamivir) and >10 000-fold (oseltamivir carboxylate) the extrapolated CNS concentrations achieved with standard oseltamivir dosing, neither oseltamivir nor oseltamivir carboxylate produced a significant inhibition of human recombinant or tissue-derived neuraminidases;^[5] a recent study by Hata et al.^[30] fully confirms the lack of any inhibitory activity of oseltamivir carboxylate at or below a concentration of 1 nM. These data demonstrate that oseltamivir has no significant inhibitory activity on human host neuraminidases at therapeutically relevant concentrations and that a potential interaction between oseltamivir and human host neuraminidases is thus very unlikely to be a mechanism for producing or exacerbating NPAEs in humans.

7.3 Interactions with Other CNS Molecules and Receptors

Possible effects of oseltamivir and oseltamivir carboxylate on host molecular targets could provide the basis for potential pharmacological activity in the CNS. Interactions with 155 known molecular targets, including several targets that could potentially underlie mechanisms for triggering or exacerbating NPAEs, such as dopamine and serotonin receptors and transporters, as well as ionotropic and metabotropic glutamate receptors, were examined using *in vitro* radioligand binding and functional assays. Oseltamivir and oseltamivir carboxylate were found to have no relevant pharmacological activity on any of the targets tested; the highest concentration tested (30 μ M is approximately 100 and 30 times, respectively, the oseltamivir phosphate and oseltamivir carboxylate plasma $C_{\max}$ values achieved from the 75-mg twice-daily clinical dose, and >4000- and >300-fold the extrapolated oseltamivir and oseltamivir carboxylate CNS concentrations achieved with standard oseltamivir dosing.^[5]

8. Genetic Differences

8.1 Interference with Hydrolysis of Oseltamivir: Modelling Studies

Hydrolysis *in vitro* of oseltamivir to the active form, oseltamivir carboxylate, seems to depend mainly on HCE1, and recombinant HCE1, but not HCE2, has been shown to hydrolyse oseltamivir.^[31] These authors also described several naturally occurring HCE1 polymorphic variants with different *in vitro* hydrolysis rates to the wild-type enzyme – HCE1 S58N was slightly faster, and HCE1 C70F and HCE1 R128H markedly slower. HCE1 C70F was expressed at a much lower level than the other variants.^[31] Genetic variation in the *HCE1* and *HCE2* genes has also been reported by other groups.^[32,33] HCE1 appears to be encoded by two distinct genes that may have arisen from a duplication event.^[33,34] The clinical relevance of these genetic data, however, is unclear – the allele frequencies of several HCE polymorphisms are unknown, and the organization of the HCE1 locus complicates the prediction of enzyme activity *in vivo* based on genotype alone.^[33] There are no clinical data yet on how HCE1 polymorphisms affect the PK of oseltamivir and oseltamivir carboxylate in humans.

If metabolism of oseltamivir to oseltamivir carboxylate was completely blocked, the resultant increase in oseltamivir levels could theoretically be responsible for adverse safety findings. This possibility has been investigated using population PK modelling to simulate complete inhibition of oseltamivir hydrolysis and estimate the maximum possible resulting oseltamivir exposure. A population PK model for oseltamivir and oseltamivir carboxylate was built using data from five healthy volunteer studies, using non-linear mixed-effect modelling (NONMEM version VI). Using Berkeley Madonna (version 8.3.9), 100 individuals were simulated with both normal and completely inhibited oseltamivir hydrolysis after oral doses of 75 mg twice daily. Basing the simulations on normal metabolism (hydrolysis) of oseltamivir to oseltamivir carboxylate

as estimated by the population PK model (metabolic clearance of 96.5 L/h), the mean assumed steady state $C_{\max}$ value was 39.9 ng/mL. Assuming complete inhibition of oseltamivir to oseltamivir carboxylate conversion (metabolic clearance of 0 L/h), the simulations produced a mean steady-state $C_{\max}$ value for oseltamivir of 555 ng/mL, 14 times higher than those simulated under the normal metabolism scenario.^[5] Even still, this exposure is lower than the mean $C_{\max}$ in six subjects who received a single dose of oseltamivir 1000 mg and who experienced no NPAEs.^[5] Although the mean oseltamivir $C_{\max}$ in 99 volunteers who received oseltamivir 450 mg twice daily for 5 days was only 352 ng/mL, some individuals had $C_{\max}$ values higher than the 555 ng/mL mean value simulated in the no-metabolism scenario, but again, without provoking any NPAEs.^[5] Collectively, these data suggest that HCE polymorphisms are unlikely to provide a plausible explanation for the observed NPAEs.

8.2 Renal Excretion of Oseltamivir Carboxylate

Once formed in the body, oseltamivir carboxylate is not further metabolized, and besides glomerular filtration, is eliminated primarily via tubular secretion in the kidney,^[16] principally by the action of the active transport system OAT1 mentioned previously.^[35] Although gene polymorphisms of *OAT1* have been found, allele frequencies and levels of variability are low.^[36] Coding region variants of *OAT1* do not seem to contribute substantially to inter-individual differences in renal clearance of oseltamivir,^[36,37] which is consistent with the similarity in PK profiles of Japanese and Caucasian populations.^[18] Moreover, inhibition of OAT1 and OAT3 activity by probenecid in healthy volunteers, resulting in a 2- and 2.5-fold increase in oseltamivir carboxylate $C_{\max}$ and exposure, respectively, did not elicit NPAEs in a clinical trial setting.^[5,35] Therefore, polymorphisms of the *OAT1* gene affecting excretion of oseltamivir carboxylate are unlikely to contribute to the reported NPAEs.

8.3 Effect of Active Transport Processes for Oseltamivir and Oseltamivir Carboxylate in the CNS

As mentioned in section 6.3, except for P-gp, no other active transport systems have been identified that regulate export of oseltamivir from the CNS. As no relevant active transport of oseltamivir carboxylate through the BBB has yet been described, the very limited CNS exposure to oseltamivir carboxylate is thought to be due to passive transport.

P-gp is encoded by multidrug resistance gene 1 (*MDR1*), for which many polymorphisms in humans have been reported, with a range of allele frequencies across different populations.^[38,39] However, although *MDR1* genotypic variants are reported to influence the PK and pharmacodynamics of various drugs, clinical studies in which *MDR1* substrates were given to individuals with known *MDR1* genetic variants have proved inconclusive and sometimes contradictory,^[39] and variants were not substantially different to the wild-type when tested *in vitro*.^[40] As mentioned in section 6.3, complete inhibition of P-gp function in humans would be expected to have little effect on the safety of oseltamivir, based on the extent of changes seen in gene knock-out studies in animals, and genetic variability in *MDR1* function is therefore unlikely to result in adverse effects.

Anion transporters such as OAT1, OAT3 and OATPIA2 also contribute to regulation of the BBB.^[41] It seems unlikely, however, that pharmacogenetic variations of these transporters could be associated with NPAEs – inhibition of OAT activity by probenecid did not elicit NPAEs, as described in the preceding section. Moreover, the clinical relevance of polymorphisms in these genes has not been firmly established despite intensive investigative efforts, suggesting that the pharmacological effect of potentially functional polymorphisms in these genes is likely to be modest.^[36,37,42-44]

Despite the continuing accumulation of data on polymorphisms of genes suspected to contribute to maintenance of the BBB with respect to oseltamivir and oseltamivir carboxylate, there is no evidence that they result in a clinically relevant mechanism for producing adverse effects.

9. Conclusions

The existing and new data reviewed in this article provide some answers to the questions posed at the start of this assessment made by Roche. In patients with influenza taking oseltamivir, the most frequent NPAEs are in the categories of abnormal behaviour and delusions and perceptual disturbances. Most of the spontaneously reported NPAEs resolved, but very occasionally resulted in injury, in some cases with a fatal outcome. The majority of NPAEs have been reported in Japan, mostly in children, and more frequently in males than females, but in the context of the number of prescriptions issued for oseltamivir, the crude reporting rate shows NPAEs to be uncommon events. As the timing of most events is within the first 2 days of oseltamivir treatment, coinciding with the onset of other influenza symptoms such as fever and malaise, it is difficult to distinguish the effect of the treatment from those of the disease. In prospective clinical studies, no evidence was found for a higher incidence of NPAEs in patients who receive oseltamivir than in those who received placebo, and results of retrospective observational studies of two large US claims databases indicate that the risk of NPAEs in oseltamivir-treated patients is no higher than in patients receiving no antiviral treatment. This evidence strongly supports that the events are more likely to be caused by the disease itself rather than by oseltamivir, which is consistent with the UK GPRD medical records analysis showing that the risk of NPAEs in influenza patients is significantly higher than in the general population.

Human and animal studies show that CNS concentrations of oseltamivir and its active metabolite oseltamivir carboxylate are low relative to plasma concentrations, and that conversion of oseltamivir to oseltamivir carboxylate in the brain is very low; indeed oseltamivir appears to be actively exported from the CNS. Exposure to oseltamivir and oseltamivir carboxylate in the CNS does not result in any relevant pharmacodynamic effects, and no genetic differences between Japanese and Caucasian patients have been found that might result in differences in the concentration, metabolism or activity of

oseltamivir and oseltamivir carboxylate in the CNS. A range of clinical and animal studies have not suggested any plausible mechanisms by which oseltamivir could cause NPAEs.

The available data do not indicate that the incidence of NPAEs in patients with influenza receiving oseltamivir is higher than in those not receiving it, and do not suggest any mechanism by which oseltamivir could cause such events.

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Oseltamivir for the Treatment of H1N1 Influenza During Pregnancy

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Pregnancy heightens the risk of adverse outcomes from influenza infections. This is true for both seasonal epidemics as well as occasional pandemics. Seasonal influenza vaccines are the focus of disease prevention and are recommended for all pregnant women in any trimester of pregnancy and postpartum. Oseltamivir (Tamiflu) is currently the recommended and most commonly used pharmaceutical agent for influenza prophylaxis and treatment. Oseltamivir has been demonstrated to prevent disease after exposure, treat infected individuals, as well as lessen the likelihood of complications. The physiologic adaptations of pregnancy alter the pharmacokinetics of this important drug. Evidence of these alterations, knowledge gaps, and future investigative directions to fill these knowledge gaps are highlighted.

Pregnant women have increased susceptibilities to severe infection and worse clinical outcomes from influenza. These heightened risks are noted both during seasonal epidemics as well as the occasional pandemic, including the recent 2009 H1N1 experience.¹ Appropriately, much attention is focused on use of the inactivated vaccine for primary prevention of influenza in pregnancy. However, the modest efficacy and marginal uptake of influenza vaccine in pregnancy continue to highlight the importance of optimizing the use of antiviral medications such as oseltamivir (Tamiflu) against influenza exposure and disease given its demonstrated efficacy.¹

BASIC INDICATIONS AND PHARMACOLOGY OF OSELTAMIVIR

Neuraminidase inhibitor drugs (oseltamivir, zanamivir, peramivir, etc.) are competitive inhibitors of the neuraminidase (NA) enzyme on the influenza virus, acting on sialic acid residues. Blocking this surface receptor enzyme prevents the release of infectious virus from host cells, limiting the propagation of infection. Currently, both oseltamivir and zanamivir are recommended for the prevention and treatment of influenza among exposed and/or infected individuals, respectively. The current recommended doses of oseltamivir and zanamivir are 75 mg as an oral capsule and 10 mg as a dry powder inhaler, respectively, taken daily for 7–10 days after exposure (prevention dose), and 75 mg tablet and 10 mg powder inhaler twice daily, respectively, for 5 days (treatment dose).¹ Due to the fact that pregnant

women are almost completely excluded from participation in clinical trials of new therapeutic agents, no pharmacologic data have been generated in this population during the drug development or advanced clinical trial phase investigations of oseltamivir (or zanamivir). Thus, at the outset of the recent 2009 H1N1 influenza pandemic scant data were available to inform optimal use of these critically important antiviral agents in this vulnerable patient population. Even less data existed for zanamivir in pregnancy and clinical use of zanamivir was less often chosen, thus the focus was on oseltamivir.

Oseltamivir phosphate (OP) is an orally administered prodrug that is well absorbed. It then undergoes significant conversion by hepatic carboxylesterases (carboxylesterase-1) to the single active metabolite oseltamivir carboxylate (OC) (Figure 1).² Only 5% of OP is excreted unchanged in the urine. Earlier pharmacokinetic (PK) studies in healthy subjects following oral administration of oseltamivir phosphate and intravenous administration of OC suggest that ~80% of orally administered oseltamivir reaches systemic circulation as active metabolite.³ Peak plasma concentrations of OC are achieved in ~2–4 hours and the PK of OC appears to be linear across a large dose range. OC is exclusively eliminated by renal excretion, with an elimination half-life in the range of 6–10 hours, and there are minimal known drug–drug interactions. Given the known marked effects of pregnancy on the functions of the gastrointestinal, hepatic, and renal systems, biologic plausibility exists for altered PK of oseltamivir with subsequent implications for dosing recommendations.⁴ Moreover,

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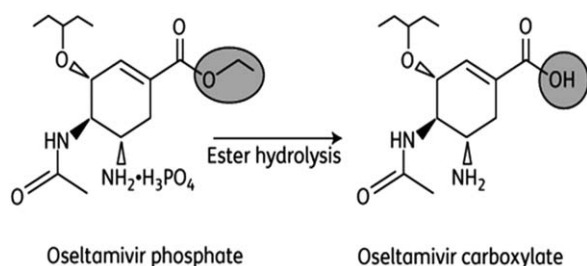


Figure 1 Structure of oseltamivir parent drug (OP) and active metabolite (OC).

given the noted increased likelihood of untoward outcomes from influenza in pregnancy, precise data regarding PK (and ideally pharmacodynamics (PD)) are warranted and of significant importance in this population.

AVAILABLE INVESTIGATIONS

To fill this large data gap, investigations were undertaken by the National Institutes of Health's (NIH) Obstetric-Fetal Pharmacologic Research Unit (OPRU) Network, as well as others.^{5–7} In addition to the potential impact on efficacy due to PK alterations, antimicrobial agents also have the additional consideration of the potential for drug resistance from subtherapeutic levels, further emphasizing the importance of investigations to determine optimal dosing. Both investigations used an "opportunistic" study design, enrolling pregnant women already on treatment courses of oseltamivir for influenza. This study design does pose some challenges because of the inability to alter the dosing schedule; however, it is an effective way of obtaining modest amounts of data in pregnancy, given that women are already receiving drug. Such an approach can also minimize some of the logistical barriers to performing research on therapeutics in pregnancy.

The OPRU network study enrolled 29 pregnant women receiving oseltamivir treatment and across all gestational ages along with 35 nonpregnant contemporaneous controls (who ingested oseltamivir solely for study purposes).^{5,6} This design offered the advantage of having a comparator population of nonpregnant women providing data within the same investigation, thus undergoing the same statistical and methodological approach. Eighty-nine percent of the pregnant women were on oseltamivir for treatment of influenza or influenza-like illness (mostly on standard twice daily doses) and the remaining 11% were on the 75 mg once-daily prophylactic dose. Despite these differences in dosing within the pregnant cohort, all women in both cohorts underwent intensive PK sampling after being on oseltamivir therapy for at least 48 hours. Dose-adjusted PK data were used in this investigation to control for these noted differences in schedule. It was found that the physiologic changes of pregnancy produced an ~30% lower exposure ($2,786 \pm 879$ ng/ml*hr vs. $3,840 \pm 1,117$ ng/ml*hr, $P = 0.0001$) to the active metabolite OC when compared to nonpregnant women. These pharmacologic changes correlated with the increased apparent oral drug clearance, presumably from the enhanced renal elimination in pregnancy.

Importantly, in these investigations the renal excretion of oseltamivir exceeded the glomerular filtration rate (GFR), suggesting

that tubular secretion via an organic anion transporter (OAT) is likely a contributing factor.⁸ Although there are no direct data on the impact of pregnancy and specific gestational age on human OAT activity in the kidney, the increase in activity can be indirectly inferred from a previously reported PK study of amoxicillin in pregnant women.⁹ The renal clearance of amoxicillin is significantly reduced by probenecid, suggesting that amoxicillin is a substrate of OATs. Both renal clearance and renal secretion of amoxicillin is increased by more than 50% during the second and third trimester of pregnancy. Additionally, the renal secretion was reported to account for more than 50% of the renal clearance of amoxicillin. This observation suggests that OAT activity is increased during pregnancy. Therefore, it is assumed that the renal secretion of OC (also a substrate of OAT) is increased along with increased GFR during pregnancy, leading to decreased systemic exposure of OC in pregnant women.

These findings suggest that altered dosing schedules among pregnant women may be required to better approximate the drug exposure among nonpregnant subjects, although the exact clinical impact of such an approach remains poorly understood. Definitive recommendations regarding pregnancy-specific dosing await further investigation, given the modest sample size. An additional benefit provided by these data are the ability to now perform various pharmacologic modeling investigations that aim to better define the precise pharmacology of this important antiviral drug. Such investigations combined with ongoing and future clinical investigations will likely enable more robust evidence-based recommendations for oseltamivir dosing schedules in pregnancy.

A related yet distinct opportunistic investigation was carried out by Greer *et al.*⁷ and published contemporaneously with the previous investigation. These researchers looked at the PK of oseltamivir in pregnancy with the primary aim of defining and comparing potential trimester-specific differences in drug metabolism. Thirty women (10 per trimester) were enrolled and all were taking either the usual adult recommended treatment dose of 75 mg twice daily or the prophylactic dose of 75 mg once daily. Unlike the OPRU study, blood sampling occurred before and after the first dose of drug. This group did not find significant differences in the usual PK parameters (C_{max} , T_{max} , AUC_{0-12}) for the parent prodrug when comparing different gestational ages. Similarly, when they looked at the active metabolite OC they noted similar PK by trimester, with the only finding of C_{max} being statistically higher in the third trimester. Moreover, it was suggested that despite these small fluctuations, values were well within the available pharmacologic range for clinical efficacy against circulating strains of influenza, and thus the findings were mostly of academic importance. The final conclusion reached by these investigators is that the PK of oseltamivir (and its active metabolite OC) does not differ significantly by trimester.⁷ However, it should be noted that this study was not performed at steady state. Given the combination of noted findings in both available studies it appears that formal recommendations addressing potential dosing alterations await clinical data informing the impact of the noted PK-based alterations.

An additional important consideration for oseltamivir in pregnancy (as well as any pharmacologic agent used in pregnant women) is safety of the drug and its potential to cross the placenta. The available safety data in animals suggest that use of oseltamivir at clinically recommended dosages is unlikely to pose any adverse effects on fetal growth and development.¹⁰ Additionally, more recently available observational studies also fail to suggest that clinical use in pregnancy is of any real concern.^{11–14} The most important message is that given the known increased risk to pregnant women and their fetuses/newborns from influenza infection (and the absence of data suggesting deleterious effects) treatment with oseltamivir should be prioritized in this patient population. A recent case report addressed the issue of placental perfusion and suggested that OC will traverse the placenta and be detected in the fetal compartment, although at substantially lower levels than in the maternal circulation.¹⁵ More specifically, a separate investigation using a dual placental perfusion study reveals that fetal to maternal concentration ratio of oseltamivir carboxylate is 0.35 ± 0.075 .¹⁶ Although it appears that a fraction of the drug may in fact get to the fetus, the full implications of these findings remain to be fully evaluated and are unlikely to be detrimental in any clinically relevant fashion.

It should also be emphasized that currently the relationship between the previously noted PK findings of oseltamivir (in both the general and pregnant populations) and their direct PD implications are not fully understood. Because of the potential severity of influenza in varied populations (including pregnant women), the potential for antiviral resistance, and the need to optimize antiviral treatment, this indeed is an obviously important endpoint to delineate. Investigators have suggested a theoretical model that might approximate the relationship using an *in vitro* surrogate system.¹⁷ It has been proposed that the variable $AUC_{24}:IC_{50}$ might be a useful surrogate endpoint permitting improved PD approximations with correlations to PK. While intriguing, the overall value of this proposal remains to be better delineated.

CONCLUSION

Oseltamivir is a critically important pharmacologic agent for use in pregnant women due to the heightened risks of influenza in pregnancy. The pharmacology of this important drug in pregnancy is beginning to be fully understood and these findings suggesting a lower overall exposure during pregnancy can be used to shape future investigations aimed at delineating optimal use. Such future investigations should provide for more evidence-based care of this important and uniquely susceptible patient population.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Population pharmacokinetics of oseltamivir in non-pregnant and pregnant women

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Oseltamivir (OS) is approved for the prevention and treatment of influenza viral infections.
- Pregnant women are at great risk for complications associated with influenza infections.
- The current dosing recommendation of OS in pregnant women is based on studies in men and non-pregnant women with influenza infections. However, physiological changes during pregnancy may alter the pharmacokinetics of drugs in pregnant women.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

- The clearance of oseltamivir carboxylate was higher during pregnancy, resulting in lower systemic exposure of oseltamivir carboxylate in pregnant women.
- We suggest an increase in dose of OS during pregnancy in order to achieve comparable drug exposure to that of non-pregnant women.

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AIMS

Physiological changes in pregnancy are expected to alter the pharmacokinetics of various drugs. The objective of this study was to evaluate systematically the pharmacokinetics of oseltamivir (OS), a drug used in the treatment of influenza during pregnancy.

METHODS

A multicentre steady-state pharmacokinetic study of OS was performed in 35 non-pregnant and 29 pregnant women. Plasma concentration–time profiles were analyzed using both non-compartmental and population pharmacokinetic modelling (pop PK) and simulation approaches. A one compartment population pharmacokinetic model with first order absorption and elimination adequately described the pharmacokinetics of OS.

RESULTS

The systemic exposure of oseltamivir carboxylate (OC, active metabolite of OS) was reduced approximately 30 (19–36)% ($P < 0.001$) in pregnant women. Pregnancy significantly ($P < 0.001$) influenced the clearance (CL/F) and volume of distribution (V/F) of OC. Both non-compartmental and population pharmacokinetic approaches documented approximately 45 (23–62)% increase in clearance (CL/F) of OC during pregnancy.

CONCLUSION

Based on the decrease in exposure of the active metabolite, the currently recommended doses of OS may need to be increased modestly in pregnant women in order to achieve comparable exposure with that of non-pregnant women.

Introduction

Pregnant women with influenza viral infections are at higher risk for severe illness, hospitalizations and mortality than non-pregnant women with influenza [1, 2]. Influenza infections may also adversely affect the pregnancy, leading to complications including premature delivery and fetal growth alterations [1, 3, 4]. The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) have recommended oseltamivir (OS, Tamiflu®) as one of the primary pharmacological options for disease mitigation [5].

OS is an orally administrated pro-drug. It is extensively hydrolyzed by hepatic carboxylesterases to the active drug oseltamivir carboxylate (OC) [6]. The oral bioavailability of OS is approximately 80%. The active metabolite, OC, is a major circulating component (95%) in plasma, and the pro-drug OS accounts for only approximately 5% of the circulating component in plasma [7]. OS is moderately bound to plasma proteins (42%) with a steady-state volume of distribution (V_{ss}/F) of 1768 ± 1445 l, and a half-life of 1–3 h [6, 8]. Oral intake does not appear to have significant effects on the pharmacokinetics of OS [9]. OC is poorly bound to plasma protein (<3%), and the volume of distribution is 23 to 26 l. It is eliminated entirely (>99%) through renal excretion by glomerular filtration and active tubular secretion with a half-life of 6–10 h [6].

Physiological alterations that occur during pregnancy have been reported to alter the exposure of various therapeutic agents in pregnant women [10]. A previous report from our group has shown that exposure to the active metabolite, OC, was reduced by approximately 30% in pregnant women compared with non-pregnant women. It was proposed that an increase in the dose of OS may be considered for the treatment of influenza infections in pregnant women [8]. However, the conclusions of this earlier study were limited by a relatively small sample size, demographic differences (race and age) between the pregnant and non-pregnant groups, and the use of an empirical method of data analysis. These limitations suggested that additional clinical pharmacokinetic analysis of OS in pregnant women was warranted.

Population pharmacokinetic (pop PK) modelling (with simulations) is a powerful tool often used to estimate the pharmacokinetics of a therapeutic agent using the concentration–time profiles from a small number of subjects and limited sampling from a large number of subjects. Until recently, very limited pop PK studies of OS have been reported in healthy and influenza infected subjects [11–17]. However, no pop PK studies have been reported comparing the exposure of OC between pregnant and non-pregnant women. The objective of this study was to develop and validate a pop PK model for OS and OC in a large group of demographically-balanced pregnant and non-pregnant

women. We also evaluated the covariates that influence the exposure of OC in pregnant women.

Methods

Data

Data were obtained from non-pregnant reproductive-aged women and pregnant women who were recruited between 2007 and 2012 from four clinical research centres, including Magee Women's Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA, University of Texas Medical Branch, Galveston, TX, University of Washington Medical Center, Seattle, WA and Georgetown University, Washington, DC, USA. Part of the data was previously analyzed using non-compartmental pharmacokinetic analysis and was published elsewhere [8]. Additional subjects were only enrolled at the Pittsburgh site. All protocols were approved by each site's institutional review board and all participants underwent the informed consent process before entering the study. All of the non-pregnant control subjects received standard oral doses of OS at 75 mg once daily or 75 mg twice daily for at least 48 h prior to reporting for study procedures, and pregnant subjects were continued on their clinical doses either for prophylaxis or for treatment of influenza viral infection/influenza like illness, with no changes made in the dose of OS for study purposes. A previous publication [18] has reported no significant differences in the pharmacokinetics of OC between healthy subjects and influenza viral infected patients.

Sample collection and bioanalysis

On the study day, all participants underwent a pre-dose blood draw (trough) and received a 75 mg oral dose of OS. Subsequently, serial blood samples were collected over one dosing interval at 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h after the dose. For once daily dosing, an additional blood sample was collected at 24 h after the dose. Blood samples were collected into K3-EDTA/sodium fluoride tubes and centrifuged at $3000 \text{ rev min}^{-1}$ for 10 min, and plasma was separated and stored at -80°C until analysis.

OS and OC were analyzed by a previously validated method [19] using liquid chromatography with tandem mass spectrometry and positive electrospray ion mode. The assay sensitivity in terms of lower limit of quantification for OS was 1 ng ml^{-1} and OC was 10 ng ml^{-1} . The coefficient of variation (CV%) for the accuracy and precision of the assay was <3% and <6%, respectively.

Non-compartmental pharmacokinetic analysis

Plasma concentration–time profiles of OS and OC in non-pregnant and pregnant women are shown in Figure 1. The maximum plasma concentration ($C_{\max}$), area under the concentration–time curve ($\text{AUC}(0, t_{\text{last}})$), clearance

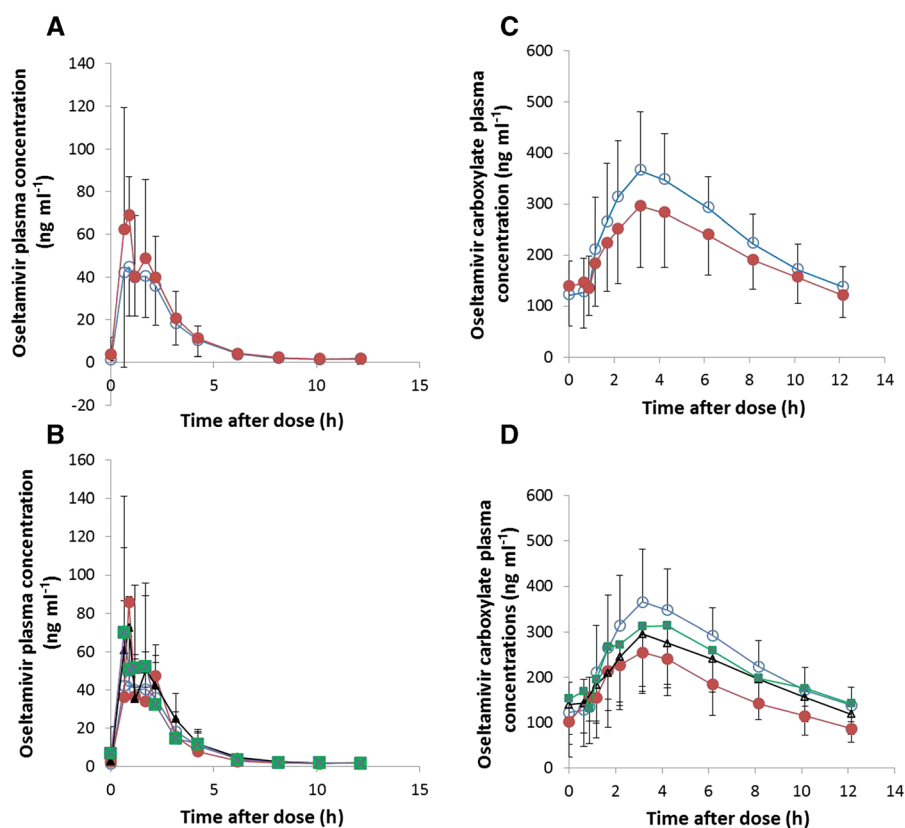


Figure 1

Mean plasma concentration–time profiles of oseltamivir (A and B) and oseltamivir carboxylate (C and D) in non-pregnant and pregnant women. A and C — non-pregnant, — pregnant. B and D — non-pregnant, — trimester 1, — trimester 2, — trimester 3

(CL/F), volume of distribution ($V_{d,ss}$) and half-life ($t_{1/2}$) were calculated with a non-compartmental approach using Phoenix WinNonlin® version 6.1 (Pharsight Corp, Cary, North Carolina, USA).

Population pharmacokinetic modelling

Pop PK modelling was developed using non-linear mixed effects modelling software (nonmem version 7.1; ICON Development Solutions, Hanover, MD, USA), GNU Fortran 95 compiler and PLT tools (version 5.1.0). Earlier reports suggested that the pharmacokinetics of OS were linear up to 500 mg oral dose [20]. OS is extensively metabolized (~95%) to its active metabolite, OC in humans [7]. Approximately 94.5% of OS was recovered as OC in urine samples from both non-pregnant and pregnant women. The elimination of OC is predominantly through the renal route [21]. Therefore, the following assumptions were made prior to model building, 1) the pharmacokinetics of OS are linear, 2) the fraction of OS metabolized to OC (f_m) is fixed to 0.945 and 3) OC and the remaining OS are completely eliminated through renal route.

The general linear model under steady-state was constructed using ADVAN5 SS5 subroutines. Both zero and first order absorption models were tested. Similarly, one compartment and two compartment models were fitted to the current data. The first order conditional

estimation method with interaction was used for the parameter estimation. The inter-individual variability (IIV) in pharmacokinetic model parameters was estimated using an exponential model,

$$P_{ij} = TV(P_j) \times e^{\eta_{ij}}$$

where P_{ij} is the i th individual's estimate of the j th pharmacokinetic parameter, $TV(P_j)$ is the typical value of the j th pharmacokinetic parameter, and η_{ij} is a random variable for the i th individual and the j th pharmacokinetic parameter distributed with mean zero and variance of ω_j^2 .

The random residual variability was modelled using combined error model,

$$C_{obs} = C_{pred} \times (1 + \varepsilon) + \varepsilon'$$

where C_{obs} and C_{pred} are the observed and predicted concentrations, respectively, and ε and ε' are normal random variables with means of zero and variances of σ^2 and σ'^2 , respectively.

In order to identify the covariates that influence the pharmacokinetics of OC, the following covariates including age (years), body weight (kg), height (cm), race, pregnancy, gestational age, trimester of pregnancy, albumin, serum creatinine (mg dl^{-1}), creatinine clearance (CL_{CR} , ml min^{-1}), blood urea nitrogen (BUN, mg dl^{-1}),

aminotransferases (ALT and AST) and total bilirubin were evaluated. The urinary creatinine was quantitated and used for the calculation of creatinine clearance (Cumulative amount of creatinine excreted in urine (mg)/(serum creatinine (mg dl⁻¹) × time (h)). For covariate selection, univariate analysis with stepwise forward addition ($P < 0.01$) and backward elimination ($P < 0.001$) procedures were followed. Covariate-parameter relationships were evaluated as random variability of model parameter vs. covariate plots and the graphical trend was assessed by univariate linear regression analysis (data not shown). The covariates that significantly influence the pharmacokinetics of OS and its metabolite were incorporated in the final model.

The adequacy of the model was evaluated using the following criteria: examination of goodness of fit diagnostic plots for observed vs. population predicted or individual predicted concentration–time profiles, weighted residuals vs. predicted concentrations, change in minimum objective function values (OFV) (>3.84 , considered statistically significant based on chi-square distribution with 1 degree of freedom) and extent of interindividual and residual random variability. Precision of parameter estimation and stability of the model parameter estimates were evaluated with bootstrapping (resampling repeated 500 times) using Wings for nonmem® [22]. Non-parametric statistics (median, 95% confidence interval) of parameter estimates obtained from bootstrapping were compared with the point parameter estimates obtained from the model.

The predictive performance of the model was internally evaluated using a prediction corrected visual predictive check, in which 1500 data sets were simulated using the parameter estimates in the final model. The 50th percentile concentration (median) and the 5th and 95th percentile concentrations (90% prediction interval) were plotted and compared with the observed concentrations.

Additional statistical analysis

The statistical analysis was performed using Graph Pad Prism version 5.04 (La Jolla, CA, USA). Statistical comparison between two groups was analyzed using two-sided Student's *t*-test, whereas three or more groups were statistically compared using one way analysis of variance (ANOVA) followed by Tukey's *post hoc* test. A *P* value of < 0.05 was considered statistically significant.

Results

Demographic data

A total of 763 samples were collected from 35 non-pregnant and 29 pregnant women enrolled in this study. The number of pregnant subjects in trimester 1 (TRI1), trimester 2 (TRI2) and trimester 3 (TRI3) of pregnancy were 4, 16 and 9, respectively. For pregnant subjects, 18

out of 29 subjects tested positive for polymerase chain reaction proven influenza virus A/B and the remaining subjects either tested as negative or were not tested. Among the 64 subjects, one subject from the non-pregnant and two subjects from the pregnant categories possessed atypical concentration–time profiles with fewer than three points in the terminal disposition phase, and were subsequently not included for non-compartmental analysis. However, all the subjects were included in the population pharmacokinetic analysis. The demographics and clinical characteristics of the non-pregnant and pregnant women are presented in Table 1. The median age of the pregnant women was slightly, but significantly, lower than non-pregnant women. Serum albumin, serum creatinine and blood urea nitrogen were significantly reduced whereas body weight and creatinine clearance were significantly increased in pregnant women as compared with non-pregnant women.

Non-compartmental pharmacokinetic analysis

The pharmacokinetic parameters estimated from the plasma concentration–time profiles of OS and OC are

Table 1

Demographic and clinical characteristics of non-pregnant and pregnant women

Parameter	Non-pregnant	Pregnant
Number of subjects	35	29
Trimester 1		4
Trimester 2		16
Trimester 3		9
Age (years)	28 (18–50)	24 (18–40)*
Gestational age (weeks)	0	25 (6–37)
Body weight (kg)	71 (52–113)	82 (48–147)*
BMI (kg m ⁻²)	28 (19–44)	30 (18–50)
Race		
Caucasian	24	11
African American	11	18
Site		
UPMC, Pittsburgh	3	27
UT, Galveston	20	2
UW, Seattle	10	
GU, Washington, DC	2	
Albumin (g dl ⁻¹)	4.3 (2.8–5.6)	2.8 (2.2–3.8)*
Serum creatinine (mg dl ⁻¹)	0.7 (0.55–1)	0.6 (0.4–0.9)*
Blood urea nitrogen (mg dl ⁻¹)	12 (7–19)	7 (2–13)*
Creatinine clearance (ml min ⁻¹)	128 (69–254)	163 (52–327)*
AST (IU l ⁻¹)	23 (10–62)	18 (11–79)
ALT (IU l ⁻¹)	29 (10–116)	29 (10–72)
ALK (IU l ⁻¹)	82 (40–127)	78 (42–176)
BIL (mg dl ⁻¹)	0.5 (0.1–1.6)	0.2 (0.1–0.7)

Values are expressed as median (range). * $P < 0.05$ vs. non-pregnant, unpaired, two sided *t*-test

Table 2

Parameter estimates from non-compartmental pharmacokinetic analysis of oseltamivir and oseltamivir carboxylate

	Non-pregnant		Pregnant	
	OS	OC	OS	OC
$C_{\max}$ (ng ml ⁻¹)	71 ± 36	397 ± 113	85 ± 43	318 ± 107**
AUC(0, t_{last}) (ng ml ⁻¹ h)	145 ± 46	3507 ± 992	178 ± 68*	2653 ± 928**
CL/F (l h ⁻¹)	569 ± 173	23 ± 6	478 ± 168*	33 ± 16**
$V_{d,ss}/F$ (l)	1909 ± 860	149 ± 35	1342 ± 635**	184 ± 73*
$t_{1/2}$ (h)	3.0 ± 1.9	5.9 ± 1.5	3.8 ± 1.7	6.3 ± 2.2

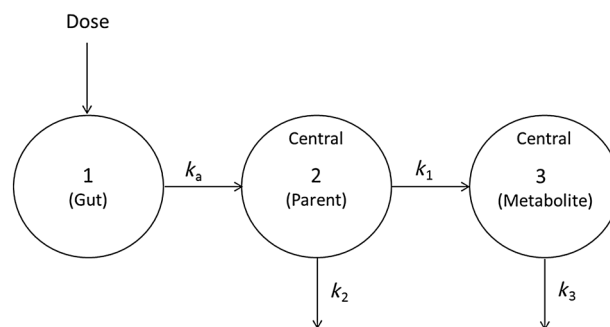
Values are represented as mean ± SD; * $P < 0.05$ and ** $P < 0.01$ vs. non-pregnant, unpaired two sided t -test

shown in Table 2. The exposure to the parent compound OS was only slightly but significantly ($*P < 0.05$) increased in pregnant women ($178 \pm 68 \text{ ng ml}^{-1} \text{ h}$) compared with non-pregnant women ($145 \pm 46 \text{ ng ml}^{-1} \text{ h}$) with a corresponding minimal decrease in CL/F ($478 \pm 168 \text{ l h}^{-1}$ vs. $569 \pm 173 \text{ l h}^{-1}$) during pregnancy. The $V_{d,ss}/F$ of OS was significantly ($P < 0.05$) reduced (1909 ± 860 vs. $1342 \pm 635 \text{ l}$) during pregnancy. The $C_{\max}$ and $t_{1/2}$ of OS were not different between pregnant ($71 \pm 36 \text{ ng ml}^{-1}$ and $3.8 \pm 1.7 \text{ h}$, respectively) and non-pregnant ($85 \pm 43 \text{ ng ml}^{-1}$ and $3.0 \pm 1.9 \text{ h}$, respectively) women.

The $C_{\max}$ and exposure (AUC(0, t_{last})) of the active metabolite, OC, were significantly lower ($P < 0.01$) in pregnant women ($318 \pm 107 \text{ ng ml}^{-1}$ and $2653 \pm 928 \text{ ng ml}^{-1} \text{ h}$, respectively) compared with non-pregnant women ($397 \pm 113 \text{ ng ml}^{-1}$ and $3507 \pm 992 \text{ ng ml}^{-1} \text{ h}$, respectively). This was associated with an increase ($P < 0.05$) in clearance (CL/F) of OC ($33 \pm 16 \text{ l h}^{-1}$ vs. $23 \pm 6 \text{ l h}^{-1}$) during pregnancy. The $V_{d,ss}/F$ of OC was also significantly ($P < 0.05$) increased (184 ± 73 vs. 149 ± 35) during pregnancy. However, the half-life ($t_{1/2}$) of OC was not different between pregnant ($6.3 \pm 2.2 \text{ h}$) and non-pregnant ($5.9 \pm 1.5 \text{ h}$) women.

Population pharmacokinetic modelling

The structure of population pharmacokinetic model is shown in Figure 2. A model incorporating first order absorption was selected due to its superiority over zero order absorption of OS. Similarly, a one compartment model produced a better fit than a two compartment model using the current data. The final model selection was supported by the symmetrical distribution of observed vs. model predicted concentrations around the lines of identity (goodness of fit diagnostic plots), and homoscedastic distribution of weighted residuals over time (weighted residuals vs. time after dose plots) (Figure 3). Parameters that were estimated using this model included absorption rate constant (k_a) of OS, and clearance/bioavailability (CL/F) and volume of distribution/bioavailability (V_d/F) of OS and OC. Since

**Figure 2**

Structure of oseltamivir carboxylate population pharmacokinetic model. k_a , absorption rate constant; k_1 , conversion rate constant of oseltamivir to oseltamivir carboxylate; k_2 and k_3 , elimination rate constant of oseltamivir and oseltamivir carboxylate, respectively

the oral bioavailability could not be calculated in this study, the clearance and volume of distribution were reported as CL/F and V_d/F . The first value below the quantitation limit value (BLQ) was replaced with lower limit of quantitation value (LOQ)/2 and the remaining BLQ values were ignored for the analysis. The BLQ values observed in this study were less than 7%. Only two non-pregnant subjects whose missing covariate values (weight, height and serum biochemistry values such as serum creatinine, blood urea nitrogen, creatinine clearance, AST, ALT, ALK and bilirubin) were substituted with median covariate values from the population.

Using univariate analysis, the influential covariates were selected based on the initial screening of individual covariate followed by forward addition ($P < 0.01$) and backward elimination ($P < 0.001$) processes. Covariate analysis suggested that weight and pregnancy significantly influence the CL/F of OS whereas renal function markers such as creatinine clearance and serum creatinine significantly influence the CL/F of OC. In addition, the covariate pregnancy also significantly influenced the V_d/F of OC. We observed a significant interaction between the covariates of pregnancy and weight, as well as pregnancy and renal function markers. Therefore, we chose pregnancy as a covariate of OC CL/F and V_d/F in the final model. The final model showed significant decreases in the OFV (25.4, $P < 0.001$, Chi-square distribution, $df = 2$). The inclusion of pregnancy as a covariate modestly reduced the IIV of CL/F and V_d/F of OC from 35% to 31% and 40% to 36%, respectively. The pop PK parameter estimates, IIV and random residual variability are represented in Table 3.

The CL/F of OS was minimally but significantly reduced in pregnant women ($504 \pm 178 \text{ l h}^{-1}$; $*P < 0.05$) compared with non-pregnant women ($606 \pm 178 \text{ l h}^{-1}$). Although $V_{d,ss}/F$ of OS was increased slightly in pregnant women ($404 \pm 315 \text{ l}$), the data were not significantly different from non-pregnant women ($369 \pm 235 \text{ l}$). The CL/F of OC was relatively higher in pregnant women ($\sim 43\%$; $30.0 \pm 10.7 \text{ l h}^{-1}$; $P < 0.001$) than non-pregnant women ($21.0 \pm 5.4 \text{ l h}^{-1}$). When compared with the

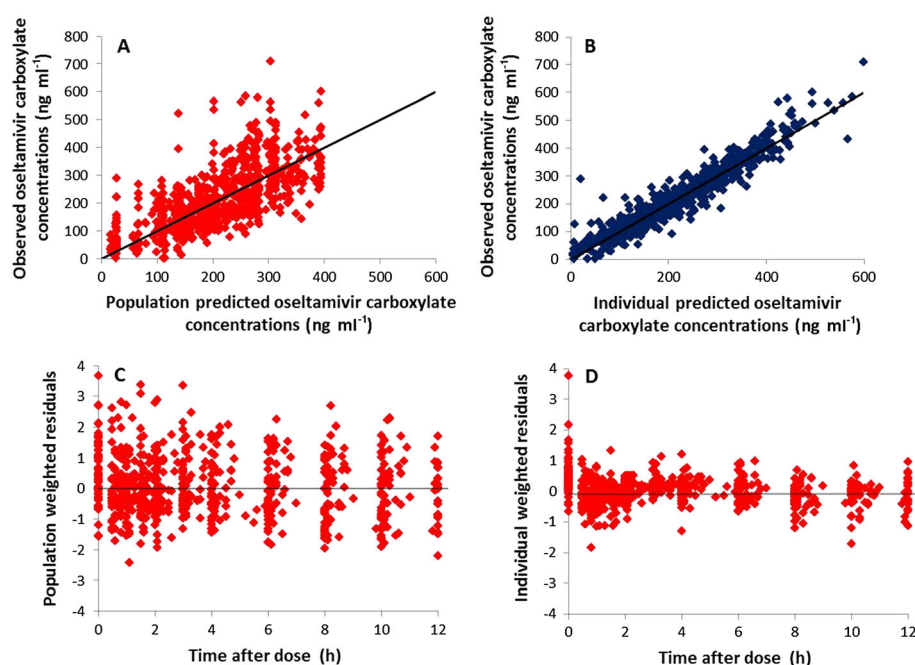


Figure 3

Goodness of fit diagnostic plots for oseltamivir carboxylate concentrations fitted using one compartment model with first order absorption and elimination. Observed plasma concentrations vs. population predicted concentrations (A), observed concentrations vs. individual predicted concentrations (B), population weighted residuals vs. time after dose (C) and individual weighted residuals vs. time after dose (D). The solid line indicates the line of identity

Table 3

Parameter estimates from population pharmacokinetic analysis and bootstrap analysis of oseltamivir and oseltamivir carboxylate

Parameter	Final model Estimate	% RSE	Bootstrap (n = 500) Median	2.5–97.5 percentile
k_a	0.6	8.3	0.65	0.56–1.09
CL/F OS	532	4.9	546	492–600
CL/F OC	20	4.9	20	18–23
V_d /F OS	289	17.6	346	224–697
V_d /F OC	152	5.6	155	137–172
PG effect on CL/F OC	8.1	25.9	8.3	4.2–12.9
PG effect on V_d /F OC	56	28.8	68	27–114
Inter-individual variability (%CV)				
k_a	38.1	15.4	30.3	0.3–60
CL/F OS	39.2	10.4	34.1	25–43
CL/F OC	30.8	4.8	30.8	26–36
V_d /F OS	92.7	27.1	78.0	30–110
V_d /F OC	35.9	14.0	31.1	23–45
Residual variability				
Proportional error for OS	50.3 %CV	6.6	46.3 %CV	42–51 %CV
Additive error for OS	1.5 ng ml ⁻¹ (LOQ 2 ng ml ⁻¹)	58.4	1.6 ng ml ⁻¹	1.1–5.2 ng ml ⁻¹
Proportional error for OC	15 %CV	Fixed	5 %CV	Fixed
Additive error for OC	35.7 ng ml ⁻¹ (LOQ 10 ng ml ⁻¹)	0.1	34.9 ng ml ⁻¹	28–41 ng ml ⁻¹

non-pregnant women, the first trimester of pregnancy appears to have higher CL/F (66%) of OC than second (45%) and third trimester (28%) of pregnancy (Figure 4). The $V_{d,ss}/F$ of OC was also significantly ($P < 0.001$)

increased (213 ± 63 vs. 155 ± 39 l (non-pregnant)) during pregnancy. The AUC distribution of OC was shifted towards the lower side in agreement with an increase in clearance during pregnancy (Figure 5).

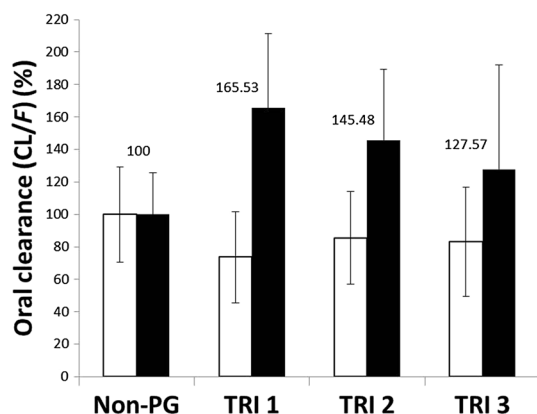


Figure 4

% oral clearance (CL/F) of oseltamivir and oseltamivir carboxylate in non-pregnant and first (TRI1), second (TRI2) and third (TRI3) trimester of pregnancy. Open bar indicates CL/F of oseltamivir whereas the filled bar represents CL/F of oseltamivir carboxylate. The results are expressed as mean $\pm$ SD. * $P < 0.05$ and ** $P < 0.01$ vs. non-pregnant oseltamivir carboxylate, one way ANOVA followed by Tukey's multiple comparison *post hoc* test

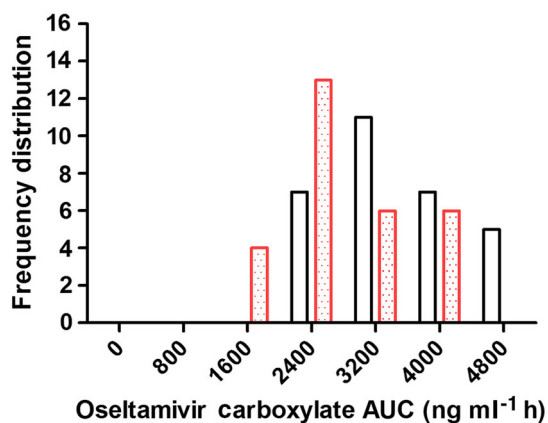


Figure 5

Frequency distribution of oseltamivir carboxylate area under the concentration-time (AUC) curve between non-pregnant and pregnant women. The frequency distribution of AUC of non-pregnant and pregnant women is shown as the open and dotted bar, respectively

Model validation

The stability of the model was evaluated by generating 500 datasets (resampling with replacement) using bootstrapping analysis. The median and 2.5–97.5th percentiles of parameter estimates from the bootstrapping analysis were compared with final parameter estimates (Table 3). Additionally, the model performance was evaluated by simulating 1500 virtual datasets using the final model by visual predictive check (VPC). The visual inspection was performed at observed concentrations that were plotted against 5, 50 and 95 percentiles of the simulated concentrations at each time point (Figure 6).

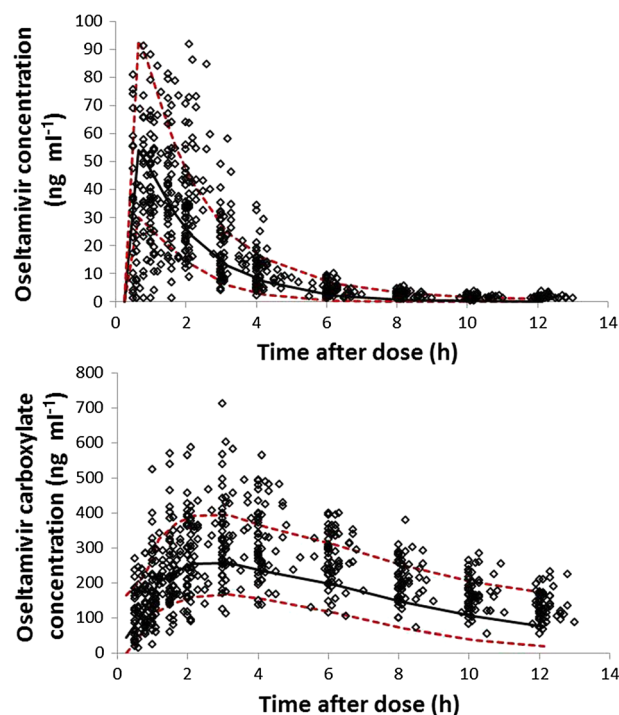


Figure 6

Predictive performance of the final model was analyzed using visual predictive check plots. The model predicted concentrations of oseltamivir (top) and oseltamivir carboxylate (bottom) were shown as 5, 50 and 95 percentiles lines and were plotted against observed concentrations at each time after dose. — 5th and 95th percentile, — 50 percentile (median), $\diamond$ Observants.

Discussion

Pregnant women are at greater risk for poor clinical outcomes from influenza infections. The detrimental effects of influenza in pregnancy include higher rates of severe maternal illness, need for hospitalization and maternal death, as well as adverse effects on the pregnancy itself, including preterm birth and adverse fetal growth [23–25]. Although influenza infections can be primarily controlled by influenza vaccination, the vaccine uptake rate still needs to be improved [26]. Given these noted increased risks, precise and accurate pharmacological therapy with neuraminidase inhibitors such as OS are of prime importance [5].

Delineating the various pharmacokinetic parameters of drugs during pregnancy presents a challenge. This is partly due to the physiological changes during pregnancy which impact gastrointestinal absorption, plasma volume and protein binding, thereby influencing volume of distribution, gut and liver metabolism and renal elimination of drugs [10]. On the basis of non-compartmental pharmacokinetic analysis, our earlier study suggested that the systemic exposure of OC was lowered approximately 30% in pregnant women compared with non-pregnant women [8]. For this report we recruited additional subjects to balance better the demographic parameters between

pregnant and non-pregnant women, and we performed both non-compartmental pharmacokinetic analysis and pop PK modelling to evaluate the pharmacokinetics of OS during pregnancy.

Non-compartmental pharmacokinetic analysis from this study suggested that the clearance (CL/F) of OC was increased by approximately 45% in pregnant women compared with non-pregnant women. These findings with an increased number of subjects and demographically comparable subjects were similar to our earlier observations. Considering the limitations associated with non-compartmental analysis, we performed a pharmacokinetic analysis using non-linear mixed effects modelling in non-pregnant and pregnant women.

Pop PK modelling provides a greater flexibility for estimation of the pharmacokinetic parameters of drugs under various scenarios including different dosing intervals, various sampling times, alternate routes of drug administration, and a multitude of demographic and physiologic covariates [27]. This is the first study to evaluate the pharmacokinetics of OS in pregnant women based on pop PK approach. In this study, the plasma concentration–time profile of OC fitted well with a one compartment model with first order absorption and elimination. In order to avoid any erroneous covariate vs. parameter relationship, a parsimonious approach ($P < 0.001$) was used for the identification of significant covariates in the initial covariate screening. The significant covariate identified in this study was pregnancy. Population pharmacokinetic analysis indicates that pregnant women exhibit approximately 43% higher clearance (CL/F) with a corresponding decrease (~30%) in exposure (AUC) of OC compared with non-pregnant women. The magnitude of increase in CL/F of OC for the first, second and third trimester of pregnancy was 66%, 45% and 28%, respectively (Figure 3). Since OC is primarily eliminated through renal pathways, the higher clearance of OC during the first trimester could be due to the ~50% increase in renal blood flow and glomerular filtration rate during the first trimester of pregnancy [28]. It should be noted that the number of subjects in the first and third trimester of pregnancy was relatively low. Moreover, the trimester of pregnancy did not influence the pharmacokinetics of OS in this model. Interestingly, our results are in agreement with Greer *et al.* [29] that the trimester of pregnancy does not significantly affect the pharmacokinetics of OS during pregnancy.

In conclusion, both non-compartmental and pop PK approaches suggest that approximately 30% decrease in exposure to OC during pregnancy. Additionally, the trimester of pregnancy does not affect the pharmacokinetics of OS. In order to attain comparable systemic exposure with non-pregnant women, the currently recommended doses of OS may need to be increased (105 mg once daily for prophylaxis and 105 mg twice daily for treatment of influenza infections) in pregnant women.

There is a lack of clinical evidence that supports OC exposure (AUC) and influenza viral suppression in humans. Considering a large variability in effective concentration that inhibits 90% of viral activity (0.004 to $>100 \mu\text{M}$; 1.14 ng mL^{-1} to $>24800 \text{ ng mL}^{-1}$; www.fda.gov), emerging strains of influenza viruses, OS resistant cases, and the complications associated with influenza infections during pregnancy, we suggest a pharmacokinetic guided approach to increase the dose of OS in the pregnant population in order to achieve comparable exposure with that of non-pregnant women. However, additional pharmacodynamic studies are necessary to support the dosing guidelines of OS during pregnancy.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.or/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work and no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. K.H. was working with Roche Pharmaceuticals in the previous 3 years. There are no other relationships or activities that could appear to have influenced the submitted work.

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Pharmacokinetics of oseltamivir: an oral antiviral for the treatment and prophylaxis of influenza in diverse populations

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Influenza is a transmissible viral pathogen that continues to cause substantial morbidity and mortality. Oseltamivir is an orally administered antiviral medication that selectively inhibits the influenza neuraminidase enzymes that are essential for viral replication. Treatment of infected children ≥ 1 year and adults of all ages may decrease the severity and duration of the symptoms of infection, while prophylactic dosing can prevent their onset. Oseltamivir is ingested in the form of a prodrug (oseltamivir phosphate) that is rapidly converted by hepatic esterases into the active metabolite, oseltamivir carboxylate. Oseltamivir carboxylate has high bioavailability and penetrates sites of infection at concentrations that are sufficient to inhibit viral replication. The pharmacokinetics of oseltamivir and oseltamivir carboxylate are dose proportional after repeated doses of up to 500 mg twice daily. This predictable profile means that oseltamivir is suitable for use in diverse patient populations, which may include young children and elderly patients, various ethnic groups and those with renal or hepatic impairment. As the potential for drug interactions is low, oseltamivir is also suitable for use in patients with co-morbid conditions who are likely to be receiving concomitant medications.

Keywords: mechanism of action, dosing, drug interactions

Introduction

Influenza is an infectious viral agent that continues to cause considerable morbidity and mortality.¹ The pathogenicity of the influenza virus is now well understood, and this has led to the development of a range of antiviral agents for the treatment and prevention of its debilitating symptoms.² Oseltamivir (Tami-flu®; F. Hoffmann-La Roche Ltd) is an orally administered antiviral for the management of influenza A and B infections in children ≥ 1 year and adults of all ages.³ It is a widely used medication, with global experience now exceeding 65 million treatment courses. For therapeutic use, oseltamivir is taken as a twice-daily regimen for 5 consecutive days, while for prophylaxis it is taken on a once-daily schedule for up to 42 days.³ Adults take oseltamivir at a standard dose of 75 mg, while children receive unit doses that are selected on the basis of body weight.³ Oral capsule (35, 40 and 75 mg) and suspension formulations are now readily available.³

Oseltamivir is ingested in the form of an oral prodrug (oseltamivir phosphate; OP) that is rapidly metabolized to the active form, oseltamivir carboxylate (OC) (Figure 1).⁴ In infected patients, OC binds to and inhibits the active site of the neuraminidase enzymes that are present on all influenza viruses and are essential for the release of progeny virions from infected host cells (Figure 2).² In this way, OC can reduce viral replication, which in turn can limit the viral load and course of infection in

the host. When started within 48 h of the onset of illness, this action can limit the severity and duration of the symptoms of influenza and the risk of associated complications, such as bronchitis, pneumonia and otitis media.² Symptomatic illness can also be prevented with prophylactic administrations.²

Since the active site of the neuraminidase enzyme is highly conserved, oseltamivir has activity against all of the neuraminidase subtypes so far tested *in vitro*.⁵ These include the neuraminidases of human seasonal viruses, avian viruses and pandemic viruses,⁵ including the newly emergent pandemic (H1N1) 2009 virus.⁶ A variety of laboratory strains and clinical isolates have shown susceptibility to OC, with 50% inhibitory concentrations (IC₅₀s) ranging from 0.01 to 69.2 nM, depending on the influenza strain (Table 1).^{5,7–9} To place this in context, the average minimum plasma concentration of OC achieved with the twice-daily treatment regimen at the standard 75 mg dose is ~ 330 nM.⁴ Importantly, OC is highly selective for influenza neuraminidase, and shows little or no activity against neuraminidases of other viruses, bacteria or human liver microsomes.¹⁰

Pharmacokinetics of oseltamivir and OC

To effectively limit viral replication and the viral load, therapeutic concentrations of OC must be achieved at all sites of infection and maintained for the duration of the dosing interval. For this

reason, the pharmacokinetic profiles of oseltamivir and OC have been extensively studied in healthy volunteers and infected patients. Inter- and intra-subject variability across different demographic populations has also been widely investigated.

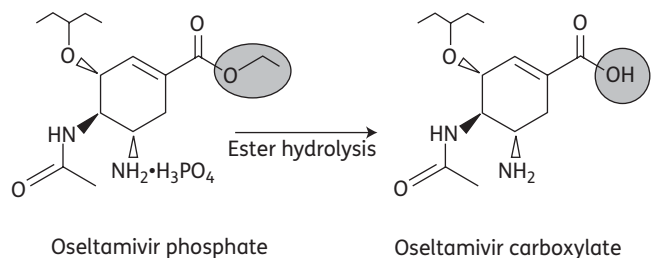


Figure 1. Structures of oseltamivir phosphate (prodrug) and oseltamivir carboxylate (active metabolite).

Absorption, distribution, metabolism and elimination

Following oral administration of OP, oseltamivir is rapidly absorbed from the gastrointestinal tract and converted by hepatic esterases into the active metabolite OC, giving an absolute bioavailability of ~80%.^{4,11} OC is detectable in plasma within 30 min of dosing, and concentrations reach near-maximal levels after 3–4 h, exceeding oseltamivir concentrations by >20-fold.^{4,11} OC plasma concentrations display minimal inter- and intra-subject variability, and concomitant food intake has little effect on bioavailability.^{4,11} The absorption rate of oseltamivir is unaffected under conditions of altered gastric pH, such as that induced by cimetidine and antacids.^{4,11}

The volume of distribution of OC after intravenous administration in man is 23–26 L.^{4,11} This value is similar to the extracellular volume of body water in humans, suggesting that the metabolite may penetrate infection sites at concentrations similar to those in plasma. Indeed, oseltamivir and OC are systemically distributed, with therapeutic concentrations attained in the lung, trachea and nasal mucosa,⁴ as well as the sinuses

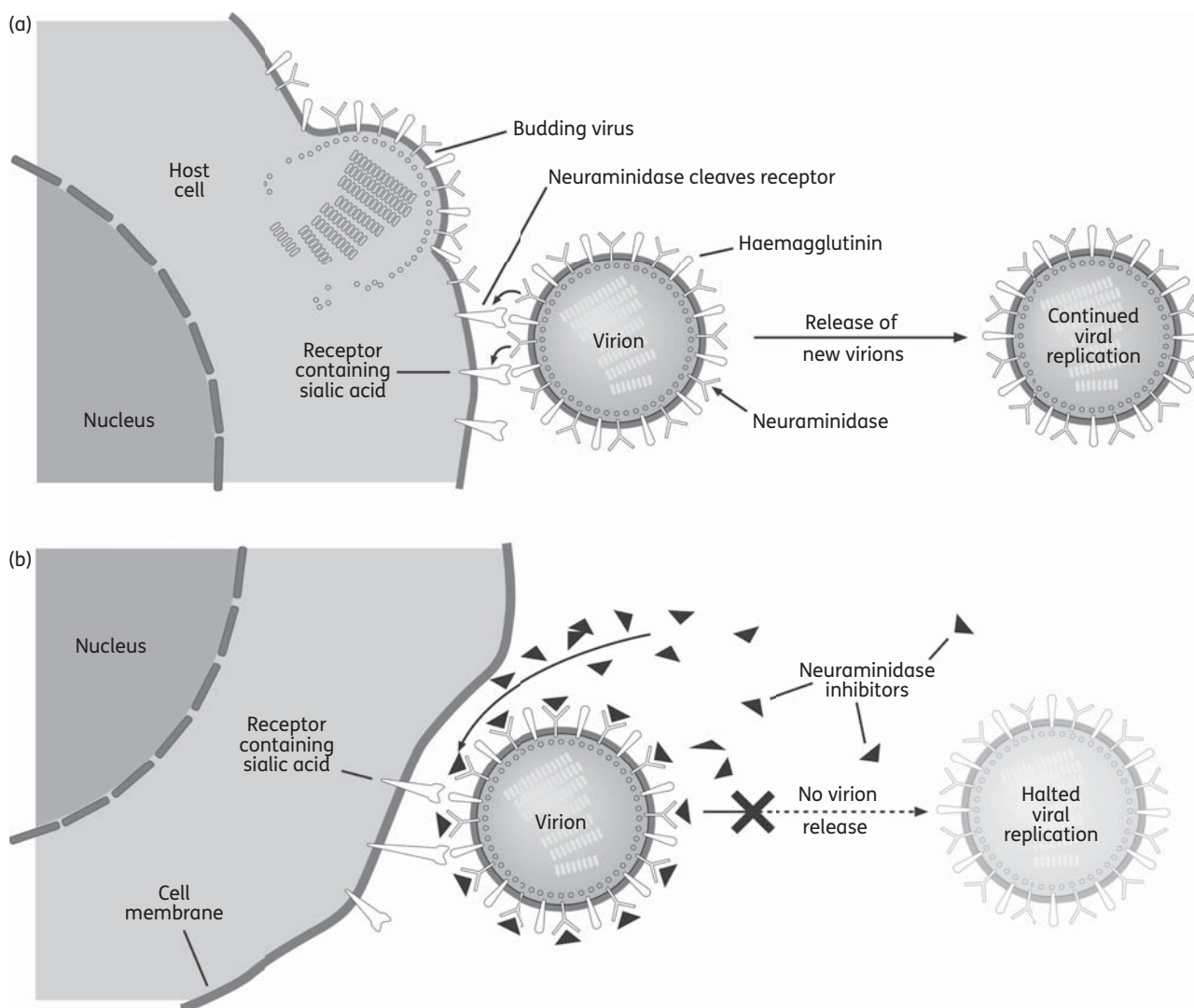
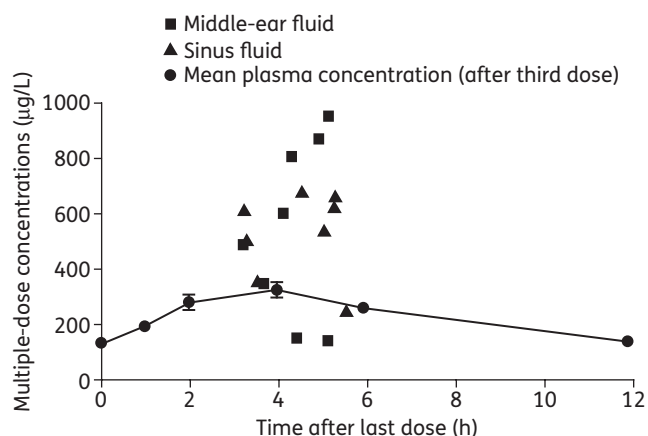


Figure 2. Influenza virus replication in (a) the absence and (b) the presence of neuraminidase inhibitors. Reproduced from Moscona² with permission.

Table 1. Inhibitory concentrations (IC₅₀s) of oseltamivir carboxylate against different neuraminidase subtypes *in vitro*^{5,7–9}

Virus subtype	IC ₅₀ (nM)	Virus subtype	IC ₅₀ (nM)
H1N1	0.7 ⁸ –2.2 ⁸	H6N5	33.2 ⁹
H1N9	0.3 ⁵	H7N2	2.7 ⁹
H2N2	0.3 ⁵ –9.0 ⁷	H7N7	4.4 ⁹
H2N3	0.01 ⁸ –3.3 ⁹	H8N4	0.4 ⁵ –47.0 ⁹
H3N2	0.2 ⁸ –0.6 ⁸	H9N2	1.9 ⁹ –15.0 ⁷
H3N8	0.8 ⁵	H10N7	0.8 ⁵ –8.2 ⁹
H4N6	0.4 ⁵ –3.2 ⁹	H10N8	29.7 ⁹
H4N8	69.2 ⁹	H11N9	9.5 ⁹ –17.7 ⁹
H5N1	7.0 ⁷	H12N5	1.5 ⁵
H5N3	2.9 ⁹	H13N6	4.9 ⁹
H6N1	36.1 ⁹	H14N5	36.8 ⁹
H6N2	0.84 ⁸	B	1.7 ⁵ –24.3 ⁸

**Figure 3.** Concentration–time curves for oseltamivir carboxylate in plasma, middle ear and sinuses after five twice-daily doses of 75 mg of oseltamivir (*n*=24). Reproduced from Kurowski *et al.*¹² with permission.

and middle ear (Figure 3).¹² Eisenberg *et al.*¹³ also confirmed that OC reached the lung following oral dosing in rats, and was detected in the bronchoalveolar lining fluid with equal or greater exposure to that in plasma and a slower clearance.

At least 75% of an oral dose of the prodrug is converted into OC by first-pass metabolism, and <5% is recovered in urine as OP.^{4,11} Neither oseltamivir nor OC interacts with human cytochrome P450 mixed-function oxidases or glucuronyl transferases *in vitro*. OP and OC are eliminated primarily by renal excretion, but small amounts (<20% of the oral dose) of both compounds are also eliminated in faeces.⁴ Following oral dosing, plasma concentrations of oseltamivir decline rapidly (apparent elimination half-life of 1–3 h), while OC concentrations persist for longer (apparent elimination half-life of 6–10 h), permitting twice-daily dosing. Renal clearance of both compounds exceeds the glomerular filtration rate, indicating that renal tubular secretion contributes to elimination; for OC, this has been shown to proceed via the anionic transport process.^{4,11}

Oseltamivir has shown a high safety margin in acute, sub-acute and chronic toxicity studies.⁴ The pharmacokinetics of

oseltamivir are linear and dose proportional at doses of up to 500 mg twice daily.^{4,11} Only modest accumulation (<2-fold) of OC is noted prior to attainment of steady state. The pharmacokinetics of multiple dose administration can be predicted from those of single dosing and provide no indication of a temporal change in the disposition of either oseltamivir or OC. Steady-state plasma concentrations of OC are achieved within 2–3 days of twice-daily administration.^{4,11} Recently, the pharmacokinetics of high doses of oseltamivir have been examined in healthy Thai volunteers.¹⁴ In a dose-escalation study, 21 individuals received single doses of oseltamivir at four increasing dose levels, giving a total of 125 individual series. Doses of up to 675 mg were well tolerated. Pharmacokinetics were dose-linear, with rapid absorption and conversion (median=93%) into OC. Median [95% confidence interval (CI)] elimination half-lives were 1.0 (0.9–1.1) h for oseltamivir and 5.1 (4.7–5.7) h for OC. One subject repeatedly showed markedly reduced conversion of oseltamivir into OC due to constitutionally impaired carboxylesterase activity.¹⁴

Influence of patient demographics and ethnicity

Overall, there are no clinically relevant differences in the pharmacokinetics of oseltamivir or OC between healthy volunteers and infected patients; this applies in adults of different sexes, ages and weights.¹¹ Equally, ethnicity does not appear to affect the pharmacokinetics of the prodrug or active metabolite. In a study in which healthy Japanese and Caucasian subjects were randomized to 75 or 150 mg of oseltamivir or placebo twice daily for 6 days, with a single dose on day 7, individual and mean pharmacokinetics of oseltamivir and OC were similar between the two groups (Figure 4).¹⁵ Ethnic differences produced no observable effect on individual exposures at steady state. Although a prospective comparison has not been performed in children, data from four separate studies involving 141 Caucasian and 18 Japanese children have been pooled to compare plasma concentrations.¹⁶ After normalization to a 2 mg/kg dose, interquartile ranges for oseltamivir concentration were 3.63–26.75 ng/mL (Caucasian) and 3.95–22.05 ng/mL (Japanese). Results for OC were very similar.

Influence of renal or hepatic impairment

Exposure to OC is increased as a result of decreased renal function, and severe renal insufficiency (creatinine clearance rates of <30 mL/min) is associated with a marked increase in exposure.^{4,17} In this patient group, a reduced treatment dose of 75 mg once daily is recommended.³ Oseltamivir is not recommended for patients with end-stage renal disease (creatinine clearance <10 mL/min).³ *In vitro* experiments indicate that the metabolic pathway of oseltamivir conversion into OC in the liver is unlikely to be appreciably altered in subjects with moderate hepatic impairment.¹⁸ This has been confirmed in a clinical study, and no dose adjustment is recommended for patients with mild to moderate hepatic impairment.¹¹

Influence of age

Exposure to oseltamivir in elderly patients increases in proportion to the usual age-related decline in renal function.^{4,11,19} However,

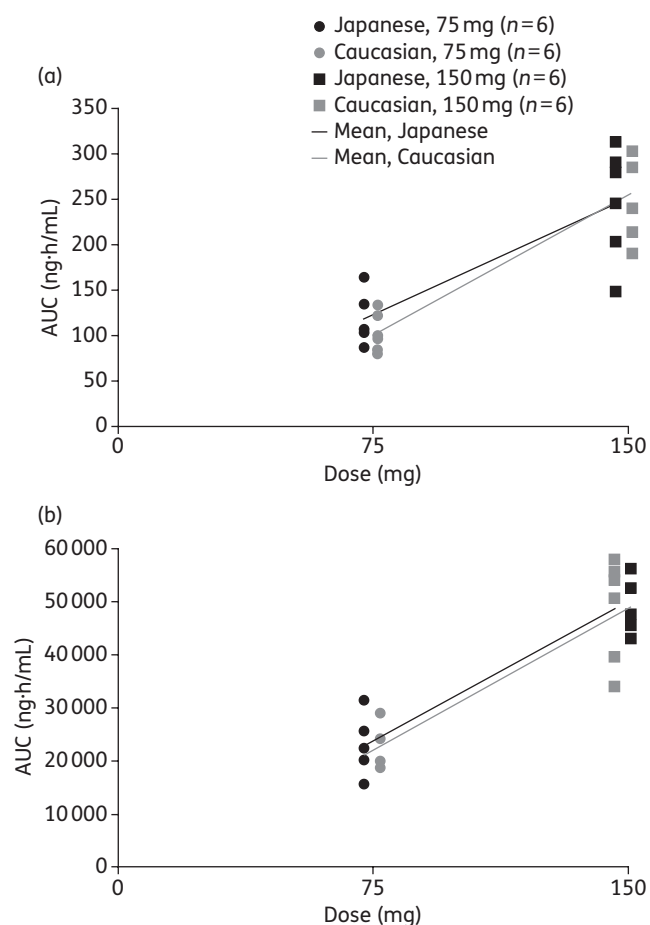


Figure 4. Distribution of the mean and individual values of the area under the concentration-time curves from time 0 to 12 h post-dose (AUC_{0-12}) for (a) oseltamivir and (b) oseltamivir carboxylate following 7 days of treatment with oseltamivir in healthy Caucasian and Japanese adult volunteers. Reproduced from Schentag *et al.*¹⁵ with permission.

as this increase is small relative to the known safety margin, no dose adjustment is necessary. There are no clinically relevant differences in the pharmacokinetics of oseltamivir or OC between healthy children and infected children.²⁰ Clearance of OC increases with increasing body weight, and hence age, and this is particularly apparent when the OC clearance is expressed per kg of body weight. The OC rate of clearance per kg of body weight in children decreases with advancing age, such that exposure in children ≥ 13 years is similar to that in adults.²⁰ Although the range of exposures in children and adolescents ≤ 16 years following a 2 mg/kg oseltamivir dose was within the range that was safe and effective in adults receiving 75 or 150 mg doses twice daily, there was a clear trend towards higher systemic clearance per kg of body weight in younger children. Administration of 2 mg/kg to children in the age range 3–16 years demonstrated a significant downward trend with decreasing age (Figure 5). Therefore, a simple age- and weight-based unit dosing algorithm was developed to ensure exposures in children comparable to those in adults.³ The algorithm is based on a target exposure window and a simple linear regression

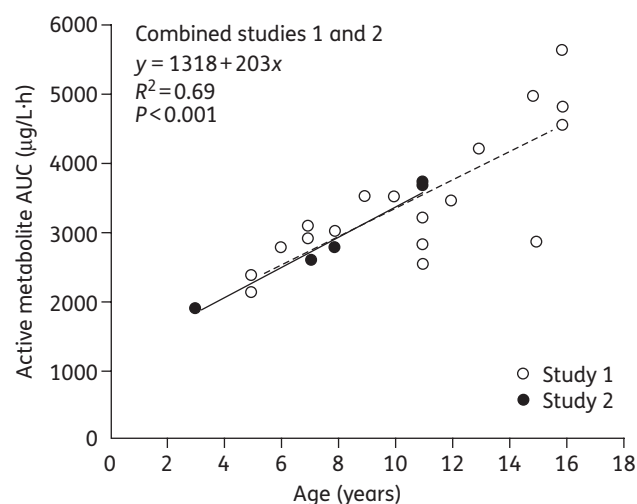


Figure 5. Area under the plasma concentration-time curve (AUC) for oseltamivir carboxylate in children aged 3–16 years administered 2 mg/kg oseltamivir (two pooled studies). The broken line represents the regression line for the open circles (study 1) and the continuous line represents the regression line for the filled circles (study 2). Reproduced from Oo *et al.*²⁰ with permission.

analysis of pharmacokinetic data from children and adolescents following a single 2 mg/kg dose of oseltamivir. The algorithm was shown to maintain drug exposure within the target efficacy/safety window, while also allowing for a convenient dose regimen.²⁰

Drug interactions

Patients with influenza often take over-the-counter medications to ease their symptoms. In addition, many patients with co-morbidities receive concomitant drugs. Drug interactions could adversely affect the pharmacokinetics of the co-administered medications, and thus their efficacy and safety. With this in mind, the potential for clinically relevant interactions between oseltamivir and OC and a variety of commonly used medications has been widely studied.

Oseltamivir has limited potential for clinically relevant interactions with commonly co-administered drugs. When oseltamivir was taken with paracetamol (acetaminophen), plasma concentrations of OC and paracetamol remained unaffected.⁴ Equally, co-administration of aspirin²¹ or antacids²² with oseltamivir had no relevant effect on the pharmacokinetics of these compounds. Further studies indicated that neither cimetidine nor amoxicillin exhibited any interaction with oseltamivir.²³ Furthermore, the latter investigation confirmed that oseltamivir is a weak competitor for the anionic renal tubular secretion processes and that its potential to compete effectively with other organic acids that undergo renal tubular secretion is minimal.²³ Care should be taken with medications with a narrow therapeutic margin that are co-excreted, e.g. methotrexate. In renal transplant patients, co-administration of oseltamivir was shown not to change the pharmacokinetics of the immunosuppressant drugs cyclosporin, mycophenolate mofetil and tacrolimus, and the

pharmacokinetics of oseltamivir itself in these patients were found to be similar to those in patients with native kidneys.²⁴

Several groups have studied the co-administration of oseltamivir and probenecid.^{14,25,26} The ability of probenecid to modify the renal secretion of other drugs has previously been exploited, and its use as a 'sparing agent' to extend oseltamivir supplies in the event of an influenza pandemic has been suggested.^{27,28} In one study, co-administration of oseltamivir and probenecid resulted in an increase of ~2.5-fold in exposure to OC, indicating that tubular secretion of the latter proceeds via the anionic pathway.²³ Although this pathway is shared by some other drugs, clinically relevant interactions are unlikely. A more recent investigation found a mean decrease in the apparent volume of OC distribution of 40% (95% CI, 37%–44%) and mean reduction in renal elimination of 61% (58%–62%), resulting in an increase in the median AUC for OC of 154% (range, 71%–278%).¹⁴

Two groups have recently investigated the pharmacokinetics of oseltamivir/probenecid combinations in more detail.^{25,26} In the first of these, Holodniy *et al.*²⁵ compared the pharmacokinetics of the combination (oseltamivir 75 mg once every 48 h plus probenecid 500 mg four times a day) with oseltamivir alone (75 mg once daily). Oral clearance of OC was found to be ~25% lower with the combination, and 48 h plasma exposure results showed a lack of bioequivalence. However, the mean trough concentrations of OC at the end of a dosing interval in the two groups were not significantly different, suggesting that co-administration of probenecid might allow reduction of oseltamivir dose without compromising neuraminidase inhibition.²⁵ In the second study, Rayner *et al.*²⁶ used a population pharmacokinetic model to simulate combination regimens of oral oseltamivir (45 and 30 mg twice daily) and oral probenecid (500 mg/6 hourly). Probenecid plus 45 mg of oseltamivir achieved all the pharmacokinetic parameters expected of oseltamivir alone, but combination with 30 mg of oseltamivir and dose interval extension approaches did not.²⁶ It is noteworthy, however, that unsuitable oseltamivir/probenecid regimens, or non-compliance with suitable regimens, could increase the risk of emergence of resistant virus via suboptimal dosing. Moreover, co-administration could compromise the systemic distribution of OC, which could be vital in cases of infection with highly pathogenic virus. Alongside the potential for multiple, clinically relevant drug interactions and adverse events with probenecid, the utility of the combination strategy appears to be limited.²⁶

Oseltamivir has not previously been associated with haematological adverse reactions or interference with the coagulation process. However, following sporadic post-marketing reports of bleeding in patients on anticoagulant therapy, the pharmacokinetic interaction between the agents was re-evaluated in 20 patients receiving daily warfarin and with international normalized ratio (INR) values of 2.0–3.5 during the previous 2 weeks.²⁹ These volunteers were randomized to twice-daily 75 mg of oseltamivir for 4 days with a single 75 mg dose on day 5, or warfarin alone in a two-way crossover design separated by a wash-out of 4–8 days. Anticoagulant effects were assessed by calculating overall change (AUEC_{0–96}) and maximum absolute change from baseline ($E_{\max}$) in INR and Factor VIIa, and change in vitamin K1 concentrations. For both treatments, changes from baseline in INR and Factor VIIa during treatment were small and there were also no statistically significant differences between treatments in mean $E_{\max}$ for INR and Factor VIIa, or in the change

from baseline in vitamin K1 concentration. Oseltamivir did not alter warfarin pharmacokinetics. Oseltamivir was well tolerated in this population, with no adverse safety findings.²⁹

Conclusions

Oseltamivir is an orally administered antiviral for the treatment and prophylaxis of influenza A and B infections in adults and children aged ≥ 1 year. After dosing, the prodrug (OP) is readily absorbed from the gastrointestinal tract and rapidly converted into the active metabolite, OC. In all patient groups, OC has high bioavailability and is systemically distributed to infection sites at concentrations sufficient to inhibit a range of influenza virus neuraminidases. Oseltamivir has a predictable linear pharmacokinetic profile and is suitable for a variety of patient populations and age groups. The potential for clinically relevant drug interactions is low. These characteristics underpin the use of oseltamivir in the diverse patient populations that are likely to be affected by seasonal and pandemic influenza viruses.

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Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials



Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto

Summary

Background Despite widespread use, questions remain about the efficacy of oseltamivir in the treatment of influenza. We aimed to do an individual patient data meta-analysis for all clinical trials comparing oseltamivir with placebo for treatment of seasonal influenza in adults regarding symptom alleviation, complications, and safety.

Methods We included all published and unpublished Roche-sponsored randomised placebo-controlled, double-blind trials of 75 mg twice a day oseltamivir in adults. Trials of oseltamivir for treatment of naturally occurring influenza-like illness in adults reporting at least one of the study outcomes were eligible. We also searched Medline, PubMed, Embase, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov trials register for other relevant trials published before Jan 1, 2014 (search last updated on Nov 27, 2014). We analysed intention-to-treat infected, intention-to-treat, and safety populations. The primary outcome was time to alleviation of all symptoms analysed with accelerated failure time methods. We used risk ratios and Mantel-Haenszel methods to work out complications, admittances to hospital, and safety outcomes.

Findings We included data from nine trials including 4328 patients. In the intention-to-treat infected population, we noted a 21% shorter time to alleviation of all symptoms for oseltamivir versus placebo recipients (time ratio 0.79, 95% CI 0.74–0.85; $p < 0.0001$). The median times to alleviation were 97.5 h for oseltamivir and 122.7 h for placebo groups (difference –25.2 h, 95% CI –36.2 to –16.0). For the intention-to-treat population, the estimated treatment effect was attenuated (time ratio 0.85) but remained highly significant (median difference –17.8 h). In the intention-to-treat infected population, we noted fewer lower respiratory tract complications requiring antibiotics more than 48 h after randomisation (risk ratio [RR] 0.56, 95% CI 0.42–0.75; $p = 0.0001$; 4.9% oseltamivir vs 8.7% placebo, risk difference –3.8%, 95% CI –5.0 to –2.2) and also fewer admittances to hospital for any cause (RR 0.37, 95% CI 0.17–0.81; $p = 0.013$; 0.6% oseltamivir, 1.7% placebo, risk difference –1.1%, 95% CI –1.4 to –0.3). Regarding safety, oseltamivir increased the risk of nausea (RR 1.60, 95% CI 1.29–1.99; $p < 0.0001$; 9.9% oseltamivir vs 6.2% placebo, risk difference 3.7%, 95% CI 1.8–6.1) and vomiting (RR 2.43, 95% CI 1.83–3.23; $p < 0.0001$; 8.0% oseltamivir vs 3.3% placebo, risk difference 4.7%, 95% CI 2.7–7.3). We recorded no effect on neurological or psychiatric disorders or serious adverse events.

Interpretation Our findings show that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting.

Funding Multiparty Group for Advice on Science (MUGAS) foundation.

Introduction

Neuraminidase inhibitors were developed in the 1990s as a novel approach to prophylaxis and treatment of influenza.¹ Zanamivir and oseltamivir selectively block the conserved enzymatic activity of all influenza viruses, making them useful in prophylaxis and treatment for both seasonal and pandemic disease.^{2–4} The oral drug oseltamivir has received more attention, especially regarding pandemic preparedness.⁵ The drug was widely used for treatment during the 2009 influenza pandemic. However, questions persist about the efficacy of oseltamivir, with some investigators even suggesting that the drug has no antiviral effect.⁶ Concerns also exist about the drug's adverse effects and whether these outweigh the benefits. Such conclusions arose in a meta-analysis based on clinical trial study reports rather than individual patient data.⁶

To explore these issues further, we did a meta-analysis of all available randomised treatment trials of oseltamivir in adults. Our meta-analysis is the first to use individual patient data and includes both published and unpublished trials thereby overcoming previous concerns regarding potential publication bias. We focused on both intention-to-treat analyses and analyses restricted to individuals with documented influenza infection. We assessed possible side effects of oseltamivir and the incidence of complications.

Methods

Search strategy and selection criteria

We included all published and unpublished Roche-sponsored randomised placebo-controlled, double-blind trials of oseltamivir treatment in adult influenza.^{7–12} Individual patient data were provided by Roche by use of

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	Intention to treat infected					Intention to treat				
	Oseltamivir N	Placebo N	Estimates of median time and their difference (h)			Oseltamivir N	Placebo N	Estimates of median time and their difference (h)		
			Oseltamivir	Placebo	Difference			Oseltamivir	Placebo	Difference
M76001	681	355	96.3	120.5	-24.2	933	473	97.7	114.7	-17.1
WV15819_876_978	223	254	150.0	174.9	-24.9	358	375	139.2	149.0	-9.8
WV15670	157	161	87.4	116.5	-29.1	240	235	97.6	116.1	-18.5
WV15812_872	118	133	151.5	161.0	-9.5	199	202	143.0	163.0	-20.0
JV15823	121	130	70.0	93.3	-23.3	152	158	63.1	81.8	-18.6
WV15671	121	128	71.5	103.3	-31.7	204	200	76.3	97.0	-20.7
WV16277	119	109	80.3	99.3	-19.0	226	225	88.8	100.3	-11.5
WV15730	19	19	78.2	143.9	-65.8	31	27	74.5	109.8	-35.3
WV15707	6	6	53.3	31.3	22.0	17	9	88.8	56.2	32.7
Overall*	1565	1295	97.5	122.7	-25.2 (-36.2 to -16.0)	2360	1904	99.4	117.2	-17.8 (-27.1 to -9.3)

*Medians and differences in medians for individual trials are from Kaplan-Meier estimates. The overall estimated medians, differences (and 95% CI) are from the accelerated failure time model adjusted for trial.

Table 1: Estimates of median time to alleviation of all symptoms by treatment group in the intention-to-treat infected and intention-to-treat populations, both overall and for each trial

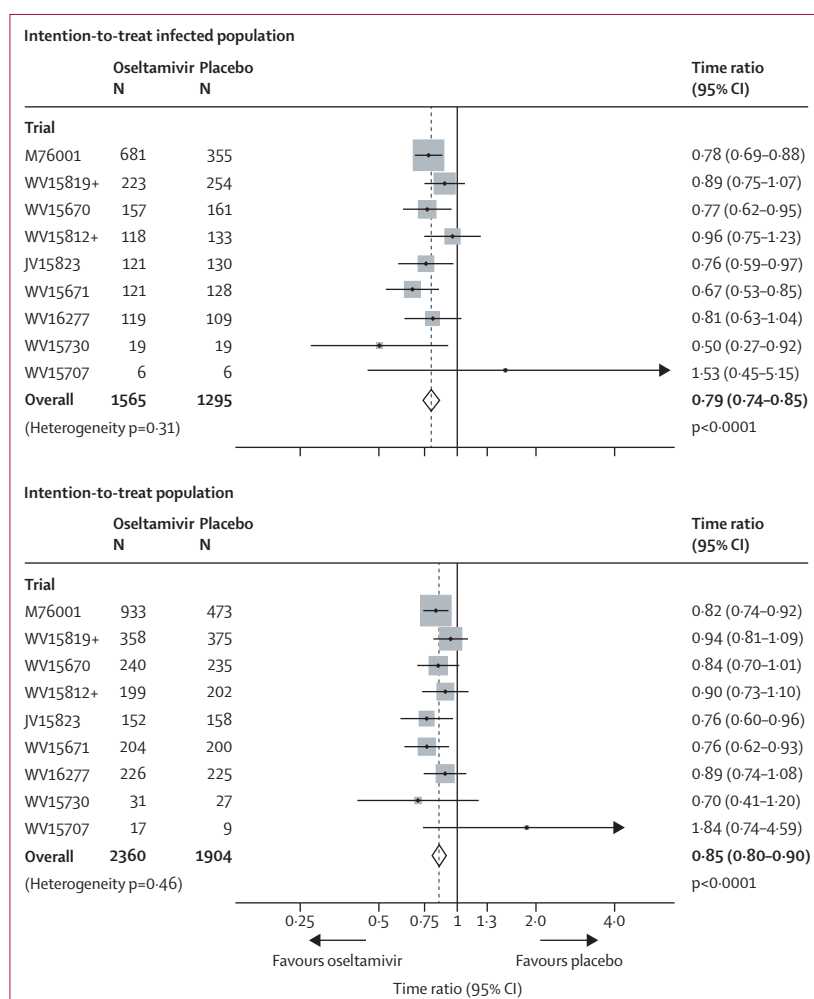


Figure 1: Fixed effect meta-analysis for time to alleviation of all symptoms
The overall time ratio is calculated from an accelerated failure time model adjusted for trial.

secure web-access. Roche provided data clarifications but had no involvement in the design, conduct, or reporting of the meta-analysis. All trials satisfied relevant good clinical practice criteria, with approval from ethics committees and regulatory authorities. Furthermore, data quality was assured by thorough data audits by the US Food and Drug Administration (FDA). Additionally, we searched Medline (and PubMed), Embase, the Cochrane Central Register for Controlled Trials, and the ClinicalTrials.gov trials register for other relevant trials published before Jan 1, 2014 (appendix pp 1–2). We incorporated all trials of treatment in adults included in a previous meta-analysis plus one additional trial (JV15823).⁶ We excluded a Chinese treatment trial in adults because individual patient data were not available.¹³ We also excluded one very small trial in adults and children (n=19).¹⁴ After extensive searches by both Jefferson and colleagues⁶ and ourselves, no other adult trials of oseltamivir treatment were identified.

Study design

The nine trials were done between 1997 and 2001. Eligible participants were within 36 h of feeling unwell, with a fever ($\geq 38^{\circ}\text{C}$ if aged <65 years, $\geq 37.5^{\circ}\text{C}$ if aged ≥ 65 years), and with at least two influenza symptoms (one respiratory: cough, sore throat or coryza; and one constitutional: headache, myalgia, sweats or chills, or fatigue). Participants received oseltamivir or placebo for 5 days at 12 h intervals. Total follow-up was 21 days. Recruitment began upon detection of a local influenza outbreak. Participants received the first dose of the randomised study drug during their enrolment clinic visit. Participants were subsequently identified as influenza-infected by a positive culture from a nasal or throat swab (viral shedding at baseline or during follow-up) or four-fold or greater increase from baseline in antibody titre (trial definition). In some trials, virus culture was not done at all centres (in these centres

influenza infection was based on antibody titre rise only). We focused on 75 mg twice a day of oseltamivir because this is the standard prescribed dose.

Efficacy analyses were first for participants getting at least one dose of study drug and who were identified as influenza-infected (intention-to-treat infected population), and then repeated for the intention-to-treat population, which included all treated participants. Both these population definitions were those used in the individual trials. A few participants (18 in the oseltamivir group and 12 in the placebo group) were excluded because they received no study drug and had no follow-up data. Main analyses were also repeated in the intention-to-treat-not infected population. Safety analyses were by treatment received and in participants taking at least one dose of study drug (safety population). Follow-up was from first study drug intake, as was done in individual trial reports. For brevity we refer to randomisation as time of randomisation and first study drug intake were very similar.

Outcomes

The primary outcome was time to alleviation of all symptoms. Seven influenza symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches, and chills or sweats) were scored as absent, mild, moderate, or severe. Alleviation was defined to arise when all symptoms scored as absent or mild, and remained so for at least 21·5 h.

The main complication was lower respiratory tract complication more than 48 h after randomisation requiring antibiotics (preferred terms containing “bronchitis”, “pneumonia”, “lower respiratory tract infection”). Lower respiratory tract complications requiring antibiotics might better represent clinically relevant disease, and oseltamivir would be unlikely to affect lower respiratory tract complications before 48 h. The 48 h cut-off was previously used in some of the individual trial reports. Sensitivity analyses included complications occurring before 48 h. Participants taking antibiotics at baseline were excluded. Diagnosis of complications was based on participant report and the investigator’s clinical judgment. No diagnostic tests were needed. We also analysed admittance to hospital for any cause from randomisation as an indicator of complications.

Safety outcomes included death, treatment withdrawals, treatment withdrawals due to adverse events, all adverse events, serious adverse events, adverse events by body system class (including psychiatric disorders and neurological disorders), and preferred terms nausea, vomiting, and diarrhoea.

Statistical analyses

In view of the similar study designs of the trials, we used fixed-effect methods of meta-analysis. We noted little statistical heterogeneity, and sensitivity analyses with random effect methods for key findings gave very similar results. For time to alleviation of all symptoms, we

initially assessed Kaplan-Meier plots by treatment group and we obtained a treatment effect estimate (time ratio) from a log-logistic accelerated failure time model adjusted for trial.¹⁵ We did not use proportional hazards models because non-proportionality of hazards was evident. We estimated treatment difference in median time to alleviation of symptoms adjusted for trial along with a bootstrap confidence interval (2000 repetitions, stratified by trial and treatment group).

We assessed statistical heterogeneity in time ratios across trials by a likelihood ratio test. As a sensitivity analysis, separate accelerated failure time models were fitted for each trial and log time ratios were meta-analysed with inverse-variance weighting. We did pre-specified exploratory subgroup analyses for age, high-risk participants, time from symptom onset to randomisation, virus type, and total baseline symptom score. We did likelihood ratio tests of interaction.

We explored the difference between treatment groups in the pooled Kaplan-Meier estimates of the proportions with alleviation of all symptoms at 12 h, 24 h, then every 24 h to establish when a significant difference became apparent.

See Online for appendix

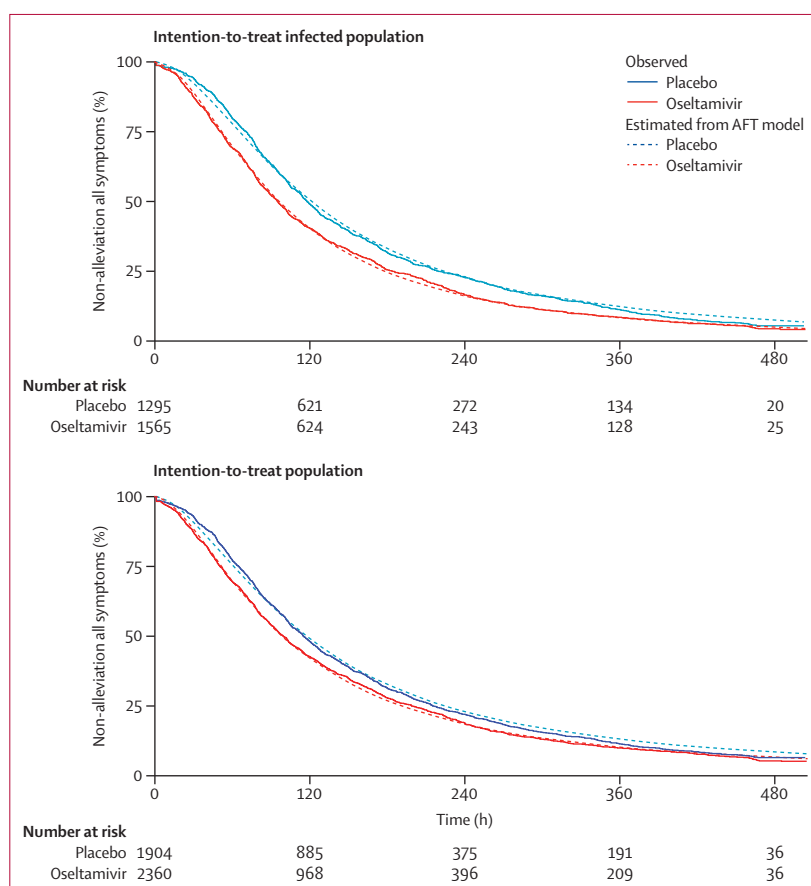


Figure 2: Overall Kaplan-Meier curves and estimated survival curves from AFT model (adjusted for trial) by treatment group for time to alleviation of all symptoms in all trials combined
AFT=accelerated failure time.

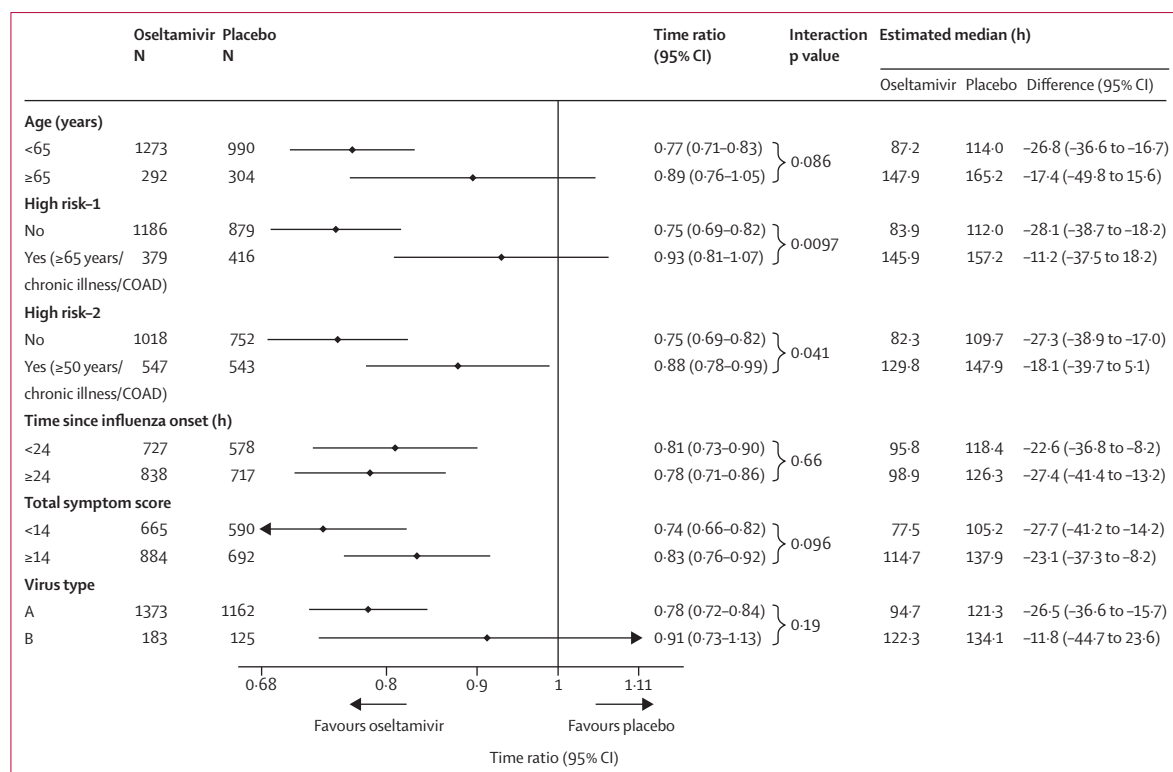


Figure 3: Subgroup analyses for time to alleviation of all symptoms in the intention-to-treat infected population

COAD=chronic obstructive airways disease. Estimated median (h)=estimated median time to alleviation of all symptoms from accelerated failure time model adjusted for trial. Diff (95% CI)=the difference in the estimated medians with bootstrap 95% CI.

Binary outcomes (eg, complications and adverse events) were meta-analysed with risk ratios and a Mantel-Haenszel fixed effect approach without continuity correction.^{16,17} We excluded trials with no events in both groups and did χ^2 tests of heterogeneity. To obtain an overall risk difference, we applied the overall risk ratio (and 95% CI) to the pooled placebo group risk to calculate a risk difference and 95% CI.^{17,18} Exploratory subgroup analysis for the lower respiratory tract complication outcome used inverse-variance weighting to assess heterogeneity between subgroups.

For complication and adverse event outcomes, we excluded events arising beyond 28 days after randomisation. We analysed adverse events separately for on treatment and off treatment periods. On treatment was defined as up to 2 days after the last dose of study drug. For psychological and neurological disorders, we did a sensitivity analysis in participants infected with influenza only because these events might be directly related to influenza symptoms. Additionally, the two trials with a 150 mg twice a day oseltamivir dose compared with placebo were included to investigate potential associations between dose and response. For nausea and vomiting, we also did separate analyses for influenza-infected and non-influenza infected participants.

Because post-baseline data was used in the definition of influenza infection, we repeated efficacy analyses for

participants who were influenza-infected on the basis of viral shedding at baseline only. All analyses used Stata version 13.1.

Role of the funding source

The meta-analysis was funded by the Multiparty Group for Advice on Science (MUGAS) who assembled a multidisciplinary team to examine the overall data from trials of oseltamivir in adults. The team agreed an individual patient data analysis was the most robust approach, and to cover the costs the MUGAS Board applied for an unrestricted grant from Roche. This unrestricted grant stipulates that Roche would not be involved in the actual review process in any way other than providing the requested data dictionaries and datasets. The results were not shared with Roche until the analysis was completed. The London School of Hygiene & Tropical Medicine received a grant from MUGAS to partly fund Joanna Dobson's salary while she worked on this project. RJW and AMS received travel expenses from MUGAS for investigator meetings in London.

Results

In the intention-to-treat population 2402 participants were randomly assigned to receive 75 mg oseltamivir twice a day and 1926 to placebo (one trial had 2:1 randomisation). Of these, 1591 (66%) in the oseltamivir

group and 1302 (68%) in the placebo group were influenza-infected constituting the intention-to-treat infected population. The appendix shows characteristics of the nine included trials (appendix p 3). Most participants had influenza virus type A (2558/2893 [88%]); A-H3N2 was the main strain (appendix p 4). The safety population comprised 2401 participants on oseltamivir and 1917 on placebo. Two trials (protocol numbers WV15819_876_978 and WV15707) were in elderly participants (≥ 65 years), and one was in participants with chronic cardiac or respiratory disease or both (WV15812_872). Three trials did not meet planned recruitment targets but were still included (WV16277, WV15730, and WV15707). Baseline characteristics were balanced between treatment groups for each trial (appendix p 5).

64 (1.5%) of 4328 participants were missing time to alleviation of all symptoms. The median time to alleviation of symptoms in the placebo group varied across trials (table 1) and was longer in the trials with participants with chronic illnesses and in elderly people. In the intention-to-treat infected population, there was a 21% shorter time to alleviation of all symptoms for oseltamivir compared with placebo (time ratio 0.79, 95% CI 0.74–0.85; $p < 0.0001$; figure 1). Across all trials, the estimated median time to alleviation of all symptoms was 97.5 h for oseltamivir, 122.7 h for placebo (difference -25.2 h, 95% CI -36.2 to -16.0). In the intention-to-treat population, the estimated time reduction attenuated to 15% but remained highly significant (time ratio 0.85, 95% CI 0.80–0.90; $p < 0.0001$). The treatment difference in median time to symptom alleviation became -17.8 h (95% CI -27.1 to -9.3). The accelerated failure time model provided a good fit to the data (figure 2). Sensitivity analyses with a two-stage meta-analysis method produced similar results (data not shown). We noted no heterogeneity in time ratios across trials (interaction $p = 0.31$ [intention-to-treat infected], $p = 0.46$ [intention-to-treat]). In the intention-to-treat-not infected population, the estimated time ratio was close to unity (time ratio 0.99, 95% CI 0.88–1.12; $p = 0.91$), so only participants identified as influenza-infected benefited from oseltamivir.

In exploratory analyses with pooled Kaplan-Meier estimates of percentage without symptoms, a marked treatment difference emerged by 24 h after randomisation (intention-to-treat infected: difference 5.2%, 95% CI 3.4–7.0; $p < 0.0001$; intention-to-treat: difference 4.6%, 95% CI 3.1–6.2; $p < 0.0001$).

Figure 3 shows exploratory subgroup analyses for time to alleviation of all symptoms in the intention-to-treat infected population. The time ratio of oseltamivir versus placebo recipients was attenuated for high-risk participants (≥ 65 years or in chronic illness trial or chronic obstructive airways disease at baseline; interaction $p = 0.0097$). Findings of an alternative high-risk subgroup analysis, with participants aged 50 to 64 years also as high risk, were supportive of this finding.

For age, time from influenza onset, total symptom score, and virus type, we noted no heterogeneity in time ratios.

In the intention-to-treat infected population, we recorded a lower respiratory tract complication arising after 48 h after randomisation requiring antibiotics in 65 (4.2%) of 1544 participants given oseltamivir and 110 (8.7%) of 1263 participants given placebo (figure 4). An estimated 44% reduction in risk of lower respiratory tract complications was attributable to oseltamivir treatment (RR 0.56, 95% CI 0.42–0.75; $p = 0.0001$), with absolute risk difference of -3.8% (95% CI -5.0 to -2.2). Components of this outcome were 56 (3.6%) versus 87 (6.9%) bronchitis, nine (0.6%) versus 21 (1.7%) pneumonia, and one (0.1%) versus four (0.3%) lower respiratory tract infection in oseltamivir and placebo groups, respectively. Risk ratios for pneumonia and bronchitis were 0.40 (95% CI 0.19–0.84; $p = 0.015$) and 0.62 (95% CI 0.45, 0.85; $p = 0.0030$), respectively. In the intention-to-treat population, 105/2330 (4.5%) oseltamivir and 147/1872 (7.9%) placebo subjects experienced a lower

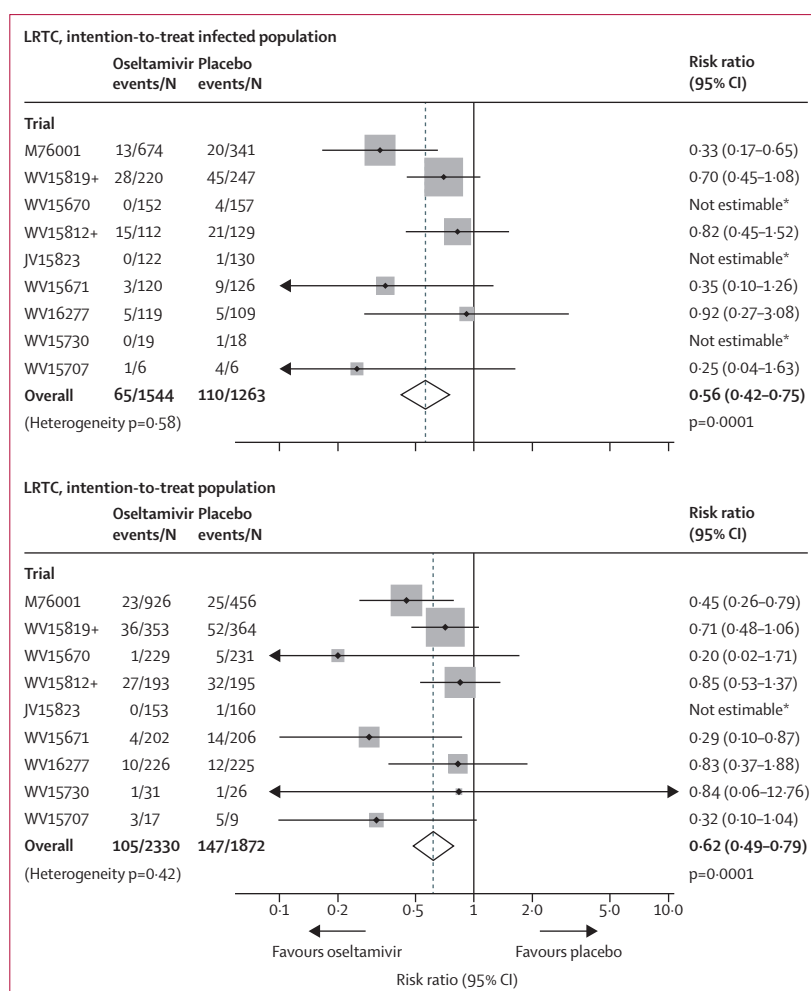


Figure 4: LRTC, intention-to-treat infected, and intention-to-treat population

LRTC=lower respiratory tract complications. Events=number of participants who had one or more events. *No events in oseltamivir group. The trial still contributes to the overall estimates.

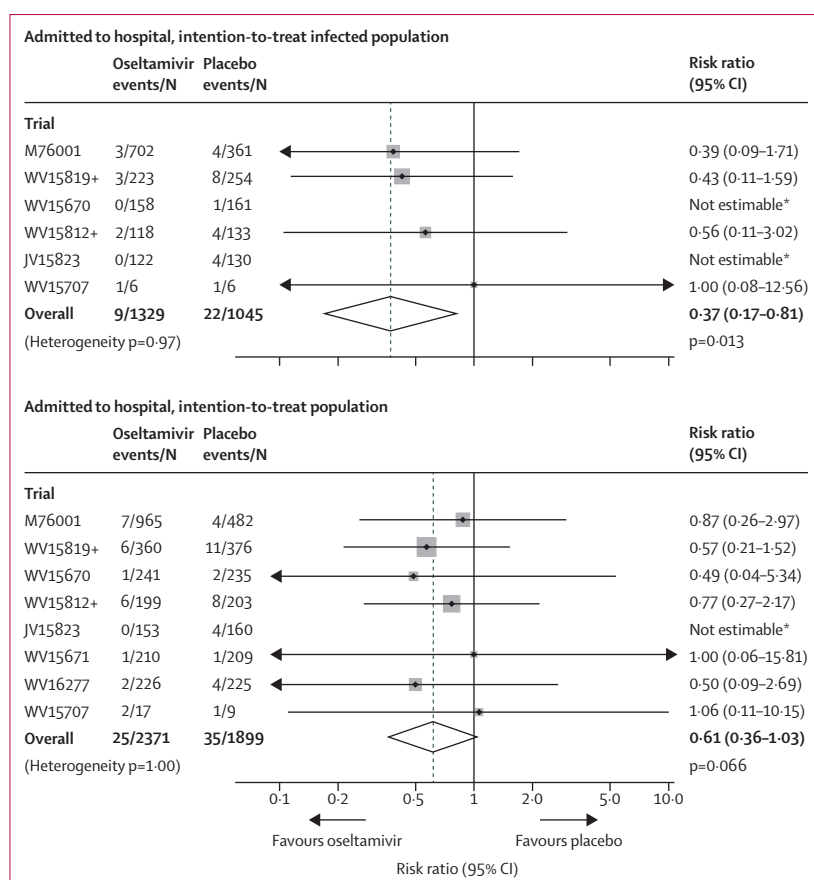


Figure 5: Admittance to hospital, intention-to-treat infected, and intention-to-treat population
 Events=number of participants who had one or more events. *No events in oseltamivir group. The trial still contributes to the overall estimates.

respiratory tract complication with risk ratio attenuated to 0.62, 95% CI 0.49, 0.79; $p=0.0001$; risk difference: -3.0% , 95% CI -4.0 to -1.7 . For pneumonia and bronchitis the intention-to-treat risk ratios became 0.34 (95% CI 0.18–0.64; $p=0.0009$, 13 [0.6%] vs 32 [1.7%]) and 0.71 (95% CI 0.54–0.93; $p=0.011$, 90 [3.9%] vs 111 [5.9%]), respectively. We noted no effect on lower respiratory tract complications in the intention-to-treat-not infected population (RR 0.82, 95% CI 0.53–1.26; $p=0.36$). We recorded no statistical heterogeneity across trials.

An exploratory subgroup analysis of lower respiratory tract complications in the intention-to-treat infected population had a relative risk of 0.70 (95% CI 0.49–0.98) in high-risk participants (45/371 in the oseltamivir group vs 72/403 in the placebo group) versus 0.39 in others (95% CI 0.23–0.66; 20/1173 in the oseltamivir group vs 38/860 in the placebo group; interaction $p=0.070$).

The addition of lower respiratory tract complications starting before 48 h (intention-to-treat infected: extra 15/1544 vs 13/1263; intention-to-treat: extra 26/2330 vs 19/1872) attenuated the risk ratios for both intention-to-treat infected and intention-to-treat populations but they remained highly significant (intention-to-treat infected:

RR 0.61, 95% CI 0.47–0.79; $p=0.0002$; intention-to-treat: RR 0.68, 95% CI 0.55–0.85; $p=0.0005$).

A sensitivity analysis for time to alleviation of all symptoms, restricting analysis to participants who were influenza-infected on the basis of viral shedding at baseline only gave an estimated time ratio similar to that in the intention-to-treat infected analysis (time ratio 0.77, 95% CI 0.71–0.84; $p<0.0001$). We noted similar results for lower respiratory tract complications (RR 0.59, 95% CI 0.40–0.88; $p=0.0089$).

In the intention-to-treat infected population, nine (0.6%) of 1591 participants had to be admitted to hospital for any cause versus 22 (1.7%) of 1302 participants given placebo (figure 5), an estimated 63% risk reduction (RR 0.37, 95% CI 0.17–0.81; $p=0.013$) with risk difference of -1.1% (95% CI -1.4 to -0.3). In the intention-to-treat population, the risk ratio attenuated and was no longer statistically significant (25/2402 oseltamivir vs 35/1926 placebo; RR 0.61, 95% CI 0.36–1.03; $p=0.066$). In the intention-to-treat-not infected population, the estimated risk ratio was close to unity (16/811 oseltamivir vs 13/624 placebo; RR 1.01, 95% CI 0.47–2.15; $p=0.99$). The causes of admittance to hospital covered many disorders with no discernible pattern (data not shown). Seven participants were admitted to hospital because of pneumonia (two in the oseltamivir group and five in the placebo group) in the intention-to-treat infected population. We noted no statistical heterogeneity across trials. One participant on placebo and not influenza-infected died because of respiratory failure.

Table 2 shows key findings for on treatment adverse events (appendix p 6 shows all adverse events and appendix p 7 shows serious adverse events and cardiac disorders). We noted highly significant excesses on oseltamivir for nausea, vomiting, and all gastrointestinal disorders. By contrast oseltamivir had significantly less diarrhoea, infections and infestations, and respiratory, thoracic and mediastinal disorders. Participants given oseltamivir had fewer cardiac disorders, and more injury and poisoning than did those given placebo, but numbers of events were small. We noted no discernible cause-specific pattern in cardiac disorders and only three participants (one in the oseltamivir group and two in the placebo group) had cardiac disorders deemed serious adverse events. We recorded no overall treatment difference in on treatment serious adverse events. There was no evidence of a treatment difference for neurological or psychiatric disorders in the safety population or in participants infected with influenza. The excess of nausea and vomiting arose both in participants influenza-infected and in others, although the risk ratio for vomiting was lower and non-significant in those not infected than in those with influenza infection. We noted no heterogeneity across trials for any adverse events (data not shown).

The incidence of on treatment psychiatric adverse events was numerically higher on the 150 mg twice a day

	Number of events		Overall risk ratio (95% CI)	p value	Placebo group risk (%) [*]	Oseltamivir group risk (%) [†]	Risk difference (95% CI)
	Oseltamivir (n=2401)	Placebo (n=1917)					
All adverse events	1033	819	0.97 (0.91 to 1.04)	0.41	42.7	41.5	-1.2% (-4.0 to 1.8)
Serious adverse events	21	22	0.79 (0.43 to 1.47)	0.46	1.1	0.9	-0.2% (-0.7 to 0.5)
Gastrointestinal disorders	574	370	1.21 (1.07 to 1.36)	0.0019	19.3	23.3	4.0% (1.4 to 6.9)
Nausea	247	118	1.60 (1.29 to 1.99)	<0.0001	6.2	9.9	3.7% (1.8 to 6.1)
Vomiting	201	63	2.43 (1.83 to 3.23)	<0.0001	3.3	8.0	4.7% (2.7 to 7.3)
Diarrhoea	147	147	0.75 (0.60 to 0.95)	0.016	7.7	5.8	-1.9% (-3.1 to -0.4)
Cardiac disorders	13	20	0.49 (0.25 to 0.98)	0.043	1.0	0.5	-0.5% (-0.8 to -0.0)
Infections and infestations	231	217	0.84 (0.70 to 1.00)	0.049	11.3	9.5	-1.8% (-3.4 to -0.0)
Injury and poisoning	15	4	3.37 (1.08 to 10.47)	0.036	0.2	0.7	0.5% (0.0 to 2.0)
Respiratory, thoracic, and mediastinal disorders	158	143	0.74 (0.60 to 0.93)	0.0081	7.5	5.5	-1.9% (-3.0 to -0.6)
Neurological disorders	124	93	1.00 (0.76 to 1.30)	0.97	4.9	4.8	-0.0% (-1.2 to 1.5)
Psychiatric disorders	11	13	0.62 (0.26 to 1.45)	0.27	0.7	0.4	-0.3% (-0.5 to 0.3)
Additional analyses in influenza- infected participants [‡]							
Neurological disorders	91	73	0.95 (0.70 to 1.29)	0.76	5.6	5.4	-0.3% (-1.7 to 1.6)
Psychiatric disorders	10	9	0.81 (0.31 to 2.08)	0.65	0.7	0.6	-0.1% (-0.5 to 0.7)
Nausea	172	85	1.60 (1.24 to 2.07)	0.0003	6.5	10.5	3.9% (1.6 to 7.0)
Vomiting	155	41	3.00 (2.11 to 4.26)	<0.0001	3.2	9.5	6.3% (3.5 to 10.3)
Additional analyses in participants without influenza [§]							
Nausea	75	33	1.67 (1.12 to 2.49)	0.011	5.3	8.9	3.6% (0.7 to 7.9)
Vomiting	46	22	1.49 (0.90 to 2.46)	0.12	3.6	5.3	1.7% (-0.4 to 5.2)

Events=number of participants who had one or more events. ^{*}Placebo group risk is calculated using all trials (including trials with no outcomes in each group). [†]Oseltamivir group risk and risk difference (95% CI) obtained by applying overall risk ratio and 95% CI to pooled placebo group risk. [‡]n=1590 in the oseltamivir group and n=1299 in the placebo group. [§]n=811 in the oseltamivir group and n=618 in the placebo group

Table 2: Meta-analyses findings for key on treatment adverse events in the safety population, by treatment received

dose than placebo but numbers of events were small (150 mg [8/447] vs placebo [3/439] RR 2.61, 95% CI 0.70–9.78; $p=0.15$). The 150 mg dose did not seem to affect neurological adverse events (data not shown).

Fewer off treatment serious adverse events arose in participants given oseltamivir (RR 0.23, 95% CI 0.09–0.58; $p=0.0018$), but numbers of events were small (6/2401 in the oseltamivir group vs 22/1917 in the placebo group; appendix p 7). No other off treatment adverse events showed a treatment difference (data not shown). Treatment withdrawal rates were similar (117/2401 in the oseltamivir group vs 79/1917 in the placebo group; RR 1.04, 95% CI 0.78, 1.39; $p=0.78$) as was treatment withdrawal due to an adverse event (36/2401 in the oseltamivir group vs 33/1917 in the placebo group; RR 0.76, 95% CI 0.46–1.25; $p=0.28$).

Discussion

Our findings show that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting.

Randomised trials done for licensing a new treatment typically focus on essential issues of efficacy and safety.

The development of treatments for influenza is no exception. Not all questions related to eventual use of a drug can be answered by such trials. These issues are usually addressed in subsequent observational studies, which are complicated by potential selection bias in who receives the intervention.^{19,20} Thus, randomised trials provide the best evidence to assess events that arise with sufficient frequency. Insight can be increased by combining evidence across trials providing their designs are similar. Such meta-analyses are best done by use of individual patient data; advantages include more thorough analysis of outcomes (eg, time to event), exploring patient subgroups, the ability to check data quality, and performance of sensitivity analyses on key outcomes.²¹

After extensive searches by both Jefferson and colleagues⁶ and ourselves, we excluded just two relevant oseltamivir treatment trials in adults from our meta-analysis: a trial in 451 Chinese adults that concluded “oseltamivir was effective and well tolerated”, and a trial that recruited only 19 adults and children (four to early oseltamivir, eight to late oseltamivir, and seven to placebo) that concluded “time to 50% decrease in symptom severity, complete symptom resolution, and first negative

culture were shortest among the early treatment group".^{13,14} Because these conclusions are broadly consistent with our findings, we believe our results based on individual patient data provide the best available evidence on oseltamivir treatment in adults. With regards to paediatric studies of oseltamivir treatment, a further individual patient data meta-analysis of three Roche-sponsored randomised trials plus two other randomised trials in children is underway and will be published separately.²²⁻²⁵

For the primary outcome of time to alleviation of all symptoms, we noted an absolute reduction of about 1 day in the intention-to-treat infected population, which was somewhat attenuated in the intention-to-treat population. These estimates are broadly compatible with those of observational studies and a previous meta-analysis.^{6,20} A basic question is what primary population should be selected for analysis? In the pivotal studies for licensure, the intention-to-treat infected population was chosen, namely those participants actually having laboratory confirmed influenza by virus isolation or rise in antibody titre. The PCR technique for identifying influenza was not yet available. Parenthetically, intention-to-treat infected is the standard analysis used worldwide by regulatory authorities for licensure.²⁶

The other approach we presented is the intention-to-treat population (ie, all treated patients whether infected or not), which inevitably dilutes estimates of any possible antiviral drug effect. The intention-to-treat population includes all randomly assigned participants and thus captures the overall drug exposure. However, the intention-to-treat infected population provides more direct insight into how the drug works in the disease being studied.

We recorded no reduction in time to symptom alleviation in participants not identified as being infected with influenza. Thus efficacy seems to be confined to the antiviral activity of the drug. Other investigators have only used the intention-to-treat population, which dilutes true efficacy, but does estimate effectiveness in a real-world setting in which some treated patients inevitably will not have influenza. Use of the intention-to-treat infected population was abandoned in a previous meta-analysis because slightly more placebo participants were documented as infected than were participants given oseltamivir, which investigators argued might introduce a bias.⁶ We used sensitivity analyses to explore this issue; by classifying as infected only patients with virus identified at enrolment, we noted little change in time to alleviation results compared with our original intention-to-treat infected analysis.

Prevention of complications was not a pre-defined focus of each trial because of insufficient power; nevertheless, combined data for complications across all trials provide important evidence. Reductions in complications, admittance to hospital, and deaths have been addressed in observational studies, especially during the 2009 pandemic, but randomised evidence is

more compelling.^{19,20,27} Complication rates are low, but still significant risk reductions were detected both in the intention-to-treat infected and intention-to-treat populations. Identification of complications was not an aim of most studies—eg, pneumonia diagnosis did not have radiographic validation. To ensure complications were not simply differentially reported because of milder symptoms on oseltamivir, we studied only those requiring antibiotics. Bronchitis could be considered part of the overall influenza syndrome, but the same pattern of reduced complications also applies to pneumonia. We noted a significant 63% reduction in the risk of hospitalisation in the intention-to-treat infected population although this was attenuated and non-significant in the intention-to-treat population. This finding is more meaningful because oseltamivir has no effect on complications in participants who do not have influenza. Our results for complications and admittance to hospital are broadly consistent with those of observational studies and some previous meta-analyses of randomised trials.^{20,28-31}

Findings of our meta-analysis confirm the clear harms of nausea and vomiting attributed to oseltamivir with estimated absolute increases of 3.7% for nausea and 4.7% for vomiting. These results are similar to anticipated rates with antimicrobial agents. Conversely, diarrhoea was more common in participants who took placebo. We did not find evidence of other harms caused by oseltamivir. Overall, we restricted our analysis to the licensed dose of 75 mg. We investigated a previous claim of a dose-response effect on incidence of psychiatric outcomes when the 150 mg dose was also investigated⁶ and noted a numerical (but non-significant) excess for the 150 mg dose. At the 75 mg dose, the incidence of psychiatric outcomes was numerically lower than on placebo.

There are several limitations in our analyses. Respiratory complications were not a pre-defined primary outcome for the original trials and specific diagnostic tests were not necessary. So caution is warranted in interpreting these results, although incorporation of antibiotic use in the definition should enhance reliable reporting of complications. For both pneumonia and hospitalisation for any cause, we noted significant differences but numbers of events were small and so effect estimates are imprecise. The absence of a significant treatment difference for uncommon events might be explained by insufficient power to detect true effects even after data across studies was combined. This meta-analysis was for trials with a 5 day treatment duration. We did not study the benefits and harms of longer term use of oseltamivir (eg, in prophylaxis).

Oseltamivir's effectiveness in the intention-to-treat population might not be generalisable because the percentage of participants infected might vary across populations, both in these trials and in real-world

experience. The balance of benefits and harms becomes less favourable if more non-infected participants are treated with oseltamivir. Treatment strategies need to avoid this—eg, through availability of rapid diagnostic testing. This highlights the value of additionally reporting results for the intention-to-treat infected population.

In conclusion, oseltamivir accelerates clinical symptom alleviation in adults infected with influenza, and also reduces the risk of lower respiratory tract complications and admittances to hospital. Whether the magnitude of these benefits outweigh the harms attributed to nausea and vomiting needs to be carefully considered.

Contributors

JD did the statistical analyses and prepared data tables and figures. All authors contributed to writing of the manuscript and made substantial contributions to conception and design of the study, and analysis and interpretation of data.

Declaration of interests

ASM reports fees from Biocryst and Roche outside of the submitted work. RJW reports fees as a board member of Gilead Sciences, funding for travel from Roche to attend an Influenza Resistance Committee meeting, and fees as Associate Editor of the *Journal of Infectious Diseases*. JD and SP declare no competing interests.

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Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Recommendations and Reports

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Please note: An erratum has been published for this report. To view the erratum, please click [here](#).

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Summary

This report updates previous recommendations by CDC's Advisory Committee on Immunization Practices (ACIP) regarding the use of antiviral agents for the prevention and treatment of influenza (CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2008;57[No. RR-7]). This report contains information on treatment and chemoprophylaxis of influenza virus infection and provides a summary of the effectiveness and safety of antiviral treatment medications. Highlights include recommendations for use of 1) early antiviral treatment of suspected or confirmed influenza among persons with severe influenza (e.g., those who have severe, complicated, or progressive illness or who require hospitalization); 2) early antiviral treatment of suspected or confirmed influenza among persons at higher risk for influenza complications; and 3) either oseltamivir or zanamivir for persons with influenza caused by 2009 H1N1 virus, influenza A (H3N2) virus, or influenza B virus or when the influenza virus type or influenza A virus subtype is unknown; 4) antiviral medications among children aged <1 year; 5) local influenza testing and influenza surveillance data, when available, to help guide treatment decisions; and 6) consideration of antiviral treatment for outpatients with confirmed or suspected influenza who do not have known risk factors for severe illness, if treatment can be initiated within 48 hours of illness onset. Additional information is available from CDC's influenza website at <http://www.cdc.gov/flu>, including any updates or supplements to these recommendations that might be required during the 2010-11 influenza season. Health-care providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information. Recommendations related to the use of vaccines for the prevention of influenza during the 2010-11 influenza season have been published previously (CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices [ACIP], 2010. MMWR 2010;59[No. RR-8]).

Introduction

In the United States, annual epidemics of influenza occur typically during the late fall through early spring. Influenza viruses can cause disease among persons in any age group, but rates of illness are highest among children (1,2). During most influenza seasons, rates of serious illness and death are highest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza (3,4). In addition, data from epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicated that the risk for influenza complications was also increased among persons who are morbidly obese (body-mass index [BMI] ≥40) and American Indians/Alaska Natives (5-8). Influenza illness caused by 2009 pandemic influenza A (H1N1) (2009 H1N1) virus is expected to occur during winter influenza seasons in the Northern and Southern hemispheres. The extent of influenza activity caused by strains of the two seasonal influenza A virus subtypes (seasonal H1N1 and H3N2) that have cocirculated since 1977 and influenza B virus strains is unpredictable, although seasonal H1N1 virus strains have been detected very rarely worldwide since 2009. In the postpandemic period, 2009 H1N1 virus strains now are considered to be the predominant seasonal influenza A (H1N1) virus strains.

On the basis of epidemiologic studies of seasonal influenza or 2009 H1N1, persons at higher risk for influenza complications include:

- children aged <5 years (especially those aged <2 years);
- adults aged ≥65 years;

- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury) (9);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged ≤ 18 years who are receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- persons who are morbidly obese (i.e., BMI ≥ 40); and
- residents of nursing homes and other chronic-care facilities.

For children, the risk for severe complications from seasonal influenza is highest among those aged < 2 years, who have much higher rates of hospitalization for influenza-related complications compared with older children (3). Medical care and emergency department visits attributable to influenza are increased among children aged < 5 years compared with older children (10). Persons aged ≤ 18 years who receive long-term aspirin therapy and have influenza are at risk for Reye's syndrome.

Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. All persons aged ≥ 6 months are recommended for annual influenza vaccination (11). Antiviral medications are effective for the prevention of influenza, and, when used for treatment, can reduce the duration and severity of illness (6,12--23). Early antiviral treatment can reduce the risk for severe illness or death related to influenza (6,12,23--27). However, the emergence of resistance to one or more of the four licensed antiviral agents (oseltamivir, zanamivir, amantadine, and rimantadine) among some circulating influenza virus strains during the past 5 years has complicated antiviral treatment and chemoprophylaxis recommendations. The selection of antiviral medications should be considered in the context of any available information about surveillance data on influenza antiviral resistance patterns among circulating influenza viruses, local, state, and national influenza surveillance information on influenza virus type or influenza A virus subtype, the characteristics of the person who is ill, and results of influenza testing if testing is done. Empiric antiviral treatment often is required to avoid treatment delays (28).

Methods

CDC's Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Work Group* meets monthly throughout the year to discuss newly published studies, review current guidelines, and consider potential revisions to the recommendations. As they review the annual recommendations for consideration of the full ACIP, members of the Work Group consider a variety of issues, including burden of influenza illness, vaccine efficacy and effectiveness, safety and coverage in groups recommended for vaccination, feasibility, cost-effectiveness, and anticipated vaccine supply. Work group members also request periodic updates on antiviral production, supply, safety, efficacy, and effectiveness from clinician researchers, regulatory agencies, public health epidemiologists, and manufacturers and review influenza surveillance and antiviral resistance data obtained from CDC's Influenza Division.

Published, peer-reviewed studies are the primary source of data used by ACIP in making recommendations for the prevention and control of influenza, but unpublished data that are relevant to issues under discussion also are considered. The best evidence for antiviral efficacy comes from randomized, controlled trials that assess laboratory-confirmed influenza virus infection as an outcome measure. However, randomized, placebo-controlled trials might be difficult to perform in populations for which antiviral treatment already is recommended. Observational studies that assess outcomes associated with laboratory-confirmed influenza virus infection can provide important antiviral effectiveness data but are more subject to biases and confounding that can affect validity and the size of effects measured. Randomized, placebo-controlled clinical trials are the best source of antiviral safety data for common adverse events; however, such studies do not have the power to identify rare but potentially serious adverse events. In cited studies that included statistical comparisons, a difference was considered to be statistically significant if the p-value was < 0.05 or the 95% confidence interval (CI) around an estimate of effect allowed rejection of the null hypothesis (i.e., no effect).

These recommendations were presented to the full ACIP and approved in June 2009. Modifications were made to the ACIP statement during the subsequent review process at CDC to update and clarify wording in the document. Data presented in this report were current as of December 2010. Further updates, if needed, will be posted at CDC's influenza website (<http://www.cdc.gov/flu>).

Primary Changes and Updates in the Recommendations

These recommendations include six principal changes or updates from previous recommendations for use of antivirals for the prevention and control of influenza:

- Antiviral treatment is recommended as soon as possible for patients with confirmed⁺ or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization.
- Antiviral treatment is recommended as soon as possible for outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions; clinical judgment should be an important component of outpatient treatment decisions.
- Recommended antiviral medications include oseltamivir and zanamivir, on the basis of recent viral surveillance and resistance data indicating that $> 99\%$ of currently circulating influenza virus strains are sensitive to these medications. Amantadine and rimantadine should not be used because of the high levels of resistance to these drugs among circulating influenza A viruses, but information about these drugs is provided for use if current recommendations change because of the reemergence of adamantane-susceptible strains.
- Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged < 1 year when indicated.
- Antiviral treatment also may be considered on the basis of clinical judgment for any outpatient with confirmed or suspected influenza who does not have known risk factors for severe illness if treatment can be initiated within 48 hours of illness onset.
- Because antiviral resistance patterns can change over time, clinicians should monitor local antiviral resistance surveillance data.

Influenza Virus Transmission

Influenza viruses are thought to spread from person to person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person) (29). Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets generally travel only short distances (approximately ≤ 6 feet) through

the air. Indirect contact transmission via hand transfer of influenza virus from virus-contaminated surfaces or objects to mucosal surfaces of the face (e.g., nose and mouth) or airborne transmission via small-particle aerosols in the vicinity of the infectious person also might occur; however, the relative contribution of the different modes of influenza transmission is unclear (29--34). Airborne transmission over longer distances (e.g., from one patient's room to another) has not been documented and is not thought to occur. However, generation of aerosols is thought to have been a possible source of nosocomial transmission from a patient receiving noninvasive ventilation to other patients on a medical ward (35). The typical incubation period for influenza is 1--4 days (average: 2 days) (36). The serial interval (time between onsets among epidemiologically related cases) for influenza among household contacts is estimated to be 3--4 days (37,38). Adults can shed influenza virus from the day before symptoms begin through 5--10 days after illness onset (39,40). However, the amount of virus shed, and presumably infectivity, decreases rapidly by 3--5 days after illness onset in an experimental adult human infection model, with shedding completed in most persons by 5--7 days after illness onset (39,40). Young children also might shed virus several days before illness onset, and children can be infectious for ≥ 10 days after onset of symptoms (41). Prolonged viral replication has been reported in adults with severe disease, including those with comorbidities or those receiving corticosteroid therapy (42,43). Severely immunocompromised persons can shed virus for weeks or months (44--48). Epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicate that viral shedding, clinical illness, and transmissibility in a household setting are similar compared with seasonal influenza (38).

Clinical Signs and Symptoms of Influenza

Uncomplicated influenza illness, including illness caused by seasonal influenza viruses or 2009 H1N1 virus, is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis) (49,50). Mild illness without fever also can occur and has been reported in 6%--33% of persons infected with 2009 H1N1 virus (38,51,52). Asymptomatic infection also can occur, but the contribution of asymptomatic infection to influenza virus transmission is uncertain. In one study, household contacts of persons with laboratory-confirmed 2009 H1N1 virus infection had baseline and convalescent serum samples collected. Among those who had serologic evidence of 2009 H1N1 virus infection, 36% did not shed detectable virus or report illness (38). Among children, otitis media, nausea, and vomiting also are reported commonly with influenza illness (53,54). Uncomplicated influenza illness typically resolves after 3--7 days for the majority of persons, although cough and malaise can persist for >2 weeks (49).

Complications from influenza virus infection can include primary influenza viral pneumonia (55); exacerbation of underlying medical conditions (e.g., pulmonary or cardiac disease); secondary bacterial pneumonia, sinusitis, or otitis media; or coinfections with other viral or bacterial pathogens (49,51,54). Young children with influenza virus infection might have initial symptoms mimicking bacterial sepsis with high fevers (10,54,56,57), and febrile seizures have been reported in 6%--20% of children hospitalized with influenza virus infection (54,58,59). One study of children hospitalized with laboratory-confirmed influenza-associated pneumonia reported a higher risk for intensive care admission, respiratory failure, and death compared with children hospitalized with influenza without pneumonia (60). Age <5 years and asthma were associated significantly with influenza-associated pneumonia (60). Severe illness with seasonal influenza virus infection can occur even among young and previously healthy persons; in one case series, 19 (50%) of 38 adults (median age: 52 years) with severe viral pneumonia caused by influenza were previously healthy; 11 (29%) had a concomitant or secondary bacterial pneumonia, 24 (63%) required intensive care unit admission for a median of 11 days, and 17 (45%) died (55).

During the 2009 H1N1 pandemic, the clinical syndrome most likely to be the cause of hospitalization was diffuse viral pneumonitis, which in some instances led to shock and respiratory failure (6,7,61--64). Infection with any influenza virus strain can lead to bacterial pneumonia and other bacterial coinfections. Secondary or concomitant bacterial pneumonia caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *S. pyogenes*, or other virulent bacteria has been suspected or identified in 20%--38% of 2009 H1N1 patients who died or required intensive care unit admission (51,63--67). Exacerbation of underlying comorbidities such as asthma, chronic obstructive pulmonary disease (COPD) or cardiac disease was also a major contributor to morbidity and mortality. One or more underlying comorbidities were present in 50%--80% of adults and children requiring hospitalization (6,7,63). Pregnant and postpartum (within 2 weeks of delivery) women were at increased risk for severe illness requiring hospitalization in multiple studies, accounting for 6%--10% of patients who required hospitalization or died in some case series (6,7,12,25,68).

Population-based studies among hospitalized children with laboratory-confirmed seasonal influenza have demonstrated that although the majority of hospitalizations are brief (≤ 2 days), 4%--11% of children hospitalized with laboratory-confirmed influenza required treatment in the intensive care unit, and 3% required mechanical ventilation (10,54). Among 1,308 hospitalized children in one study, 1,046 (80%) were aged <5 years, and 353 (27%) were aged <6 months (54). In another study of 4,015 laboratory-confirmed seasonal influenza hospitalizations in children, the median length of hospitalization was 3--4 days; 1,894 (40%) children had at least one chronic high-risk medical condition, and the highest hospitalization rate was in children aged <6 months (69). Influenza virus infection also has been associated rarely with encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye's syndrome (53,59,70--76). Secondary bacterial pneumonia or bacterial co-infection can lead to severe illness (77,78). Influenza complications among children during the 2009 influenza A (H1N1) pandemic were generally similar to those observed among children with seasonal influenza. However, much higher rates of illness among children observed during the 2009 H1N1 pandemic compared with most influenza seasons resulted in much higher rates of children hospitalized with complications. One study reported more neurologic complications associated with 2009 H1N1 virus infection among children compared with seasonal influenza virus infections (79). In one study, rates of hospitalization were estimated to be tenfold higher during the pandemic compared with a typical influenza season (62).

Respiratory illnesses caused by influenza virus infection are difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of signs and symptoms alone. Sensitivity and positive predictive value of clinical definitions vary, depending on the prevalence of other respiratory pathogens and the level of influenza activity in the community. Among generally healthy older adolescents and adults living in areas with confirmed influenza virus circulation, estimates of the positive predictive value of a simple clinical case definition of influenza (acute onset of cough and fever) for laboratory-confirmed influenza virus infection have varied (range: 79%--88%) (80--82).

Young children are less likely to experience typical influenza signs and symptoms (e.g., fever and cough). In studies conducted during a winter influenza season among children aged 5--12 years, the positive predictive value of fever and cough together was 71%--83%, compared with 64% among children aged <5 years (81). In one large, population-based surveillance study in which all children with fever or symptoms of acute respiratory tract infection during influenza season were tested for influenza (with test results not available until after discharge), 55 (70%) of 79 hospitalized children aged <6 months with laboratory-confirmed influenza were reported to have

fever and cough, compared with 74 (91%) of 81 hospitalized children aged 6 months--5 years (10). Among children aged <5 years who subsequently were shown to have laboratory-confirmed influenza, only 22 (28%) of 79 hospitalized children and 47 (17%) of 274 children treated as outpatients had a discharge diagnosis of influenza (10). The predominance of atypical presentations involving primarily dehydration, irritability or poor oral intake have been reported among some young children with 2009 H1N1 virus infection (77,78).

Clinical case definitions have performed poorly in some studies of older patients. A study of nonhospitalized patients aged ≥60 years indicated that the presence of fever, cough, and acute onset had a positive predictive value of 30% for influenza (83). Among 56 hospitalized patients aged ≥65 years with chronic cardiopulmonary disease, a combination of fever, cough, and illness of <7 days had a positive predictive value of 53% for confirmed influenza virus infection (84). In addition, the absence of symptoms of influenza-like illness (ILI) does not effectively rule out influenza; among hospitalized adults with laboratory-confirmed influenza in two studies, only 44%--51% had typical ILI symptoms (85,86). A study of 94 vaccinated older persons with chronic lung disease reported that cough was not predictive of laboratory-confirmed influenza virus infection, although having both fever or feverishness and myalgia had a positive predictive value of 41% (87). These results highlight the challenges of identifying influenza illness in the absence of laboratory confirmation and indicate that the diagnosis of influenza should be considered in patients with respiratory symptoms or fever during influenza season.

Role of Laboratory Diagnosis

Influenza surveillance information and diagnostic testing can aid clinical judgment and help guide treatment decisions. In some surveys, 60%--69% of practitioners reported testing patients for influenza during the influenza season (88,89). The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza (80--87) (see Clinical Signs and Symptoms of Influenza).

Diagnostic tests available for influenza include viral culture, serology, rapid diagnostic (antigen) testing, reverse transcription-polymerase chain reaction (RT-PCR), and immunofluorescence assays (90). Serologic testing requires paired acute and convalescent sera, is not widely available, and is not recommended except for epidemiologic investigations and research. As with any diagnostic test, influenza test results should be evaluated in the context of other clinical and epidemiologic information available to health-care providers. Sensitivity and specificity of any test for influenza, including those that detect 2009 H1N1 virus, can vary by the laboratory that performs the test, the type of test used, the type of specimen tested, the quality of the specimen, and the timing of specimen collection in relation to illness onset. Among respiratory specimens for viral isolation or rapid detection of influenza viruses, nasopharyngeal and nasal specimens generally have higher yields than throat swab specimens (91). In addition, positive influenza tests that yield vaccine virus strains have been reported up to 7 days after receipt of live attenuated influenza virus vaccine (92).

Commercial rapid influenza diagnostic tests (RIDTs) are available that can detect influenza virus antigens within 15 minutes of testing (93,94). Certain tests are cleared by the Food and Drug Administration (FDA) for use in any outpatient setting whereas others must be used in a moderately complex clinical laboratory. These RIDTs differ by whether they can distinguish between influenza virus types. Available tests can either 1) detect influenza A and B viruses but not distinguish between the two types or 2) detect both influenza A and B viruses and also distinguish between the two types. None of the rapid influenza diagnostic tests specifically identifies any influenza A virus subtypes.

The types of specimens acceptable for use (i.e., nasopharyngeal or nasal aspirates, swabs, and washes or throat swabs) also vary by test, but all perform best when collected as close to illness onset as possible (e.g., ≤72 hours after onset). RT-PCR can be used to detect viral RNA in upper and lower respiratory tract specimens. Endotracheal aspirate or bronchoalveolar lavage specimens have higher yields in patients with lower respiratory tract illness, especially later in the course of illness. In addition, repeated collection of specimens from the upper and lower respiratory tract might be necessary if results are initially negative for a patient in whom clinical suspicion of influenza is high (51).

Rapid diagnostic tests for influenza have high specificity (>90%) but have low to moderate sensitivity (20%--70%) compared with other influenza tests. The sensitivities of RIDTs are lower than for viral culture or RT-PCR and vary by test (94--98). Recent studies have found sensitivity to be as low as 42% in clinical practice and 19% among adults participating in a clinical study (96,99). RIDTs appear to have higher sensitivity when used in young children, compared with adults, possibly because young children with influenza typically shed higher concentrations of influenza viruses than adults (100). Similar to results for other influenza virus strains, the specificity of available RIDTs for detection of 2009 H1N1 virus is high (>95%), but sensitivity is 11%--70%. These data indicate that negative RIDT results should not be used to make treatment or infection-control decisions especially when influenza viruses are known to be circulating in the community (51,101--104).

The limitations of RIDTs must be understood for results to be interpreted properly. Positive rapid influenza diagnostic test results are generally reliable when community influenza activity is high and might be useful in deciding whether to initiate antiviral treatment. Negative rapid test results are not helpful in making treatment decisions for individual patients when influenza activity in a community is high because of the limited sensitivity of the rapid tests. If a definitive diagnosis is needed, providers should consider confirming negative test results with more sensitive and specific influenza testing. More sensitive and specific tests include viral culture or RT-PCR. The positive predictive value of RIDTs will be lower during periods of low influenza activity, and clinicians should consider the positive and negative predictive values of any test in the context of the level of influenza activity in their community when interpreting results (105). When local influenza activity is high, persons with severe respiratory symptoms or persons with acute respiratory illness who are at higher risk for influenza complications are recommended for empirical influenza antiviral treatment despite a negative rapid influenza test result unless illness can be attributed to another cause. However, because certain bacterial infections can produce symptoms similar to influenza, providers should consider the possibility of bacterial infections or coinfections and treat accordingly. In addition, secondary invasive bacterial infections can be a severe complication of influenza. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid influenza diagnostic tests. Additional updated information concerning diagnostic testing is available at <http://www.cdc.gov/flu/professionals/labdiagnosis.htm>.

Clinical specimens collected in virus surveillance systems for viral culture are critical for monitoring influenza virus activity. Only culture isolates of influenza viruses can provide specific information regarding the antigenic characteristics of influenza viruses, and data on antiviral resistance and influenza A virus subtype cannot be obtained from RIDTs. This information is needed to compare current circulating influenza virus strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis,

and to select vaccine virus strains for the coming year. Virus isolates are needed to monitor antiviral resistance in circulating human influenza virus strains and the emergence of novel influenza A virus infections in humans that might pose a pandemic threat (e.g., human infection with swine or avian influenza A viruses). Influenza surveillance by state and local health departments and CDC can provide information regarding the circulation of influenza viruses in the community, which can help inform decisions about the likelihood that a compatible clinical syndrome is indeed influenza. Influenza testing guidance for clinicians is available from the Infectious Diseases Society of America (IDSA) (105,106).

RT-PCR is the most accurate and sensitive test for detecting influenza viruses, including the 2009 H1N1 virus (51,105). RT-PCR platforms capable of subtyping influenza A viruses are available in state public health and some reference laboratories. A standardized influenza real-time RT-PCR protocol and platform developed by CDC has been distributed (107). The capacity to subtype influenza A viruses can be important when antiviral resistance patterns differ between circulating influenza A virus subtypes. The time required for testing and the limited availability of RT-PCR capable of subtyping limits the usefulness of this test for medical management of individual patients. However, surveillance data provided by public health departments or other laboratories with RT-PCR subtyping capacity can be useful in identifying the presence of each influenza A virus subtype in the community, and should be consulted routinely by clinicians when feasible (108). RT-PCR tests for seasonal influenza are unable to provide subtyping information when used to test specimens from patients with 2009 H1N1 virus infections. RT-PCR tests for the detection of 2009 H1N1 virus were developed by CDC and distributed to state public health and other reference laboratories. One RT-PCR test that can distinguish 2009 pandemic H1N1 virus from other influenza A viruses has been cleared by FDA, and this test appears to have similar sensitivity and specificity compared with the test developed by CDC (109).

Antiviral Agents for Influenza

Four licensed prescription influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Zanamivir and oseltamivir are related antiviral medications in a class of medications known as neuraminidase inhibitors. These two medications are active against both influenza A and B viruses. They differ in pharmacokinetics, safety profiles, routes of administration, approved age groups, and recommended dosages (Table 1).

Amantadine and rimantadine are related antiviral drugs in a class of medications known as adamantanes. These medications are active against influenza A viruses but not influenza B viruses. In recent years, widespread adamantane resistance among influenza A (H3N2) virus strains has made this class of medications less useful clinically. In addition, circulating 2009 H1N1 virus strains are resistant to adamantanes (110). Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.

Antiviral Drug Resistance Among Influenza Viruses

Oseltamivir and Zanamivir (Neuraminidase Inhibitors)

Oseltamivir or zanamivir are the primary antiviral agents recommended for the prevention and treatment of influenza (28,51,105). Antiviral resistance profiles for currently circulating influenza A and B viruses are listed (Table 2).

Because currently circulating influenza A (H3N2) and 2009 H1N1 viruses are resistant to adamantanes, these medications are not recommended for use against influenza A virus infections. However, influenza A and B virus strains are, with rare exception, susceptible to oseltamivir and zanamivir (110). Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified, including with rare episodes of limited transmission (111--115), but the public health impact has been limited to date. However, additional sporadic cases of oseltamivir-resistant 2009 H1N1 virus infection can be expected, and ongoing surveillance for oseltamivir resistance among influenza viruses is essential for public health because oseltamivir is the most widely used antiviral medication.

Development of resistance to zanamivir or oseltamivir also has been identified during treatment of seasonal influenza (116--120). One study reported that oseltamivir-resistant seasonal influenza A viruses were isolated from nine (18%) of 50 Japanese children during treatment with oseltamivir (121). Transmission of neuraminidase-inhibitor--resistant influenza B viruses has been reported among household contacts (122). Development of resistance to oseltamivir during treatment was more common among seasonal influenza A (H1N1) virus infections (27%) compared with seasonal influenza A (H3N2) (3%) or B (o) viruses in another study (123). Sporadic cases of resistance to oseltamivir have been observed among persons with 2009 H1N1 virus infection (e.g., immunosuppressed patients with prolonged viral replication during oseltamivir treatment and persons who developed illness while receiving oseltamivir chemoprophylaxis) (114,124). Emergence of oseltamivir-resistant 2009 H1N1 virus strains within 48 hours after initiation of treatment has been reported (125). Transmission of oseltamivir-resistant influenza B virus strains or 2009 H1N1 virus strains acquired from persons treated with oseltamivir is rare but has been documented (112,122). Isolation of influenza A viruses with reduced susceptibility to zanamivir have been reported rarely, although the number of posttreatment isolates tested is limited (117--119,126). Clinical isolates with reduced susceptibility to zanamivir have been obtained occasionally from immunocompromised children on prolonged therapy (118,127). Prolonged shedding of oseltamivir- or zanamivir-resistant virus by severely immunocompromised patients, even after cessation of oseltamivir treatment, has been reported (118,127--129). Rare cases of infection with 2009 H1N1 virus resistant or with reduced susceptibility to multiple neuraminidase inhibitors in severely immunosuppressed pediatric patients with prolonged viral replication have been reported (130,131).

During 2007--2008, increased resistance to oseltamivir associated with a specific mutation causing a histidine to tyrosine substitution (H275Y) in neuraminidase was reported among seasonal influenza A (H1N1) virus strains in many countries and became prevalent worldwide (132--134). Most persons infected with oseltamivir-resistant seasonal influenza A (H1N1) virus strains had not received oseltamivir treatment previously and were not known to have been exposed to a person receiving oseltamivir treatment or chemoprophylaxis (133,135). Influenza caused by oseltamivir-resistant seasonal influenza A (H1N1) virus strains appears to be similar to illness caused by oseltamivir-sensitive virus strains (133,134,136). Since the recent emergence of 2009 H1N1 virus, oseltamivir-resistant seasonal influenza A (H1N1) virus has been of less clinical concern because very few seasonal influenza A (H1N1) virus strains have been circulating (113). Nearly all sporadic cases of oseltamivir-resistant 2009 H1N1 virus infections identified to date also have been associated with the H275Y mutation in neuraminidase; these oseltamivir-resistant H275Y virus infections are susceptible to zanamivir. As of December 2010, no evidence existed of ongoing transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide.

Amantadine and Rimantadine (Adamantanes)

Adamantane resistance among circulating influenza A viruses increased rapidly worldwide beginning during 2003--2004. The percentage of influenza A virus isolates submitted from throughout the world to the World Health Organization Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at CDC that were adamantane-resistant increased from 0.4% during 1994--1995 to 12.3% during 2003--2004 (137). During the 2005--06 influenza season, CDC determined that 193 (92%) of 209 influenza A (H3N2) viruses isolated from patients in 26 states demonstrated a change at amino acid 31 in the M2 gene that confers resistance to adamantanes (138). Resistance to adamantanes remains high among influenza A isolates, with resistance detected among all tested influenza A (H3N2) and 2009 H1N1 viruses tested (113). Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.

Use of Antivirals

Treatment Efficacy and Effectiveness Studies

Randomized, controlled trials conducted primarily among persons with mild illness in outpatient settings have demonstrated that zanamivir or oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day when administered within 48 hours of illness onset compared with placebo (15,16,19--21,139--142). One randomized, controlled trial of oseltamivir treatment among 408 children aged 1--3 years reported that when oseltamivir was started within 24 hours of illness onset, the median time to illness resolution was shortened by 3.5 days compared with placebo (143). Minimal or no benefit was reported in healthy children and adults when antiviral treatment was initiated >2 days after onset of uncomplicated influenza. The amount of influenza viral shedding was reduced among those treated, but studies on whether the duration of viral shedding is reduced have been inconsistent (38,40,144,145) and the temporal and causal relationships between changes in influenza viral shedding and clinical outcomes have not been well-established. One evidence review concluded that neuraminidase inhibitors were not effective in reducing the severity or duration of ILI (defined as acute respiratory infection with fever and cough). However, a variety of pathogens can cause ILI besides influenza viruses, and this review did not conclude that neuraminidase inhibitors were ineffective in reducing laboratory-confirmed influenza among adults (146,147).

Data are limited about the effectiveness of zanamivir and oseltamivir treatment in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). In a study that combined data from 10 clinical trials, the risk for pneumonia among those participants with laboratory-confirmed influenza receiving oseltamivir treatment was approximately 50% lower than among those persons receiving a placebo and 34% lower among patients at risk for complications ($p < 0.05$ for both comparisons) (22). Although a similar significant reduction also was determined for hospital admissions among the overall group, the 50% reduction in hospitalizations reported in the small subset of high-risk participants was not statistically significant (22). One randomized, controlled trial found a decreased incidence of otitis media among children treated with oseltamivir (21). A randomized, controlled trial among children aged 1--3 years found an 85% reduction in acute otitis media when oseltamivir treatment was started within 12 hours of illness onset, but no reduction when treatment was started >24 hours from symptom onset (143). Another randomized, controlled study conducted among influenza virus-infected children with asthma reported greater improvement in lung function and fewer asthma exacerbations among oseltamivir-treated children compared with those who received placebo but did not determine a difference in symptom duration (148). Insufficient data exist regarding the effectiveness of any of the influenza antiviral drugs for use among children aged <1 year.

Observational studies have determined that oseltamivir reduces severe clinical outcomes in patients hospitalized with influenza. A large prospective observational study assessed clinical outcomes among 327 hospitalized adults with laboratory-confirmed influenza whose health-care provider chose to use oseltamivir treatment compared with untreated influenza patients. The average age of adults in this study was 77 years, and 71% began treatment >48 hours after illness onset. In a multivariate analysis, oseltamivir treatment was associated with a significantly decreased risk for death within 15 days of hospitalization (odds ratio [OR] = 0.2; 95% CI = 0.1--0.8). Benefit was observed even among those starting treatment >48 hours after symptom onset. However, oseltamivir treatment did not reduce either the duration of hospitalization or 30-day mortality after hospitalization significantly. An additional 185 hospitalized children with laboratory-confirmed influenza were identified during this study, but none received antiviral treatment, and no assessment of outcomes based on receipt of antiviral treatment of hospitalized children could be made (23). A study in Thailand of patients with laboratory-confirmed influenza also found a significant (OR = 0.13 (95% CI = 0.04--0.40) reduction in mortality among patients who received oseltamivir treatment (149). A retrospective cohort study of 99 hospitalized persons (median age: 70 years) with laboratory-confirmed influenza who received oseltamivir indicated that persons who received oseltamivir treatment >48 hours from illness onset had a median length of stay of 6 days, compared with 4 days for persons who received oseltamivir within 48 hours of symptom onset ($p < 0.0001$) (26), and a subsequent analysis of these data showed benefit for patients who received oseltamivir up to 96 hours after illness onset (27). A prospective study of 754 hospitalized adults (mean age: 70 years) with laboratory-confirmed seasonal influenza reported that oseltamivir treatment initiated within 2 days was associated with earlier hospital discharge, and improved survival was observed when oseltamivir was administered within 4 days from illness onset (150). One small observational study found that treatment of persons with leukemia who acquired influenza was associated with a decreased risk for death (151).

In one observational study, oseltamivir treatment of young adults with mild illness from 2009 H1N1 virus infection was reported to reduce the development of radiographically confirmed pneumonia, and initiation of treatment within 2 days of onset reduced the duration of fever and viral RNA shedding (152). Earlier neuraminidase inhibitor treatment was associated with less severe disease, and any neuraminidase inhibitor treatment had a survival benefit in observational studies of patients hospitalized with 2009 H1N1 virus infection (6,12,65,153,154). However, additional data on the impact of antiviral treatment on severe outcomes are needed.

More clinical data are available concerning the efficacy of zanamivir and oseltamivir for treatment of influenza A virus infection than for treatment of influenza B virus infection. Data from human clinical studies have indicated that zanamivir and oseltamivir have activity against influenza B viruses (21,116,145,155,156). However, an observational study among Japanese children with culture-confirmed influenza and treated with oseltamivir demonstrated that children with influenza A virus infection resolved fever and stopped shedding virus more quickly than children with influenza B, suggesting that oseltamivir might be less effective for the treatment of influenza B (157).

Treatment Indications

Clinical judgment based on underlying conditions, disease severity, and time since symptom onset are also important factors in treatment decisions. Antiviral treatment is recommended as soon as possible for all persons with suspected or confirmed influenza requiring hospitalization or who have progressive, severe or complicated illness regardless of previous health or vaccination status

(28,51,105). In observational studies conducted among severely ill patients, both early initiation of antiviral treatment (<2 days from illness onset) and treatment up to <5 days after onset were associated with reduced morbidity and mortality, with greater benefit associated with earlier initiation of treatment (6,7,51). Additional research is needed to better assess the impact of treatment, but on the basis of these limited data, treatment of severely ill patients as soon as possible is strongly recommended. Treatment should not be delayed while the results of diagnostic testing are awaited (Box). Empiric antiviral treatment is often necessary, and providers should not delay initiation of treatment while awaiting confirmatory diagnostic tests results or if specimens are not obtained. Patients with suspected influenza should complete antiviral treatment for a full treatment course regardless of negative initial test results unless an alternative diagnosis can be established and clinical judgment suggests that influenza is unlikely (28,51).

Among outpatients, antiviral treatment with a neuraminidase inhibitor is recommended for all persons with suspected or confirmed influenza who are at higher risk for influenza complications because of age or underlying medical conditions (Box). Although all children aged <5 years are considered at higher risk for complications from influenza, the highest risk is for those aged <2 years, with the highest hospitalization and death rates among infants aged <6 months. On the basis of epidemiologic studies of patients with seasonal influenza or 2009 H1N1, persons at higher risk for influenza complications who are recommended for antiviral treatment for suspected or confirmed influenza (11) include:

- children aged <2 years;
- adults aged ≥65 years;
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged <19 years who are receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- persons who are morbidly obese (i.e., BMI ≥40); and
- residents of nursing homes and other chronic-care facilities.

Some treatment recommendations from other expert advisory groups are more definite about the need to treat all persons at higher risk for influenza complications who are suspected of having influenza, especially if the suspected cause is 2009 H1N1 virus infection. The World Health Organization (WHO) has recommended empiric neuraminidase inhibitor treatment for all persons with suspected or confirmed 2009 H1N1 virus infection who are at increased risk for influenza complications (51), and similar recommendations were made by CDC during the 2009 H1N1 pandemic and the subsequent 2009–10 influenza season (28). IDSA recommends that all persons with laboratory-confirmed or highly suspected influenza virus infection who are at high risk for developing complications receive treatment, when treatment can begin within 48 hours after symptom onset (105). Clinicians who prefer not to treat empirically should discuss signs and symptoms of worsening illness with such patients and arrange for follow up by telephone or in the clinic. Options for close follow-up should be considered carefully.

Clinicians should monitor local, state, and national recommendations during the influenza season to determine the most appropriate treatment practices and receive updates on antiviral resistance profiles of the circulating viruses (Table 3). Treatment options could become complicated if oseltamivir-resistant seasonal influenza A (H1N1) virus strains that circulated during 2007–2009 reappear or if neuraminidase inhibitor resistance becomes more common among circulating H3N2 or 2009 H1N1 virus strains. The lack of influenza A virus subtyping and antiviral resistance testing availability in most settings might present additional challenges in determining optimal antiviral therapy if oseltamivir resistance among circulating influenza virus strains becomes more prevalent.

The benefits of antiviral treatment are likely to be greatest if treatment is started as soon as possible after illness onset, and evidence for benefit is strongest in studies in which treatment was started within 48 hours of illness onset. However, treatment of any person with confirmed or suspected influenza who requires hospitalization is recommended, even if the patient presents >48 hours after illness onset (12,28,51,105). Patients with influenza are at high risk for such secondary bacterial complications as bacterial pneumonia. Antibacterial therapy plus antiviral treatment are recommended for patients with community-acquired pneumonia when influenza also is suspected. Antibiotic treatment should be directed at likely bacterial pathogens associated with influenza such as *S. pneumoniae*, *S. pyogenes*, and *S. aureus*, including methicillin-resistant (MRSA), especially for hospitalized patients (158,159). Clinicians should consider influenza virus infection as the possible cause of any febrile respiratory illness requiring hospitalization during influenza season and consider testing for influenza and starting empiric antiviral therapy (159).

Treatment also can be considered, on the basis of clinical judgment, for outpatients with uncomplicated, suspected, or confirmed influenza who are not known to be at increased risk for developing severe or complicated illness if antiviral treatment can be initiated within 48 hours of illness onset. Persons with influenza who present with an uncomplicated febrile illness typically do not require treatment unless they are at higher risk for influenza complications, but early empiric antiviral treatment of these patients also might provide benefit (e.g., a shortened duration of illness). Persons with influenza who are already beginning to recover do not need to start treatment. Treatment decisions, especially those involving empiric treatment, should be informed by knowledge of influenza activity in the community. Empiric treatment for febrile respiratory illness when influenza activity in the community is low is likely to result in a large proportion of persons without influenza receiving unnecessary influenza antivirals. In addition, patients not at increased risk for developing severe or complicated illness and who have mild, uncomplicated illness are less likely to benefit from treatment if initiated more than 48 hours after illness onset.

Treatment Issues for Patients Hospitalized with Suspected or Confirmed Influenza

Treatment of patients with severe influenza (e.g., those requiring hospitalization) presents multiple challenges. The effect of specific antiviral strategies in serious or life-threatening influenza is not established from clinical trials conducted to support licensure of oseltamivir and zanamivir, as those studies were conducted primarily among previously healthy outpatients with uncomplicated illness. However, a number of more recent observational studies have reported that oseltamivir treatment up to 96 hours after illness onset of patients hospitalized with suspected or confirmed influenza is associated with lower risk for severe outcomes (12,23,27,65,150). For this reason, recommendations in this report do not necessarily represent FDA-approved uses of antiviral products but are based on

published expert opinion and observational studies and are subject to change as the developmental status of investigational products and the epidemiologic and virologic features of influenza change over time.

Initiation of antiviral treatment as early as possible is recommended for hospitalized patients. However, antiviral treatment might be effective in reducing morbidity and mortality in hospitalized patients even if treatment is not started until >48 hours after onset of illness. Data from observational studies indicates the benefit of antiviral treatment for hospitalized persons even when treatment is delayed (12,23,26--28,150). Careful attention to ventilator and fluid management and to the prevention and treatment of secondary bacterial pneumonia (e.g., *S. pneumoniae*, *S. pyogenes*, and *S. aureus*, including MRSA) also is critical for severely ill patients (66,158--161).

Treatment regimens might need to be altered to fit the clinical circumstances. For example, clinical judgment should be the guide regarding the need to extend treatment regimens longer than 5 days for patients whose illness is prolonged. No data are available to evaluate the effectiveness of larger doses of antivirals to treat severe influenza illness (e.g., viral pneumonia requiring admission to an intensive care unit), and one study indicated that enteric absorption among critically ill patients was adequate (162). However, doubling the dose of oseltamivir (e.g., 150 mg twice daily in adults) has been advocated as an appropriate strategy in the treatment of severely ill patients with influenza A (H5N1), and limited data suggest this dosage is well tolerated (163) and might be beneficial (164).

Limited data indicate that administering oseltamivir via a gastric tube can provide systemic absorption in some critically ill patients with 2009 H1N1 or H5N1 (162,165,166), and these findings might be applicable to severe illness with other influenza virus infections. However, gastric stasis or bleeding can make this administration route problematic because of the potential for reduced absorption of medication (165,167). For these patients, parenteral medications might be preferable, but no clinical trials have demonstrated increased benefit, and none are FDA-approved. Clinical trials are needed to better understand optimal treatment approaches, and clinicians interested in enrolling patients in clinical trials of experimental intravenous antivirals and combination antiviral treatment should consult the National Institutes of Health (available at <http://www.clinicaltrials.gov> ). For patients who are not eligible for clinical trial enrollment, physicians might wish in some instances to pursue single-patient emergency Investigational New Drug (IND) protocols for antivirals that are not licensed. Clinicians may contact the study sponsor or manufacturer to explore this possibility and obtain information about implementing an IND protocol; contact information is available at <http://www.clinicaltrials.gov> .

Patients receiving antiviral medications who do not respond to treatment might have an infection with an antiviral-resistant influenza virus. Oseltamivir resistance, sometimes within 1 week of treatment initiation, has been reported particularly among immunocompromised patients with 2009 H1N1 virus infection who were receiving treatment with oseltamivir (114,168--170). Infection-control measures are especially important for patients who are immunocompromised to reduce the risk for transmission of oseltamivir-resistant viruses (104,105).

Investigational parenterally administered products that can be obtained via IND or other protocols in clinical trials include peramivir and zanamivir. Peramivir is an investigational neuraminidase inhibitor medication that has variable activity against influenza A and B viruses as reported in human and animal studies with small sample sizes (171,172). Investigational preparations of zanamivir that can be administered parenterally have been reported to reduce the likelihood of infection in a challenge model of experimental infection with influenza A virus (171,173). Intravenous zanamivir has been used with success in clinical settings (169,170). Intravenous zanamivir is the recommended antiviral treatment for severely ill patients with highly suspected or confirmed oseltamivir-resistant 2009 H1N1 virus infection (51,169,174).

For patients who are intubated, use of the zanamivir disc inhaler is not possible. Suboptimal delivery to sites of infection in patients with pneumonic or extrapulmonary disease is also of concern for patients with severe respiratory illness (171). Limited experimental use of an unlicensed nebulized formulation of zanamivir has been well tolerated (175), but use of the nebulized preparation of the licensed powder formulation contained in the disc inhaler is not recommended because it has been demonstrated to clog ventilator tubing (176).

Concerns about influenza viruses with pandemic potential, the appearance and widespread transmission of 2009 pandemic influenza A (H1N1), and the limited treatment options available for severely ill patients has prompted renewed interest in development of additional antiviral drugs with activity against influenza viruses (171,177). Clinicians should be alert to the future availability of new therapeutic options and recommendations. In addition, careful attention to infection-control measures is recommended (104,105), particularly in hospital areas that house immunocompromised patients.

Postexposure Chemoprophylaxis Effectiveness

In randomized, placebo-controlled trials, both oseltamivir and zanamivir were efficacious in the prevention of influenza illness among persons administered chemoprophylaxis after a household member or other close contact had laboratory-confirmed influenza (zanamivir: 72%--82%; oseltamivir: 68%--89%) (13,14,17,18,141,178,179). Postexposure chemoprophylaxis with neuraminidase inhibitors generally should be reserved for those who have had recent close contact with a person with influenza. Persons who can be considered for antiviral chemoprophylaxis include family or other close contacts of a person with a suspected or confirmed case who are at higher risk for influenza complications but have not been vaccinated against the influenza virus strains circulating at the time of exposure (28,105). Unvaccinated health-care workers who have occupational exposures and who did not use adequate personal protective equipment at the time of exposure are also potential candidates for chemoprophylaxis (28). Because of widespread resistance among currently circulating influenza A virus strains and inherent nonsusceptibility among influenza B viruses, adamantanes have limited use in the prevention of influenza. Persons who receive an antiviral medication for chemoprophylaxis might still acquire influenza virus infection and be potentially able to transmit influenza virus, even if clinical illness is prevented (180,181). Development of illness caused by oseltamivir resistant 2009 H1N1 virus infection has been reported among persons receiving oseltamivir chemoprophylaxis (115), and one report of a small community cluster indicates that person-to-person transmission is possible among healthy persons who are not receiving oseltamivir (112).

Postexposure Chemoprophylaxis Indications

Clinical judgment and advice from local authorities are important factors in making postexposure chemoprophylaxis decisions. Decisions on whether to administer antivirals for chemoprophylaxis should take into account the exposed person's risk for influenza complications, the type and duration of contact, recommendations from local or public health authorities, and clinical judgment. Generally, postexposure chemoprophylaxis for persons should be only used when antivirals can be started within 48 hours of the most recent exposure (28). In areas with limited antiviral medication availability, local public health authorities might provide additional

guidance about prioritizing chemoprophylaxis within groups at higher risk for complications. In certain situations, CDC or local public health authorities might recommend that antiviral medication resources be primarily directed at treatment and that antiviral chemoprophylaxis be used only in certain limited situations (28).

Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available. Adverse events associated with antiviral medications are generally mild and self-limited (see Adverse Events) but might result in morbidity resulting from medication side effects that outweigh the potential benefit of antiviral chemoprophylaxis (182,183). In addition, indiscriminate use of chemoprophylaxis might promote resistance to antiviral medications (115,184) or reduce antiviral medication availability for treatment of persons at higher risk for influenza complications or who are severely ill (28).

Patients receiving postexposure antiviral chemoprophylaxis should be informed that chemoprophylaxis lowers but does not eliminate the risk for influenza, that susceptibility to influenza returns once the antiviral medication is stopped, and that influenza vaccination is recommended if available. Patients receiving chemoprophylaxis should be encouraged to seek medical evaluation as soon as they develop a febrile respiratory illness suggestive of influenza because influenza virus infection still can occur while a patient is on chemoprophylaxis and might indicate infection with a virus resistant to the antiviral medication used. Either oseltamivir or zanamivir is recommended for antiviral chemoprophylaxis of 2009 H1N1, influenza A (H3N2), or influenza B influenza virus infection (Table 1).

An emphasis on early treatment is an alternative to chemoprophylaxis in managing certain persons who have had a suspected exposure to influenza virus (28). Persons with risk factors for influenza complications who are household or close contacts of persons with confirmed or suspected cases and health-care personnel who have occupational exposures can be counseled about the early signs and symptoms of influenza and advised to contact their health-care provider immediately for evaluation and possible early treatment if clinical signs or symptoms develop. Health-care providers should use clinical judgment regarding situations in which early recognition of illness and treatment might be an appropriate alternative. In some exposure circumstances (e.g., when the person exposed is at higher risk for complications of influenza virus infection), health-care providers might choose to give the exposed patient a prescription for an influenza antiviral. Providers may request that the patient contact the provider if signs or symptoms of influenza develop, obtain an antiviral medication as quickly as possible, and initiate treatment. These patients also should be counseled about influenza antiviral medication adverse events and informed that they remain susceptible to influenza virus infection after the antiviral medications are stopped.

Preexposure Chemoprophylaxis

In community studies of healthy adults administered antiviral medications during influenza virus activity, both oseltamivir and zanamivir had similar efficacy in preventing febrile, laboratory-confirmed influenza illness (zanamivir: 84%; oseltamivir: 82%) (13,17). Studies also have demonstrated efficacy for prevention of influenza among patients in institutional settings (179,185–187). For example, a 6-week study of oseltamivir chemoprophylaxis among nursing home residents demonstrated a 92% reduction in influenza illness (185). A 4-week study among community-dwelling persons at higher risk for influenza complications (median age: 60 years) demonstrated that zanamivir had an 83% effectiveness in preventing symptomatic laboratory-confirmed influenza (188). The efficacy of antiviral agents in preventing influenza among severely immunocompromised persons is unknown. A small nonrandomized study conducted in a stem cell transplant unit suggested that oseltamivir can prevent progression to pneumonia among influenza virus-infected patients and that therefore prevention of severe illness might be achievable with chemoprophylaxis (189).

When used, preexposure chemoprophylaxis must be administered for the duration of time when exposure might occur. The adverse events associated with long-term use are uncertain (181), and prolonged use of antivirals might select for resistance to antiviral medications. Therefore, preexposure antiviral chemoprophylaxis should be used only for persons who are at very high risk (e.g., severely immunosuppressed patients) for influenza-related complications who cannot otherwise be protected during times when a high risk for exposure exists. In the event of concern about potential shortage of antiviral medications, CDC or other health authorities might recommend prioritizing treatment of persons at higher risk for complications or who have severe influenza illness.

Duration of Chemoprophylaxis

Postexposure chemoprophylaxis is typically administered for a total of no more than 10 days after the most recent known exposure to a close contact known to have influenza (105). The likelihood of compliance and adverse events should be considered when determining the timing and duration for administering influenza antiviral medications for chemoprophylaxis. Failure to complete a course of oseltamivir for chemoprophylaxis because of gastrointestinal adverse events is common and might lead to antiviral resistance. In one study, only 15 (48%) of 31 primary school children and 41 (76%) of 54 secondary school children who started oseltamivir chemoprophylaxis completed a full course. Gastrointestinal adverse events (e.g., nausea and stomach discomfort) were cited as the most common reason for stopping medications before the recommended course was completed (190).

The duration of pre-exposure chemoprophylaxis based on potential exposure in the community depends on the duration of community influenza activity. Regimens as long as 28 days for zanamivir, and 42 days for oseltamivir, have been well tolerated, but no published data are available regarding use of regimens lasting >6 weeks (181). To be maximally effective as pre-exposure chemoprophylaxis, the drug must be taken each day for the duration of influenza activity in the community. During periods of widespread community activity and limited or no influenza vaccine availability, such as during the 2009 H1N1 pandemic, pre-exposure chemoprophylaxis has a very limited role because of concerns about antiviral medication supply, need for long-term use, and the potential for adverse events and selection for antiviral resistance.

Considerations for Antiviral Use if Oseltamivir-Resistant Virus Strains Are Circulating

During the 2008–09 influenza season, oseltamivir resistance among circulating seasonal influenza A (H1N1) virus strains affected clinical practice by 1) presenting challenges for the selection of antiviral medications for treatment and chemoprophylaxis of influenza and 2) providing additional reasons for clinicians to test patients for influenza virus infection and to consult available influenza viral surveillance data when evaluating persons with acute respiratory illness. However, since September 2009, almost all (99%) circulating influenza A and B viruses have been susceptible to oseltamivir (seasonal influenza A [H1N1] viruses have not been detected in the United States since 2009) (191). Information about antiviral treatment options has been outlined according to the results of influenza diagnostic testing (Table 3). Testing for antiviral resistance of influenza viruses is not routinely available in clinical settings, and many settings will not have access to influenza A virus subtyping information. CDC provides weekly updates on influenza virus surveillance at the national level (available at <http://www.cdc.gov/flu/weekly/fluactivity.htm>). If oseltamivir-resistant viruses are not circulating,

antiviral treatment for influenza should consist of either oseltamivir or zanamivir. However, continued changes in antiviral resistance are likely among influenza viruses, and clinicians should remain attentive to updates in antiviral treatment guidance.

Considerations for Antiviral Use When Antiviral Supplies Are Limited

During widespread illness or a pandemic, demand for antivirals might exceed available supplies. When antiviral supplies are limited, recommendations for antiviral treatment and chemoprophylaxis might differ according to disease incidence, severity of illness, and likelihood for influenza-related complications. Conservation of antiviral supplies to prioritize use for those with higher risk for complications or severe illness might be necessary. Updated information on the most recent guidance for antiviral use from CDC and local public health officials should be sought during widespread illness or a pandemic, and medications should be reserved as much as possible for use in patients who are severely ill or at higher risk for complications.

Control of Influenza Outbreaks in Institutions

Use of antiviral drugs for treatment and chemoprophylaxis of influenza is a key component of influenza outbreak control in institutions that house patients at higher risk for influenza complications. In addition to antiviral medications, other outbreak-control measures include instituting droplet and contact precautions and establishing cohorts of patients with confirmed or suspected influenza, re-offering influenza vaccination (if available) to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients (105,192--194). Both adamantanes and neuraminidase inhibitors have been used successfully to control outbreaks caused by susceptible strains when antiviral medications are combined with other infection-control measures (104,105,192--197).

Persons who are candidates for chemoprophylaxis should be provided with medications most likely to be effective against the influenza virus that is the cause of the outbreak, if known. Respiratory specimens should be obtained from ill persons during institutional outbreaks and sent for testing to determine the virus type or subtype of influenza A virus associated with the outbreak and to guide antiviral therapy decisions. Persons whose need for chemoprophylaxis is attributed to potential exposure to a person with laboratory-confirmed 2009 H1N1, influenza A (H3N2), or influenza B should receive oseltamivir or zanamivir. Zanamivir should be used when persons require chemoprophylaxis as a result of exposure to influenza virus strains that are suspected of being oseltamivir-resistant (108).

When chemoprophylaxis is indicated, a neuraminidase inhibitor medication should be started as early as possible to reduce the spread of the virus (105). In these situations, having preapproved orders from physicians or plans to obtain orders for antiviral medications on short notice can substantially expedite administration of antiviral medications. Specimens should be collected from ill persons for influenza typing, influenza A virus subtyping, or viral culture to assess antiviral resistance and provide data on the outbreak etiology. Chemoprophylaxis should be administered to all eligible residents, regardless of whether they received influenza vaccination during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 10 days after illness onset in the last patient (105). During institutional outbreaks, chemoprophylaxis also can be offered to unvaccinated staff members who provide care to persons at high risk of complications. Chemoprophylaxis should be considered for all employees, regardless of their influenza vaccination status, if indications exist that the outbreak is caused by a strain of influenza virus that is not well matched by the vaccine. Such indications might include multiple documented breakthrough influenza-virus infections among vaccinated persons who otherwise would be expected to respond to vaccination, studies indicating low vaccine effectiveness, or circulation in the surrounding community of suspected index case(s) of strains not contained in the vaccine.

To limit the potential transmission of antiviral drug-resistant influenza virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis. Guidelines recently published by IDSA provide a summary of the prevention and management of influenza outbreaks in institutional settings (105).

Dosage

Dosage recommendations vary by age group, intended use (chemoprophylaxis or treatment), and medical conditions (Table 1).

Duration of Antiviral Treatment

The recommended duration of treatment is 5 days (105,116,156). Longer treatment regimens might be necessary in severely ill hospitalized patients or persons with immunosuppression. Additional clinical guidelines on the use of antiviral medications to treat influenza are available and contain additional detail on treatment issues (51,105,198).

Adults

Zanamivir. Zanamivir is FDA-approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus, and for chemoprophylaxis of influenza among adults. Zanamivir is not recommended for persons with underlying airways disease (e.g., asthma or chronic obstructive pulmonary diseases) (156). Zanamivir is administered via an inhaler device in 5-mg blister doses per inhalation. The recommended dosage of zanamivir for treatment of influenza is 2 inhalations (1 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart). The chemoprophylaxis dosage of zanamivir is 10 mg (2 inhalations) once a day.

Oseltamivir. Oseltamivir is FDA-approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus and for chemoprophylaxis of influenza among adults (116). Oseltamivir is available for oral administration in 30 mg, 45 mg, and 75 mg capsules and liquid suspension. Dosage and schedule recommendations are listed (Table 1).

Children

Zanamivir. Zanamivir is FDA-approved for treatment of influenza among children aged ≥ 7 years. Zanamivir is approved for chemoprophylaxis of influenza among children aged ≥ 5 years. Treatment and chemoprophylaxis dosing and frequency are the same for children as for adults.

Oseltamivir. Oseltamivir is FDA-approved for treatment and chemoprophylaxis of influenza among children aged ≥ 1 year (116). Recommended treatment dosages vary by the weight of the child: 30 mg twice a day for children who weigh ≤ 15 kg, 45 mg twice a day for children who weigh >15 kg and up to 23 kg, 60 mg twice a day for those who weigh >23 kg and up to 40 kg, and 75 mg twice a day for

those who weigh >40 kg ([Table 1](#)) (116). Dosages for chemoprophylaxis are the same for each weight group, but doses are administered only once per day rather than twice ([Table 1](#)) (116).

Children aged <1 year are at higher risk for complications from influenza virus infection, but antiviral medications are not currently FDA-approved for use in children aged <1 year. During the 2009 H1N1 pandemic, recommendations for oseltamivir dosing of children aged <1 year were developed, on the basis of very limited pharmacokinetic data. The Emergency Use Authorization (EUA) issued during the 2009 H1N1 pandemic for this indication expired on June 23, 2010 (199), but recommendations on dosing for children aged <1 year are available (28,51,200,201). CDC recommends that clinicians who treat children aged 3--11 months administer 3 mg/kg/dose twice per day for treatment, and 3 mg/kg/dose once per day for chemoprophylaxis ([Table 4](#)). Infants aged <3 months are recommended to receive 3 mg/kg/dose twice per day for treatment. However, chemoprophylaxis for infants aged <3 months is not recommended unless the exposure situation was judged to be critical, because of a lack of data on use of oseltamivir on this age group. WHO subsequently recommended that children aged <14 days who are being treated for suspected or confirmed influenza receive 3 mg/kg/dose once daily (51,201). Lower doses should be considered for infants who are not receiving regular oral feedings or those who have substantially reduced renal function (201). Clinicians who are considering administering oseltamivir to infants should consult the CDC website for treatment recommendations because these might be revised if additional data become available.

Weight-based dosing recommendations for full-term infants are thought to be inappropriate for premature infants, (i.e., might lead to excessively high plasma concentrations) who might have slower clearance of oseltamivir as a result of immature renal function (200--202). Very limited data from a small cohort of premature infants suggested that oseltamivir concentrations among premature infants administered oseltamivir 1 mg/kg twice daily would be similar to those observed with the recommended treatment dose in term infants (3 mg/kg twice daily). Observed drug concentrations were highly variable among premature infants. These data are insufficient to recommend a specific dose of oseltamivir for premature infants (202). Observed drug concentrations were highly variable among premature infants. These data are insufficient to recommend a specific dose of oseltamivir for premature infants (200--202).

Amantadine. Because of resistance in circulating influenza A virus strains, amantadine is not recommended for antiviral treatment or chemoprophylaxis of influenza A. Amantadine is FDA-approved for treatment and chemoprophylaxis of influenza A virus infections among adults and children aged ≥1 year. Use of amantadine among children aged <1 year has not been evaluated adequately. The FDA-approved dosage for children aged 1--9 years for treatment and chemoprophylaxis is 4.4--8.8 mg/kg per day, not to exceed 150 mg per day. Although further studies are needed to determine the optimal dosage for children aged 1--9 years, physicians should consider prescribing only 5 mg/kg per day (not to exceed 150 mg per day) to reduce the risk for toxicity. The approved dosage for children aged ≥10 years is 200 mg per day (100 mg twice a day); for children weighing <40 kg, prescribing 5 mg/kg per day, regardless of age, is recommended (203).

Rimantadine. Because of resistance in circulating influenza A virus strains, rimantadine is not recommended for antiviral treatment or chemoprophylaxis of influenza A. Rimantadine is FDA-approved for chemoprophylaxis of influenza A virus infections among children aged ≥1 year and for treatment and chemoprophylaxis of influenza A virus infections among adults. Although rimantadine is approved only for chemoprophylaxis of influenza A among children, certain specialists in the management of influenza consider it appropriate for treatment among children (203). Use of rimantadine among children aged <1 year has not been evaluated adequately. Rimantadine should be administered in 1 or 2 divided doses at a dosage of 5 mg/kg per day, not to exceed 150 mg per day for children aged 1--9 years. The approved dosage for children aged ≥10 years is 200 mg per day (100 mg twice a day); however, for children weighing <40 kg, prescribing 5 mg/kg per day, regardless of age, is recommended (204).

Use of Medications for Symptomatic Relief in Children

Aspirin or aspirin-containing products (e.g. bismuth subsalicylate [Pepto Bismol]) should not be administered to any person aged ≤18 years with suspected influenza because of the risk for Reye's syndrome. For relief of fever, other antipyretic medications (e.g., acetaminophen or non steroidal anti-inflammatory drugs) are recommended. Children aged <4 years should not receive over-the-counter cold medications without a health-care provider being consulted first (205).

Persons Aged ≥65 Years

Oseltamivir and Zanamivir. No reduction in dosage for oseltamivir or zanamivir is recommended on the basis of age alone (116,156).

Amantadine. Because of resistance in circulating influenza A virus strains, amantadine is not currently recommended for antiviral treatment or chemoprophylaxis of influenza A. The daily dosage of amantadine for persons aged ≥65 years should not exceed 100 mg for chemoprophylaxis or treatment of amantadine-susceptible influenza A viruses, because renal function declines with increasing age. For certain older persons, the dose should be reduced further (206,207).

Rimantadine. Because of resistance in circulating influenza A virus strains, rimantadine is not recommended for antiviral treatment or chemoprophylaxis of influenza A. Among older persons, the incidence and severity of central nervous system (CNS) side effects are substantially lower among those taking rimantadine at a dosage of 100 mg/day than among those taking amantadine at dosages adjusted for estimated renal clearance (204). However, chronically ill older persons have had a higher incidence of CNS and gastrointestinal symptoms and serum concentrations two to four times higher than among healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day (204,205,208).

For chemoprophylaxis of rimantadine-susceptible influenza A viruses among persons aged ≥65 years, the recommended dosage is 100 mg/day. For treatment of amantadine-susceptible influenza A virus infection in older persons in the community, a reduction in dosage to 100 mg/day should be considered if they experience side effects when taking a dosage of 200 mg/day. For treatment of older nursing home residents, the dosage of rimantadine should be reduced to 100 mg/day (204).

Pregnant Women

Pregnant women with confirmed or suspected influenza are recommended to receive antiviral treatment, and treatment of fever with acetaminophen (209). Pregnancy should not be considered a contraindication to oseltamivir or zanamivir use. Pregnant women are known to be at higher risk for complications from infection with seasonal influenza viruses (210,211) and severe disease among pregnant women was reported during past pandemics (209,212,213). Multiple studies have demonstrated that pregnant women are at higher risk for influenza complications from 2009 H1N1 virus infection (12,24,25,68).

Oseltamivir, zanamivir, rimantadine, and amantadine are "Pregnancy Category C" medications, indicating that data from clinical studies are not adequate to assess the safety of these medications for pregnant women (116,156). Although a few adverse events have been reported occasionally in pregnant women who took these medications, no causal relation between the use of these medications and these adverse events has been established (214, 215). In addition, fever can cause adverse fetal outcomes, and reducing fever, whether directly by using antipyretics, or indirectly by reducing the duration and severity of symptoms with antiviral medications, might reduce this risk (209). One retrospective cohort study found no evidence of an association between oseltamivir use during pregnancy and a variety of adverse events, including preterm birth, premature rupture of membranes, increased duration of hospital stay for mother or neonate, malformations, or fetal weight (214).

Oseltamivir is preferred for treatment of pregnant women. Zanamivir might be preferred by some providers because of its limited systemic absorption; however, respiratory complications that might be associated with zanamivir because of its inhaled route of administration need to be considered, especially in women at risk for respiratory problems (209). Pregnant women are recommended to receive the same antiviral dosing as nonpregnant persons (106).

As with others at high risk for influenza-related complications, treatment of pregnant women with suspected or confirmed influenza virus infection should begin as early as possible after onset of illness. Treatment should not be delayed while waiting for results of diagnostic testing (28,51).

Persons with Impaired Renal Function

Zanamivir. Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir, decreases in renal clearance, increases in half-life, and increased systemic exposure to zanamivir were reported (116). However, a limited number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose (173,214). On the basis of these considerations, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild-to-moderate or severe impairment in renal function (156).

Oseltamivir. Serum concentrations of oseltamivir carboxylate, the active metabolite of oseltamivir, increase with declining renal function (116). For patients with creatinine clearance of 10–30 mL per minute, a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the chemoprophylaxis dosage to 75 mg every other day is recommended (116,216). Treatment or chemoprophylaxis dosing recommendations have been proposed for patients undergoing routine renal dialysis treatment but are based on limited pharmacokinetic data (217,218).

Amantadine. When used for amantadine-susceptible influenza A virus infection, a reduction in dosage is recommended for patients with creatinine clearance <50 mL/min. Guidelines for amantadine dosage on the basis of creatinine clearance are located in the package insert. Because recommended dosages on the basis of creatinine clearance might provide only an approximation of the optimal dose for a specific patient, such persons should be observed carefully for adverse reactions. If necessary, further reduction in the dose or discontinuation of the drug might be indicated because of side effects. Hemodialysis contributes minimally to amantadine clearance (219).

Rimantadine. When used for rimantadine-susceptible influenza A virus infection, a reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance <10 mL/min. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including older persons, should be monitored for adverse effects, and, if necessary, either the dosage should be reduced or the drug should be discontinued. Hemodialysis contributes minimally to rimantadine clearance (204).

Persons with Liver Disease

Zanamivir and oseltamivir. Use of zanamivir or oseltamivir has not been studied among persons with liver disease.

Amantadine. No increase in adverse reactions to amantadine has been observed among persons with liver disease. Rare instances of reversible elevation of liver enzymes among patients receiving amantadine have been reported, although a specific relation between the drug and such changes has not been established (220).

Rimantadine. A reduction in dosage to 100 mg/day is recommended for persons with severe hepatic dysfunction (204).

Persons with Seizure Disorders

Zanamivir and oseltamivir. Seizure events have been reported during postmarketing use of zanamivir and oseltamivir (115,156), although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

Amantadine. An increased incidence of seizures has been reported among patients with a history of seizure disorders who have received amantadine (221). Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine.

Rimantadine. Seizures (or seizure-like activity) have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine (208). The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been evaluated adequately.

Persons with Immunosuppression

A recent retrospective case-control study demonstrated that oseltamivir was safe and well tolerated when used during the control of an influenza outbreak among hematopoietic stem cell transplant recipients living in a residential facility (222).

Adverse Events

When considering use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (Table 1); presence of other medical conditions; indications for use (i.e., chemoprophylaxis or therapy); and the potential for interaction with other medications.

Zanamivir

Limited data are available about the safety or efficacy of zanamivir for persons with underlying respiratory disease or for persons with complications of acute influenza, and zanamivir is licensed only for use in persons without underlying respiratory or cardiac disease (156). In a study of zanamivir treatment of ILI among persons with asthma or chronic obstructive pulmonary disease in which study medication was administered after use of a β 2-agonist, 13% of patients receiving zanamivir and 14% of patients who received inhaled placebo (powdered lactose vehicle alone) experienced a >20% decline in forced expiratory volume in 1 second (FEV1) after treatment (156,223). However, in a phase-I study of persons with mild or moderate asthma who did not have ILI, one of 13 patients experienced bronchospasm after administration of zanamivir (156). In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Because of the risk for serious adverse events and because efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying pulmonary disease (156). Allergic reactions, including oropharyngeal or facial edema, also have been reported during postmarketing surveillance (156,223).

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and for those receiving inhaled placebo (i.e., powdered lactose vehicle alone) (15,16,142). The most common adverse events reported by both groups were diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose, and throat infections. Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined (156). Zanamivir does not impair the immunologic response to trivalent inactivated vaccine (224).

Oseltamivir

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting: approximately 10%; vomiting: approximately 9%) than among persons receiving placebo (nausea without vomiting: approximately 6%; vomiting: approximately 3%) (91,111,188). Among children treated with oseltamivir, 14% had vomiting, compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect (21), and a limited number of adults who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (116). Similar types and rates of adverse events were reported in studies of oseltamivir chemoprophylaxis (116). Nausea and vomiting might be less severe if oseltamivir is taken with food (116). In several reports based on public health responses to school outbreaks of 2009 H1N1, self-reported nausea and vomiting have been more common than reported in clinical studies and might reduce compliance with recommended treatment or chemoprophylaxis regimens among children (155,189,190). No published studies have assessed whether oseltamivir impairs the immunologic response to trivalent inactivated influenza vaccine.

Transient neuropsychiatric events (self-injury or delirium) have been reported postmarketing among persons taking oseltamivir; the majority of reports were among Japanese adolescents and adults (225). Several recent analyses and reviews have found that oseltamivir is not associated with an increased risk for neuropsychiatric events (226,227). FDA advises that persons receiving oseltamivir be monitored closely for abnormal behavior (116).

Limited safety data on oseltamivir treatment for seasonal influenza in children aged <1 year have not demonstrated any age-related safety concerns, but careful attention to dosing is essential (200,228–230). Health-care providers should be aware of the limited data on safety and dosing when considering oseltamivir use for infants, and carefully monitor infants for adverse events. Clinicians and pharmacists should pay careful attention to the potential for dosing errors in young children (231).

Reporting of Adverse Events that Occur After Administering Antiviral Medications

Health-care professionals should report any serious adverse event after antiviral medication use promptly to MedWatch, the FDA's adverse event reporting program for medications. Serious adverse events are defined as medical events that involve hospitalization, death, life-threatening illness, disability, or certain other medically important conditions. Any serious adverse event that follows administration of medications should be reported to FDA at <http://www.fda.gov/medwatch/report/hcp.htm> .

Drug Interactions

Clinical data are limited regarding drug interactions with zanamivir. No known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro and animal study data (116,232).

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential exists for interaction with other agents excreted by this pathway. For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of oseltamivir carboxylate by approximately 50% and a corresponding approximate twofold increase in the plasma levels of oseltamivir carboxylate (163).

No published data from clinical trials are available concerning the safety or efficacy of using combinations of different classes of influenza antiviral drugs. One recent study suggested that use of oseltamivir plus zanamivir was less efficacious than monotherapy with either drug alone (233). Providers should consult package inserts for more detailed information about potential drug interactions (available at <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm> .

Emergency Use Authorization

Licensed vaccines and drugs, or approved therapeutics and medical devices treat, prevent, or mitigate disease. If an emerging public health threat is identified for which no licensed or approved product exists, the Project BioShield Act of 2004 authorizes the FDA Commissioner to issue an EUA so appropriate countermeasures (e.g., distribution of unlicensed antiviral medications) can be taken quickly to protect the safety of the U.S. population. Specifically, these countermeasures can facilitate the diagnosis, treatment, or prevention of serious or life-threatening diseases, or for conditions caused by chemical, biologic, or radiologic agents for which no adequate, approved, or available alternatives exist. CDC in conjunction with NIH provides expert consultation to the FDA Commissioner regarding the appropriateness of EUA requests and supports the distribution of products stored in the Strategic National Stockpile (SNS) formulary (234). EUAs in effect during the 2009 H1N1 pandemic have expired because there is no longer a declared emergency.

Additional Information

Each year, ACIP provides general, annually updated information regarding prevention and control of influenza. The following additional guidance on antiviral treatment of influenza and other reports related to controlling and preventing influenza among specific

populations (e.g., immunocompromised persons, health-care personnel, hospital patients, pregnant women, children, and travelers) are available:

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* A list of the members appears on page 25 of this report.

† Influenza virus infection can be confirmed by different testing methods that might be available in a clinical setting or laboratory (e.g., rapid influenza diagnostic test, immunofluorescence, reverse transcription-polymerase chain reaction, or viral culture).

TABLE 1. Recommended dosage and schedule of influenza antiviral medications* for treatment† and chemoprophylaxis§

Antiviral agent		Age group (yrs)				
		1--6	7--9	10--12	13--64	≥65
Zanamivir	Treatment, influenza A and B	NA	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
	Chemoprophylaxis, influenza A and B	NA for ages 1--4	Ages 5--9 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily
Oseltamivir¶	Treatment,** influenza A and B	Dose varies by child's weight**	Dose varies by child's weight**	Dose varies by child's weight** >40 kg = adult dose	75 mg twice daily	75 mg twice daily
	Chemoprophylaxis, influenza A and B	Dose varies by child's weight††	Dose varies by child's weight††	Dose varies by child's weight†† >40 kg = adult dose	75 mg once daily	75 mg once daily

Abbreviation: NA = not approved

* Zanamivir is manufactured by GlaxoSmithKline (Relenza --- inhaled powder). Zanamivir is approved for treatment of persons aged ≥7 years and approved for chemoprophylaxis of persons aged ≥5 years. Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease. Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu --- tablet). Oseltamivir is approved for treatment or chemoprophylaxis of persons aged ≥1 year. Oseltamivir is available for oral administration in 30 mg, 45 mg, and 75 mg capsules and liquid suspension. No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children aged <1 year. This information is based on data published by the Food and Drug Administration (FDA), available at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm100228.htm> .

† Recommended duration for antiviral treatment is 5 days. Longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.

§ Recommended duration is 10 days when administered after a household exposure and 7 days after the most recent known exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the most recent known case was identified

¶ See Table 4 for information about use of oseltamivir for infants aged <1 year. A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.

** The treatment dosing recommendation for oseltamivir for children aged ≥1 year who weigh ≤15 kg is 30 mg twice a day. For children who weigh >15 kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh >23 kg and up to 40 kg, the dose is 60 mg twice a day. For children who weigh >40 kg, the dose is 75 mg twice a day.

†† The chemoprophylaxis dosing recommendation for oseltamivir for children aged ≥1 year who weigh ≤15 kg is 30 mg once a day. For children who weigh >15 kg and up to 23 kg, the dose is 45 mg once a day. For children who weigh >23 kg and up to 40 kg, the dose is 60 mg once a day. For children who weigh >40 kg, the dose is 75 mg once a day.

TABLE 2. Summary of antiviral resistance among influenza viruses worldwide, December 2010*

Antiviral	Influenza A viruses		Influenza B viruses†
	2009 H1N1	H3N2	B
Adamantanes (not recommended currently)	Resistant	Resistant	No activity
Oseltamivir	Susceptible	Susceptible	Susceptible
Zanamivir	Susceptible	Susceptible	Susceptible

* Information regarding antiviral resistance is updated weekly and is available at <http://www.cdc.gov/flu/weekly>. Rare instances of infection with oseltamivir-resistant 2009 H1N1 virus strains have been reported; >99% of influenza viruses circulating since September 2009 have been sensitive to oseltamivir.

† Yamagata and Victoria lineages

BOX. Summary of influenza antiviral treatment recommendations

• Early antiviral treatment can reduce the risk of complications from influenza (e.g., pneumonia, respiratory failure, and death). Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who

--- is hospitalized;

--- has severe, complicated, or progressive illness; or

--- is at higher risk for influenza complications.

• Persons at higher risk for influenza complications recommended for antiviral treatment include:

--- children aged <2 years;*

--- adults aged ≥65 years;

--- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);

--- persons with immunosuppression, including that caused by medications or by HIV infection;

--- women who are pregnant or postpartum (within 2 weeks after delivery);

--- persons aged <19 years who are receiving long-term aspirin therapy;

--- American Indians/Alaska Natives;

--- persons who are morbidly obese (i.e., body-mass index ≥40); and

--- residents of nursing homes and other chronic-care facilities.

• Clinical judgment, on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important to consider when making antiviral treatment decisions for high-risk outpatients. When indicated, antiviral treatment should be started as soon as possible after illness onset.

• The greatest benefit is when antiviral treatment is started within 48 hours of influenza illness onset. However, antiviral treatment might still be beneficial in patients with severe, complicated, or progressive illness and in hospitalized patients when administered >48 hours from illness onset.

• Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.[†]

* Although all children aged <5 years are considered at higher risk for complications from influenza, the highest risk is for those aged <2 years, with the highest hospitalization and death rates among infants aged <6 months. Because many children with mild febrile respiratory illness might have other viral infections (e.g., respiratory syncytial virus, rhinovirus, or parainfluenza virus, or human metapneumovirus), knowledge about other respiratory viruses as well as influenza virus strains circulating in the community is important for treatment decisions. The likelihood of influenza virus infection in a patient depends on the prevalence of influenza activity in the local community and on the patient's signs and symptoms. Information about influenza activity in the United States during the influenza season is available at <http://www.cdc.gov/flu/weekly>. For information on local community influenza activity, clinicians should contact their local and state health departments.

[†] Recommended antiviral medications (neuraminidase inhibitors) are not licensed for treatment of children aged <1 year (oseltamivir) or those aged <7 years (zanamivir). Oseltamivir was used for treatment of 2009 pandemic influenza A (H1N1) virus infection in children aged <1 year under an Emergency Use Authorization, which expired on June 23, 2010. Limited information regarding use of oseltamivir for children from birth through age 1 year is available (see Table 4). Confirmation of influenza virus infection may be performed by different influenza testing methods. Information on influenza testing is available at <http://www.cdc.gov/flu/professionals/diagnosis/index.htm>. In areas with limited antiviral medication availability, local public health authorities might provide additional guidance about prioritizing treatment within groups at higher risk for complications. Current CDC guidance on treatment of influenza should be consulted; updated recommendations from CDC are available at <http://www.cdc.gov/flu>.

TABLE 3. Recommendations for the selection of antiviral treatment using laboratory test results and viral surveillance data*

Rapid antigen, RT-PCR or other laboratory test	Preferred medication(s)[†]	Alternative (combination antiviral treatment)
Not performed or negative but clinical suspicion for influenza [†]	Oseltamivir or zanamivir	None
Positive A or positive A+B§	Oseltamivir or zanamivir	None
Positive 2009 influenza A(H1N1)	Oseltamivir or zanamivir	None
Positive A(H3N2), or B	Oseltamivir or zanamivir	None

Abbreviation: RT-PCR = reverse transcription-polymerase chain reaction.

* Antiviral recommendations might change over time. Influenza antiviral medications used for treatment are most beneficial when initiated within the first 2 days of illness. Clinicians should consult the package insert of each antiviral medication for specific dosing information, approved indications and ages, contraindications/warnings/precautions, and adverse effects.

† Influenza viral surveillance data might help guide antiviral choices if oseltamivir resistance becomes more prevalent among circulating influenza viruses. Consult guidance from local or state public health laboratories or CDC for further information regarding currently circulating viruses. CDC viral surveillance data are updated weekly during the influenza season and is available at <http://www.cdc.gov/flu/weekly>.

§ Positive A+B indicates a rapid antigen test that cannot distinguish between influenza A and influenza B viruses.

TABLE 4. Dosing recommendations for treatment or chemoprophylaxis of children aged <1 year using oseltamivir*

Age	Recommended treatment dose for 5 days [†]	Recommended chemoprophylaxis dose for 10 days [†]
<3 mos	3 mg/kg/dose twice daily	Not recommended unless situation judged critical because of limited data on use in this age group
3--11 mos	3 mg/kg/dose twice daily	3 mg/kg/dose once daily

* Oseltamivir is not approved by the Food and Drug Administration (FDA) for use in children aged <1 year. An Emergency Use Authorization (EUA) was issued by the FDA on April 28, 2009, and expired on June 23, 2010 (available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM216494.pdf> ). This EUA allowed use of oseltamivir for treatment or chemoprophylaxis of 2009 pandemic influenza A (H1N1) virus infection during the pandemic in infants aged <1 year. Currently circulating 2009 H1N1, seasonal influenza A (H3N2), and B viruses have similar sensitivity to oseltamivir.

† Current weight-based dosing recommendations are not appropriate for premature infants. Premature infants might have slower clearance of oseltamivir because of immature renal function, and doses recommended for full-term infants might lead to very high drug concentrations in this age group. Very limited data from a small cohort of premature infants suggested that oseltamivir concentrations among premature infants administered oseltamivir 1 mg/kg twice daily would be similar to those observed with the recommended treatment dose in term infants (3 mg/kg twice daily). Observed drug concentrations were highly variable among premature infants. These data are insufficient to recommend a specific dose of oseltamivir for premature infants (202).

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Pharmacy for its funding support (\$10,000) for a study to analyse written medical information regarding the possible harms of statins. Peter Doshi is also an unpaid member of the IMEDS steering committee at the Reagan–Udall Foundation for the FDA, which focuses on drug safety research. CDeIM is the Co-ordinating Editor of the Acute Respiratory Infections Group of the Cochrane Collaboration. CDeIM reports personal fees from Key Pharmaceuticals during the conduct of the study; grants from the National Health and Medical Research Council (Australia), grants from NIHR (UK), personal fees from Elsevier and BMJ Books, from conference organisers for International Viral Infections Conference, personal fees from GlaxoSmithKline Pharmaceuticals, personal fees from Key Pharmaceutical, outside the submitted work. Rokuro Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir for the applications by their families for adverse reaction relief by the Pharmaceuticals and Medical Devices Agency (PMDA) and in the lawsuits for revocation of the PMDA's decision concerning with these reactions. Most of the cases were reported in the *International Journal of Research Studies in Management* (2008;**20**:5–36). Rokuro Hama was an expert witness in the lawsuit on the adverse reaction of (death from) gefitinib against AstraZeneca and Japanese Minister of Health Labour and Welfare, and provided scientific opinions and expert testimony. He argued that gefitinib's fatal toxicity was known before approval in Japan, as shown in 'Gefitinib story' (<http://npojip.org/english/The-gefitinib-story.pdf>) and in other articles (<http://npojip.org/>). Plaintiffs finally lost the case on 12 April 2013 at the Supreme Court of Japan. Rokuro Hama has received royalties from a published book.

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Abstract

Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data

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Background: Neuraminidase inhibitors (NIs) are stockpiled and recommended by public health agencies for treating and preventing seasonal and pandemic influenza. They are used clinically worldwide.

Objectives: To (1) describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all clinical study reports (CSRs) of published and unpublished randomised, placebo-controlled trials and regulatory comments; and (2) determine the effect of oseltamivir (Tamiflu®, Roche) treatment on mortality in patients with 2009A/H1N1 influenza.

Methods: We searched trial registries, electronic databases and corresponded with regulators and sponsors to identify randomised trials of NIs. We requested full CSRs and accessed regulators' comments. We included only those trials for which we had CSRs. To examine the effects of oseltamivir on 2009A/H1N1 influenza mortality, we requested individual patient data (IPD) from corresponding authors of all included observational studies.

Results: *Effect of oseltamivir and zanamivir (Relenza®, GlaxoSmithKline) in the prevention and treatment of influenza:* Oseltamivir reduced the time to first alleviation of symptoms in adults by 16.8 hours [95% confidence interval (CI) 8.4 to 25.1 hours]. Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days). Oseltamivir reduced unverified pneumonia in adult treatment [risk difference (RD) 1.00%, 95% CI 0.22% to 1.49%]; similar findings were observed with zanamivir prophylaxis in adults (RD 0.32%, 95% CI 0.09% to 0.41%). Oseltamivir treatment of adults increased the risk of nausea (RD 3.66%, 95% CI 0.90% to 7.39%) and vomiting (RD 4.56%, 95% CI 2.39% to 7.58%). In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75% to 10.29%). Both oseltamivir and zanamivir prophylaxis reduced the risk of symptomatic influenza in individuals (oseltamivir RD 3.05%, 95% CI 1.83% to 3.88%; zanamivir RD 1.98%, 95% CI 0.98% to 2.54%) and in households (oseltamivir RD 13.6%, 95% CI 9.52% to 15.47%; zanamivir RD 14.84%, 95% CI 12.18% to 16.55%). Oseltamivir increased psychiatric adverse events in the combined on- and

off-treatment periods (RD 1.06%, 95% CI 0.07% to 2.76%) and the risk of headaches while on treatment (RD 3.15%, 95% CI 0.88% to 5.78%). *Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza*: Analysis of summary data of 30 studies as well as IPD of four studies showed evidence of time-dependent bias. After adjusting for time-dependent bias and potential confounding variables, competing risks analysis of the IPD showed insufficient evidence that oseltamivir reduced the risk of mortality (hazard ratio 1.03, 95% CI 0.64 to 1.65).

Conclusions: Oseltamivir and zanamivir cause small reductions in the time to first alleviation of influenza symptoms in adults. The use of oseltamivir increases the risk of nausea, vomiting, psychiatric events in adults and vomiting in children. Oseltamivir has no protective effect on mortality among patients with 2009A/H1N1 influenza. Prophylaxis with either NI may reduce symptomatic influenza in individuals and in households. The balance between benefits and harms should be considered when making decisions about use of NIs for either prophylaxis or treatment of influenza.

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Glossary

Clinical study reports Detailed reports of a clinical trial, usually submitted to regulators, following a prescribed International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use format. Roche's reports follow a modular structure (see *Appendix 9*). Reports can be several hundred pages long and contain details of the planned design, conduct (protocol), analysis (reporting analysis plan) and results of the trial.

Compliharm Term describing events defined as either complications or harms according to ambiguous criteria that appeared to include time of analysis (with times either unspecified or inconsistent among trials) and whether or not participants were infected (by influenza). In oseltamivir treatment trials some potential harms or complications could be caused by both medication or influenza infection (e.g. vomiting), hence our classification as a compliharm.

Consolidated Standards of Reporting Trials-based extraction Extraction, synthesis and appraisal method used in this review for data from clinical study reports. Reconstructions were done by pairs of review authors and assessed in the authors' plenary session to decide whether or not included trials could proceed to stage 2 of the analysis. The structure of the reconstruction follows that of the Consolidated Standards of Reporting Trials statement.

Freedom of information Enshrined by law in the US and European Medicines Agency policy in Europe. Freedom-of-information requests in this review have been a means of access to clinical study reports and regulatory comments (regulatory information).

Individual patient data Anonymised individual data listings of characteristics and results, which form the basis for the synthetic analyses in clinical study reports.

Japanese Summary Basis for Approval (of a drug) Summary of the application dossiers included as one of the documents that is prepared and attached by the sponsoring pharmaceutical company. These are submitted to the regulatory body for approval of a new drug.

Modules Basic structure of Roche's trial reports. Today, the term 'Modules' refers to the components of a regulatory submission, as set by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2011). Clinical study reports are just one 'module' of a regulatory submission.

Protocol Document reporting the trial's planned design and conduct, with amendments (when relevant). Confusingly, also used in submissions and regulatory documents as synonymous with study.

Public health drugs Drugs in which a considerable quantity of public money has been invested and/or are on the World Health Organization essential drugs list.

Regulatory information Term comprising clinical study reports (data) and regulatory comments and reviews.

Reporting Analysis Plan Plan of analysis that is usually linked to the trial protocol, explaining what and how the authors intend to analyse.

Table of content of regulatory reviews and comments on industry submissions Our table of content indicates which trial is cited, in which document, on which page and how many times.

Table of contents-evidence Annotated version of the table of contents. Comments and annotation are preliminary and form the basis for the weaving of the important aspects into the review narrative.

Time lock Date (12 April 2011) after which no documentation would be reviewed in the January 2012 version of the review. A cut-off was made necessary by the sheer scale of our data holdings. We were initially funded to review the full clinical study reports of the 10 treatment trials included in the Kaiser *et al.* paper (Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 2003;**63**:1667–72). We were able to access the 10 module 1s and regulatory comments (approximately 6000 pages in total). As the funder-stipulated deadline to producing our review progressively shortened, and our understanding of the issues evolved, we received notification that although the balance of the 10 study reports was unlikely to be accessible by our deadline, we would receive substantial quantities of regulatory documents from the European Medicines Agency in four tranches. When we held our second face-to-face meeting in April 2011 we had just received our first tranche of clinical study reports, consisting of just over 10,000 pages, bringing our total holdings to 16,000 pages. We decided that we did not have the resources to review any further documentation within our current funding and imposed a data time lock. Any documentation received after this date would be reviewed if and when we had more resources. The balance of documents (a further 14,000 pages) are included in this review.

Trial ID Means of identifying a trial. Usually made up of letters and numbers (WV15799). At times the ID bears a letter suffix indicating the last version of the protocol followed in the trial (e.g. WV15799H, i.e. trial carried out following amendment H).

Trial programme Series of trials designed and carried out to achieve registration or to answer specific questions. Usually, programmes of the same drug or intervention focus on the same indication or the same study population.

List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation	ITTIINAB	intention-to-treat influenza-infected index cases who had negative virology at baseline
BMJ	<i>British Medical Journal</i>		
CDC	US Centers for Disease Control and Prevention	MD	mean difference
CENTRAL	Cochrane Central Register of Controlled Trials	NCI-CTC V2.0	National Cancer Institute-Common Toxicity Criteria Version 2.0
CI	confidence interval	NDA	New Drug Application
CONSORT	Consolidated Standards of Reporting Trials	NHS EED	National Health Service Economic Evaluation Database
CRF	case report form	NI	neuraminidase inhibitor
CSR	clinical study report	NICE	National Institute for Health and Care Excellence
CTCAE V4.0	Common Terminology Criteria for Adverse Events Version 4.0	NNTB	number needed to treat to benefit
DARE	Database of Abstracts of Reviews of Effects	NNTH	number needed to treat to harm
df	degrees of freedom	NSAID	non-steroidal anti-inflammatory drug
EMA	European Medicines Agency	OR	odds ratio
FDA	US Food and Drug Administration	PEP	post-exposure prophylaxis
FOI	freedom of information	RCT	randomised controlled trial
GSK	GlaxoSmithKline	RD	risk difference
HEED	Health Economic Evaluations Database	RR	risk ratio
HR	hazard ratio	SAP	statistical analysis plan
ILI	influenza-like illness	SBA	Summary Basis of Approval
IPD	individual patient data	td-Cox	Cox regression including treatment as a time-dependent exposure
ITT	intention to treat	TOC	table of contents
ITTI	intention-to-treat-influenza-infected	WHO	World Health Organization

Plain English summary

Regulatory information on trials of oseltamivir (Tamiflu) and zanamivir (Relenza) for influenza in adults and children

Oseltamivir and zanamivir have been stockpiled in many countries to treat and prevent seasonal and pandemic influenza, before an influenza vaccine matched to the circulating virus becomes available.

How this review has been approached

We have updated and combined our reviews on the antiviral drugs zanamivir and oseltamivir for influenza in adults and children on the basis of the manufacturers' reports to regulators (clinical study reports) and the regulators' comments. We have called these comments and reports 'regulatory information'.

What we have found

We have used data from 46 trials (20 oseltamivir and 26 zanamivir studies) in this review. We found that both drugs shorten the duration of symptoms of influenza-like illness (unconfirmed influenza or 'the flu') by less than a day (there was no effect in asthmatic children, but in otherwise healthy children there was). Oseltamivir did not affect the number of hospitalisations. In children with asthma there was no clear effect on the time to first alleviation of symptoms.

Prophylaxis trials showed that oseltamivir and zanamivir reduced the risk of symptomatic influenza.

Oseltamivir use was associated with nausea, vomiting, headaches and psychiatric events; these last two were when it was used to prevent influenza (prophylaxis).

Low-quality data, adjusted for some likely biases, failed to show a reduction in mortality in very ill patients with H1N1 2009 and treated with oseltamivir compared with those who did not receive influenza antiviral drugs.

Scientific summary

Introduction

The World Health Organization (WHO) lists oseltamivir (Tamiflu®, Roche) as an essential influenza pandemic drug and worldwide there is considerable stockpiling for emergency use, but there is uncertainty on the reliability of the evidence base of oseltamivir and its fellow neuraminidase inhibitor (NI) zanamivir [Relenza®, GlaxoSmithKline (GSK)] and on their safety and efficacy.

In 2009 it emerged that there was substantial reporting bias in published evidence, and this led us to develop a new approach in order to update and amalgamate two pre-existing Cochrane reviews on NIs in children and adults. Over a period of 4 years we worked to obtain full, unabridged, clinical study reports for all trials in both drugs' evidence development programme. We based our current review and its 2012 predecessor uniquely on clinical study reports and other regulatory material, including regulators reports, that were available in the USA as Summary Basis of Approval and in the EU as European Public Assessment Report.

This undertaking was facilitated by the change of policy at the European Medicines Agency (EMA) in late 2010, allowing release for the first time of clinical study reports that were used during the Market Authorisation Application and its processing. Additionally, this process received the backing of the *British Medical Journal*, which launched its open data campaign on the basis of our quest for clinical study reports.

Here we present our methods and results, based on the full set of clinical study reports that fit our inclusion criteria. The reports, together with all relevant correspondence and the editors' and referees' comments, are also available. We also report our efforts to develop methods of reviewing clinical study reports and putting the trial evidence in the context of the numerous non-randomised studies that have been published since the 2009 influenza outbreak in order to present a complete picture of the topic.

Objectives

Our objective was to assess the effects of the NIs zanamivir and oseltamivir for influenza on the basis of regulatory material and within their context of use. Specifically, we aimed to:

1. describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all clinical study reports of published and unpublished randomised, placebo-controlled trials and regulatory comments
2. determine the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza.

Methods

To evaluate the effectiveness of NIs for preventing and treating influenza in adults and children:

- We searched trial registries, electronic databases (to 22 July 2013) and regulatory archives, and corresponded with manufacturers to identify all trials. We also requested clinical study reports. We focused on the primary data sources of manufacturers but we checked that there were no published randomised controlled trials (RCTs) from non-manufacturer sources by running electronic searches in the following databases: the Cochrane Central Register of Controlled Trials, MEDLINE, MEDLINE (via Ovid), EMBASE, EMBASE.com, PubMed (not MEDLINE), the Database of Abstracts of Reviews of Effects, the NHS Economic Evaluation Database and the Health Economic Evaluations Database.
- We included evidence from RCTs testing the effects of NIs for prophylaxis, post-exposure prophylaxis and treatment of influenza.
- We included only trials on people who were exposed to naturally occurring influenza, with or without symptoms.
- We analysed the effects of zanamivir and oseltamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalisations and adverse events in the intention-to-treat population.
- The sizeable quantity of available data led us to subdivide the extraction, appraisal and analysis of the data into a two-stage exercise. In stage 1 we assessed the reliability and completeness of the identified trial data. We decided to include in stage 2 of the review (full analysis following standard Cochrane methods) only data that satisfied the following three criteria: (1) completeness, (2) internal consistency and (3) external consistency.
- We used regulatory information to assess the possible correlation between citation frequency of oseltamivir treatment trials in the US Food and Drug Administration regulatory documents and trial size.
- We used the random-effects approach of DerSimonian and Laird (DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88), based on mean differences with 95% confidence interval (CI) for analysis of time to first alleviation of symptoms. For all other outcomes we used the random-effects approach for binary data of DerSimonian and Laird, where tau-squared was estimated using the inverse variance method.

To determine the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza:

- We searched MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature, Web of Science and the Latin American and Caribbean Health Sciences Literature databases (see *Appendix 16* for details of our search strategy) for observational studies. We also hand-searched bibliographies from two relevant documents published by the WHO and two previous reviews.
- We included any study of patients with 2009A/H1N1 influenza reporting mortality outcomes and exposure to oseltamivir with at least 5% of patients untreated with influenza antiviral drugs and five or more deaths overall.
- We requested individual patient data (IPD) from the corresponding authors of all included studies and kept a record of all correspondence that ensued. IPD was provided for four studies, sent via e-mail in Excel® 2010 (Microsoft Corporation, Redmond, WA, USA) or Stata 12 files (StataCorp LP, College Station, TX, USA), checked for consistency and analysed in SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Effectiveness of neuraminidase inhibitors in the treatment of influenza

We obtained 107 clinical study reports from the EMA, GSK and Roche. We included 53 trials in stage 1 and 46 in stage 2, including 20 oseltamivir (9623 participants) and 26 zanamivir trials (14,628 participants). Most of the zanamivir studies and half of the oseltamivir studies were at high risk of selection bias as a result of inadequate reporting.

In adult treatment, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% CI 8.4 to 25.1 hours; $p < 0.0001$). There was no effect in asthmatic children, for whom symptoms increased by 5.2 hours (11.1 hours lower to 21.4 hours higher), but in otherwise healthy children there was reduction by 29 hours (95% CI 12 to 47 hours; $p = 0.001$). Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days; $p < 0.00001$) but the effect in children was not significant. In subgroup analysis there was no difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups ($p = 0.53$).

Oseltamivir significantly reduced unverified pneumonia [risk difference (RD) 1.00%, 95% CI 0.22% to 1.49%] in the treated population. The effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. There was no significant effect on pneumonia in children [risk ratio (RR) 1.06, 95% CI 0.62 to 1.83]. There was no significant effect of zanamivir treatment on pneumonia (RR 0.90, 95% CI 0.58 to 1.40). In two zanamivir adult trials, pneumonia reporting was based on a stricter definition of X-ray confirmation and there was also no significant treatment effect (RR 1.02, 95% CI 0.35 to 3.02). In prophylaxis, zanamivir significantly reduced the risk of unverified pneumonia in adults (RD 0.32%, 95% CI 0.09% to 0.41%) but not oseltamivir.

In adult treatment, oseltamivir increased the risk of nausea (RD 3.66%, 95% CI 0.90% to 7.39%) and vomiting (RD 4.56%, 95% CI 2.39% to 7.58%). The proportion of participants with fourfold increases in antibody titre was significantly lower with oseltamivir (RR 0.92, 95% CI 0.86 to 0.97). Oseltamivir significantly decreased the risk of diarrhoea (RD 2.33%, 95% CI 0.14% to 3.81%) and cardiac events (RD 0.68%, 95% CI 0.04% to 1.0%) during the on-treatment period. The rate of psychiatric adverse events increased in dose-dependent fashion based on a likelihood ratio test ($p = 0.038$) in the two 'pivotal' treatment trials that included two oseltamivir arms with doses of 150 mg and 300 mg daily. There was no indication of a dose-response effect of treatment on psychiatric adverse events in the only prophylaxis study with multiple dose treatment groups. In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75% to 10.29%). There was a significantly lower proportion of children on oseltamivir with a fourfold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00).

Effectiveness of neuraminidase inhibitors in the prevention of influenza

In prophylaxis trials, NIs reduced the risk of symptomatic influenza in individuals (oseltamivir RD 3.05%, 95% CI 1.83% to 3.88%; zanamivir RD 1.98%, 95% CI 0.98% to 2.54%) and in households (oseltamivir RD 13.6%, 95% CI 9.52% to 15.47%; zanamivir RD 14.84%, 95% CI 12.18% to 16.55%). There was no significant effect on asymptomatic influenza (oseltamivir RR 1.14 95% CI 0.39 to 3.33; zanamivir RR 0.97, 95% CI 0.76 to 1.24). In oseltamivir prophylaxis, psychiatric adverse events were increased in the combined on- and off-treatment periods (RD 1.06%, 95% CI 0.07% to 2.76%). Oseltamivir, on treatment, increased the risk of headaches (RD 3.15%, 95% CI 0.88% to 5.78%), renal events (RD 0.67%, 95% CI -0.01% to 2.93%) and nausea (RD 4.15%, 95% CI 0.86% to 9.51%).

Comparison of core reports compared with full clinical study reports

With more detailed information, no previous assessment of 'high' risk of bias was reclassified as 'low' or 'unclear' in the main analysis, and over half (55%, 34/62) of previous assessments of 'low' risk of bias were reclassified as 'high'. Most 'unclear' risk of bias (67%, 28/42) was reclassified as 'high' risk of bias when our judgements were based on full clinical study reports.

Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza

A total of 154 full-text articles were assessed for eligibility. Of these, 30 observational studies were eligible and a total of 11,013 patients were available for qualitative synthesis. Overall, there were 1301 deaths (12%) with the percentage of deaths receiving oseltamivir similar to that of survivors (83% vs. 82%). The IPD came from four studies including 3071 patients and 242 (8%) deaths. Analysis of the IPD showed no evidence of reduced risk of mortality with oseltamivir [hazard ratio (HR) 1.03, 95% CI 0.64 to 1.65].

Discussion

Effectiveness of neuraminidase inhibitors in the prevention and treatment of influenza

The evidence that we have presented and synthesised shows that both NIs have symptom-relieving effects, especially for self-reported outcomes, shortening symptom duration and reducing the frequency of symptoms such as cough. For oseltamivir, this effect perhaps extends to cardiac symptoms, despite the short duration of treatment (5 days). We are unsure what to make of this finding but we think it deserves further investigation.

We could not decide the level of diagnostic ascertainment of diagnosis of pneumonia and other complications. In a metaregression of all 32 included studies that reported on 'pneumonia', we found evidence that treatment effects for pneumonia are statistically different depending on the method of diagnosis.

Antibody suppression seems stronger for oseltamivir than zanamivir, probably because of the difference in bioavailability. It may be that evidence of other effects, such as hyperglycaemia and renal impairment (although significance was marginal) in the prophylaxis trials may be due to inhibition of the host's endogenous neuraminidase, which impairs the cell function of various organs.

A weak dose-dependent association between oseltamivir and psychiatric harms is evident in the two pivotal treatment trials (but not in all oseltamivir treatment trials combined). It is possible that influenza-like illness and influenza symptoms masked the harms in those who were already symptomatic and therefore recruited in the treatment trials (and influenza-type symptoms were excluded as adverse events to be reported).

Comparison of core reports compared with full clinical study reports

The Cochrane risk-of-bias tool was sometimes difficult to apply to clinical study reports. This may be because the tool was constructed to assess journal publications and comprises a checklist. As information increased in the core reports, our assessment of bias became more detailed and changed some of our assessments. Our experience suggests that a more detailed extraction sheet is needed to prompt reviewers to consider additional aspects of the study design when assessing bias.

Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza

Analysis of the summary data on the 30 studies as well as the IPD showed evidence of time-dependent bias, with bias increasing with increasing odds of treatment. Analysis of the IPD using standard Cox regression on the 2056 patients with survival times gave a HR of 0.75. However, when the time-dependent nature of oseltamivir exposure, as well as the competing risk of hospital discharge were taken into account, the HR adjusting for potential confounding variables was 1.03.

Our results are substantially different from those of three other reviews, which based their primary analysis of mortality on three small studies of 681 patients, none of which had 2009A/H1N1, did not consider time-dependent treatment exposure or appeared to not take appropriate account of time-dependent treatment exposure.

Conclusions

Oseltamivir and zanamivir cause small reductions in the time to alleviation of influenza symptoms except for asthmatic children. The use of oseltamivir increases the risk of nausea, vomiting, psychiatric events in adults and vomiting in children. Observational studies do not show that oseltamivir has a protective effect on patients with 2009A/H1N1 influenza for mortality. Evidence suggests that the risk of bias has been insufficiently reported in other Cochrane reviews that are limited to published research. The balance between benefits and harms should be considered when making decisions about the use of NIs for either prophylaxis or treatment of influenza.

Research priorities

We could not reach a consensus on whether or not further trials are warranted and whether or not current trials should be discontinued. Any future trial designs should ensure that the presence of complications is ascertained using objective diagnostic criteria. Procedures for trial unblinding and dates of unblinding should be routinely reported. Registration should be made compulsory for all studies in which human beings are randomly assigned to experimental arms. There is a further need to develop the systematic review methods for the evaluation of other drugs, using full clinical study reports. Priority could perhaps be given to first drugs of a new family, drugs considered to be innovative or those that are likely to have a big market impact. Such reviews should be publicly funded, and independent from both regulators and manufacturers. To determine the risks and benefits of drugs there will be a need to move to more comprehensive reviews that incorporate more clinical study report data.

Study registration

This study is registered as PROSPERO CRD42012002245.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction and rationale

Since the mid-2000s the use of neuraminidase inhibitors (NIs) has been endorsed and billions of pounds have been spent stockpiling the two anti-influenza drugs oseltamivir (Tamiflu®, Roche) and zanamivir [Relenza®, GlaxoSmithKline (GSK)] in preparation for an influenza pandemic. When the H1N1 pandemic emerged in 2009, the drugs were rolled out worldwide for the treatment and prevention of influenza and its complications. At that time, we were asked to conduct a systematic review for Cochrane to update evidence on their efficacy, during which it emerged that the validity of a key study underpinning the evidence on efficacy was unclear. After 3.5 years of making requests to the drug manufacturers, they provided us with full clinical study reports (CSRs).

Emergence of problems

The reasons for the stockpiling of oseltamivir and zanamivir are not well known, but the decision may be based on assumptions that the drugs would reduce hospital admissions and serious complications of influenza, such as pneumonia, by half and slow down the spread of the virus.^{1–3} Some of these assumptions were supported by a peer-reviewed pooled analysis of 10 randomised trials of oseltamivir published in the *Archives of Internal Medicine* in 2003 by Kaiser *et al.*⁴ This analysis seemed to be of high quality and formed a powerful scientific rationale for stockpiling,⁵ but during our review in 2009 it became apparent that the data underlying it were largely unpublished and inaccessible to independent scrutiny. Roche, the manufacturer of oseltamivir, funded the Kaiser review, employed some of its authors and had also sponsored the 10 trials. For 3.5 years Roche did not release the full CSRs despite a public pledge to do so made during the H1N1 ‘swine flu’ outbreak of 2009.^{6,7}

Research for our 2009 review also highlighted inconsistencies in decision-making. The US Food and Drug Administration (FDA), which had access to the full CSRs, concluded on the product label that ‘Tamiflu has not been shown to prevent such complications [serious bacterial infections]’. The European Medicines Agency (EMA), which had only partial reports, and another prominent US agency, the Centers for Disease Control and Prevention (CDC), came to the exact opposite conclusion – all apparently based on the same trials.⁸

Owing to the risk of reporting bias as a result of the large amounts of unpublished data there are uncertainties about the stated benefits of oseltamivir and about the conclusions of previous Cochrane reviews of NIs in adults and children.^{9,10} To address this, we worked for 4 years to obtain full CSRs of the oseltamivir trial programme. CSRs are considered to be the most exhaustive summaries of randomised controlled trials (RCTs) of drugs. They are usually composed of a main report of the trial (in introduction, methods, results and discussion style), with numerous appendices containing important supplementary data that are needed to understand and interpret the trial [e.g. protocol, protocol amendments, statistical analysis plan (SAP), blank case report forms (CRFs), certificates of analysis, randomisation list and informed consent forms].¹¹ In the case of oseltamivir, CSRs were of a mean length of approximately 1300 pages (median around 900 pages). As a result of increasing availability, CSRs may in the future be incorporated into systematic reviews and other forms of evidence synthesis.^{12,13}

Rationale for this review

In the midst of the A/H1N1 influenza outbreak in June 2009, the Australian and UK governments commissioned an update of our long-standing Cochrane review on NIs for influenza in (otherwise) healthy adults (known as A047). At the time of publication of the 2009 update and its linked investigation by the *British Medical Journal* (BMJ), we underestimated the extent of the oseltamivir evidence development programme, expecting it to comprise around 36 trials, with only a proportion of these fitting our inclusion criteria. We were also unaware of the size and the level of detail that the CSRs contained.

Today, the obvious source of information on CSRs would be trial registries and company websites, but most trials of both NIs were carried out before inception or wide acceptance of centralised registries and company websites. In 2009–11, company websites did not, and still do not, have extensive lists of trials with downloadable CSRs. Many people had never heard of CSRs before media coverage of our work. We decided to construct our list by using multiple cross-referencing methods. We constructed a list beginning with clinical trials that were identified from previous review updates.

To ensure that the list did not include duplicate entries, we assigned to each trial a unique trial ID. 'Author' was insufficient to provide a unique trial ID, because different authors can be present across different versions of the same trial (i.e. the authors of CSRs can be different from publications arising from the same clinical trial).

Once we had as complete a list of trials as possible, we contacted manufacturers and sent them our draft list, asking them to check the accuracy and completeness of our list. Roche, GSK and BioCryst all did so, and informed us of additional trials.

We requested from Roche and GSK a series of regulatory documents under freedom of information (FOI) policies from both the FDA and the EMA. No substantial comments were made by Roche on the protocol of the Cochrane A159 review,¹⁴ which has been publicly available since December 2010.

Soon after the publication of the review, the BMJ agreed to publish our correspondence with Roche, GSK, EMA, CDC and World Health Organization (WHO), recording our attempts at retrieving the full reports without any conditions attached, and to understand the basis for promotion of the drugs (especially oseltamivir) by public health bodies. The correspondence (which is hundreds of pages long) formed the basis for what then became the BMJ Open Data Campaign and a stimulus for the later AllTrials campaign. Public exposure of this approach and considerable media coverage led to the unconditional release of 77 reports of oseltamivir of 82 studies sponsored by Roche and the equivalent of the 30 studies we had requested from GSK. For the full correspondence, see www.bmj.com/tamiflu and www.bmj.com/relenza. The reports (amounting to over 100,000 pages) are made available with this review for the first time at: <https://datadryad.org/resource/doi:10.5061/dryad.77471/2>, a positive step for open science. We have described the posting of these reports in a blog posting at: <http://blog.datadryad.org/2014/04/17/tamiflu-data/>, and a list of neuraminidase reviews, with peer review comments and responses relevant to review A159,¹⁴ is available at www.bmj.com/content/suppl/2014/04/09/bmj.g2545.DC1/jeft017746.www8_default.pdf.

Before receiving the full reports, we resumed reviewing the remainder of the material that we had received in 2011. This mainly consisted of module 2s (Roche terminology for pre-study documents). Module 2s contained the information that was originally unavailable to us from Roche: study protocols with their amendments, randomisation lists, blank CRFs, certificates of analysis describing appearance and content of active and control capsules and, at times, SAPs. CRFs are containers for the rawest form of recorded data at the individual participant level.

While designing the tool to capture trial methods and assess bias, we also considered whether or not access to module 2 information (and later the full study reports) changed our perception of the trial and specifically our 'risk-of-bias' assessment. We found that access to what are supposed to be full study reports should provide clarity and remove the rationale for 'unclear' risk-of-bias judgements, and ideally remove the concept of risk leaving just 'bias', at least for certain study design elements, such as attrition bias. Either a design element introduces bias or it does not. In the case of the 15 full oseltamivir CSRs we reviewed when constructing our tool, only one report contained a protocol that predated the beginning of participant enrolment, only two reports had SAPs that clearly predated participants' enrolment and three reports had clearly dated protocol amendments. No CSR reported a clear date of unblinding.

During the latter part of 2013, we received from the manufacturers tens of thousands of pages of full CSRs for both programmes combined.

These events form the basis for this review.

Aims and objectives

The main goals of the reviews included in this report were to:

1. describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all CSRs of published and unpublished randomised, placebo-controlled trials and regulatory comments
2. determine the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza.

Research questions

The research questions addressed in this report are as follows:

- What are the potential benefits and harms of NIs for the prevention and treatment of influenza in adults and children?
- Does influenza virus-specific mechanism of action proposed by the producers fit the clinical evidence?
- Does treatment with oseltamivir confer protection against mortality in patients with 2009A/H1N1 influenza?

Chapter 2 Neuraminidase inhibitors for preventing and treating influenza in adults and children

Abstract

Background

Neuraminidase inhibitors are stockpiled and recommended by public health agencies for treating and preventing seasonal and pandemic influenza. They are used clinically worldwide.

Objective

To describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all CSRs of published and unpublished randomised, placebo-controlled trials and regulatory comments.

Search methods

We searched trial registries, electronic databases (to 22 July 2013) and regulatory archives, and corresponded with manufacturers to identify all trials. We also requested CSRs. We focused on the primary data sources of manufacturers but we checked that there were no published RCTs from non-manufacturer sources by running electronic searches in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE (via Ovid), EMBASE, EMBASE.com, PubMed (not MEDLINE), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Economic Evaluations Database (HEED).

Selection criteria

Randomised, placebo-controlled trials on adults and children with confirmed or suspected exposure to naturally occurring influenza.

Data collection and analysis

We extracted CSRs and assessed risk of bias using purpose-built instruments. We analysed the effects of zanamivir and oseltamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalisations and adverse events in the intention-to-treat (ITT) population. All trials were sponsored by the manufacturers.

Main results

We obtained 107 CSRs from the EMA, GSK and Roche. We accessed comments by the FDA, EMA and Japanese regulator. We included 53 trials in stage 1 (a judgement of appropriate study design) and 46 in stage 2 (formal analysis), including 20 oseltamivir (9623 participants) and 26 zanamivir trials (14,628 participants). Inadequate reporting put most of the zanamivir studies and half of the oseltamivir studies at a high risk of selection bias. There were inadequate measures in place to protect 11 studies of oseltamivir from performance bias due to non-identical presentation of placebo. Attrition bias was high across the oseltamivir studies and there was also evidence of selective reporting for both the zanamivir and oseltamivir studies. The placebo interventions in both sets of trials may have contained active substances.

Time to first symptom alleviation

For the treatment of adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours [95% confidence interval (CI) 8.4 to 25.1 hours; $p < 0.0001$]. This represents a reduction in the time to first alleviation of symptoms from 7 to 6.3 days. There was no effect in asthmatic children, but in otherwise healthy children there was a reduction by a mean difference (MD) of 29 hours (95% CI 12 to 47 hours; $p = 0.001$). Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days; $p < 0.00001$), equating to a reduction in the mean duration of symptoms from 6.6 to

6.0 days. The effect in children was not significant. In subgroup analysis we found no evidence of a difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups ($p = 0.53$).

Hospitalisations

Treatment of adults with oseltamivir had no significant effect on hospitalisations [risk difference (RD) 0.15%, 95% CI -0.78% to 0.91%]. There was also no significant effect in children or in prophylaxis. Zanamivir hospitalisation data were unreported.

Serious influenza complications or those leading to study withdrawal

In adult treatment trials, oseltamivir did not significantly reduce those complications classified as serious or those that led to study withdrawal (RD 0.07%, 95% CI -0.78% to 0.44%), or in child treatment trials; neither did zanamivir in the treatment of adults or in prophylaxis. There were insufficient events to compare this outcome for oseltamivir in prophylaxis or zanamivir in the treatment of children.

Pneumonia

Oseltamivir significantly reduced self-reported, investigator-mediated, unverified pneumonia [RD 1.00%, 95% CI 0.22% to 1.49%, number needed to treat to benefit (NNTB) 100, 95% CI 67 to 451] in the treated population. The effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. There were no definitions of pneumonia (or other complications) in any trial. No oseltamivir treatment studies reported effects on radiologically confirmed pneumonia. There was no significant effect on unverified pneumonia in children. There was no significant effect of zanamivir on either self-reported or radiologically confirmed pneumonia. In prophylaxis, zanamivir significantly reduced the risk of self-reported, investigator-mediated, unverified pneumonia in adults (RD 0.32%, 95% CI 0.09% to 0.41%; NNTB 311, 95% CI 244 to 1086) but not oseltamivir.

Bronchitis, sinusitis and otitis media

Zanamivir significantly reduced the risk of bronchitis in adult treatment trials (RD 1.80%, 95% CI 0.65% to 2.80%; NNTB 56, 95% CI 36 to 155), but not oseltamivir. Neither NI significantly reduced the risk of otitis media and sinusitis in both adults and children.

Harms of treatment

Oseltamivir in the treatment of adults increased the risk of nausea [RD 3.66%, 95% CI 0.90% to 7.39%; number needed to treat to harm (NNTH) 28, 95% CI 14 to 112] and vomiting (RD 4.56%, 95% CI 2.39% to 7.58%; NNTH 22, 95% CI 14 to 42). The proportion of participants with fourfold increases in antibody titre was significantly lower in the treated group than in the control group (RR 0.92, 95% CI 0.86 to 0.97; P statistic = 0%) (5% absolute difference between arms). Oseltamivir significantly decreased the risk of diarrhoea (RD 2.33%, 95% CI 0.14% to 3.81%; NNTB 43, 95% CI 27 to 709) and cardiac events (RD 0.68%, 95% CI 0.04% to 1.0%; NNTB 148, 95% CI 101 to 2509) compared with placebo during the on-treatment period. There was a dose-response effect on psychiatric events in the two oseltamivir 'pivotal' treatment trials: WV15670 and WV15671, at 150 mg (standard dose) and 300 mg daily (high dose) ($p = 0.038$). In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75% to 10.29%; NNTH 19, 95% CI 10 to 57). There was a significantly lower proportion of children on oseltamivir with a fourfold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00; P statistic = 0%).

Prophylaxis

In prophylaxis trials, oseltamivir and zanamivir reduced the risk of symptomatic influenza in individuals (oseltamivir RD 3.05%, 95% CI 1.83% to 3.88%; NNTB 33, 95% CI 26 to 55; zanamivir RD 1.98%, 95% CI 0.98% to 2.54%; NNTB 51, 95% CI 40 to 103) and in households (oseltamivir RD 13.6%, 95% CI 9.52% to 15.47%; NNTB 7, 95% CI 6 to 11; zanamivir RD 14.84%, 95% CI 12.18% to 16.55%; NNTB 7, 95% CI 7 to 9). There was no significant effect on asymptomatic influenza (oseltamivir, RR 1.14, 95% CI 0.39 to 3.33; zanamivir RR 0.97, 95% CI 0.76 to 1.24). Non-influenza, influenza-like illness (ILI) could not be assessed as a result of data not being fully reported. In oseltamivir prophylaxis studies,

psychiatric adverse events were increased in the combined on- and off-treatment periods (RD 1.06%, 95% CI 0.07% to 2.76%; NNTH 94, 95% CI 36 to 1538) in the study treatment population. While on treatment, oseltamivir increased the risk of headaches (RD 3.15%, 95% CI 0.88% to 5.78%; NNTH 32, 95% CI 18 to 115), renal events (RD 0.67%, 95% CI -0.01% to 2.93%; NNTH 150, NNTH 35 to NNTB > 1000) and nausea (RD 4.15%, 95% CI 0.86% to 9.51%; NNTH 25, 95% CI 11 to 116).

Authors' conclusions

Oseltamivir and zanamivir have small, non-specific effects on reducing the time to alleviation of influenza symptoms in adults, but not in asthmatic children. Using either drug as prophylaxis reduces the risk of developing symptomatic influenza. Treatment trials with oseltamivir or zanamivir do not settle the question of whether or not the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions. The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children. The lower bioavailability may explain the lower toxicity of zanamivir compared with oseltamivir. The balance between benefits and harms should be considered when making decisions about use of both NIs for either the prophylaxis or treatment of influenza. The influenza virus-specific mechanism of action proposed by the manufacturers does not match the observed clinical evidence.

Background

This review (known as A159) reports our work using unpublished CSRs (see *Appendix 1, Glossary*) and regulatory documents containing comments and reviews to evaluate the safety and efficacy of NIs. We have called the body of clinical studies and regulatory comments 'regulatory information'. For the history and evolution of the review, see *Appendix 1*.

Description of the condition

Influenza is mostly a mild, self-limiting infection of the upper airways with local symptoms, including sniffles, nasal discharge, dry cough and sore throat, and systemic symptoms such as fever, headache, aches and pains, malaise and tiredness.

Occasionally, patients with influenza develop complications such as pneumonia, otitis media and dehydration or encephalopathy with or without liver failure, which may be due to the effects of the influenza virus itself or associated secondary bacterial infections and/or adverse effects of drugs such as antipyretics [including salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs)].¹⁵

Influenza is not clinically distinguishable from ILI.¹⁶ Epidemic influenza in humans is caused by influenza A and B viruses. Currently, influenza A/H1N1, influenza A/H3N2 and influenza B cause most influenza infections worldwide.¹²

Description of the intervention

Neuraminidase inhibitors comprise inhaled zanamivir (Relenza®, GSK), oral oseltamivir (Tamiflu®, Gilead Sciences and F. Hoffman-La Roche), parenteral peramivir (Rapivab®, BioCryst Ltd), inhaled laninamivir (Inavir®, Daiichi Sankyo Co. Ltd)¹⁷ and others still under development.¹⁸ The use of NIs has increased dramatically since the outbreak of A/H1N1 in April 2009, partly because of the rise in amantadine (Symmetrel®, Endo Pharmaceuticals Inc.)/rimantadine (Flumadine®, Forest Pharmaceuticals Inc.) resistance and, in the early stages of the outbreak, the lack of a vaccine, which meant that NIs became a widespread public health intervention. WHO had previously encouraged member states to stockpile and gain experience of using NIs.^{19–21}

How the intervention might work

Although NIs may reduce the ability of the virus to penetrate the mucus in the very early stage of infection,^{6,22–24} their main mechanism of action is thought to lie in their ability to inhibit influenza viruses from exiting host cells.^{23,25} The manufacturers state that oseltamivir does not prevent infection or affect antibody production,²⁶ but it reduces symptom duration probably by reducing viral load, spread and release of cytokines,^{8,27} diminishing the chance of complications and interrupting person–person viral spread. Oseltamivir phosphate (Tamiflu) is the prodrug of oseltamivir carboxylate, the effective form. Oseltamivir phosphate dissociates in the gastrointestinal tract to form oseltamivir, which is absorbed and metabolised into oseltamivir carboxylate by hepatic carboxylesterase. Oseltamivir may have a central depressant action¹⁵ and may also inhibit human sialidase,²⁸ causing abnormal behaviour. Inhaled zanamivir reaches a far lower plasma concentration than its intravenous administration.²⁹

Any treatment that reduces the complications of influenza (e.g. pneumonia) and the excretion of the virus from infected people might be a useful public health measure to contain an epidemic by limiting the impact and spread of the virus. In addition to symptomatic treatment, prophylactic use for interrupting the spread of disease has informed pandemic planning over the past decade.

Why it is important to do this review

There are three major reasons for conducting this review, in addition to questions of efficacy associated with the clinical use of NIs for influenza:

1. Influenza antivirals are a commonly used and stockpiled drug against past and future pandemics on the basis of international and national recommendations. These recommendations are based on the claimed and assumed ability of the drug to reduce complications and transmission.^{2,3} In theory, containing the spread of influenza allows time for an organised response with longer-term interventions (such as vaccines), which take time to produce.³
2. The risk of reporting bias and publication bias leads to uncertainty about the effects of NIs and the results of previous Cochrane reviews of NIs in adults^{6,10,30,31} and children.³²
3. Oseltamivir is now on the list of WHO essential drugs.^{33,34}

Process

Review A159 is an amalgamation of two long-standing Cochrane reviews on the effects of NIs for influenza in healthy adults¹⁴ (also published in the BMJ³¹) and children,³⁵ and it is based on the assessment of trials through their CSRs and other regulatory information; a decision we made after finding substantial reporting bias in the journal publications of the relevant trials.

For the full rationale for this process, see *Appendix 1*.

Examples of discrepancies and reporting bias

We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled, Phase III treatment trials of oseltamivir have never been published. This includes M76001,³⁶ the biggest treatment trial ever undertaken on oseltamivir (with just over 1400 people of all ages). Exclusion of unpublished data changed our previous findings regarding the ability of oseltamivir to reduce the complications of influenza.^{8,31} In some cases, mistakes in the attribution of adverse events were discovered only through matching summary tables with individual participant listings.^{37–39}

A modified approach

We have modified the routine Cochrane processes to improve our previous methods, which we now consider to be inadequate. To resolve inconsistencies and under-reporting, we changed our approach by no longer including trial data as reported in papers published in biomedical journals. Instead, we treated CSRs as our basic unit of analysis. CSRs are often sent to national drug regulators, such as the FDA and the EMA (formerly the European Agency for the Evaluation of Medicinal Products), which require far more stringent standards for completeness and accuracy of reporting than biomedical journals. Journal articles

can be regarded as a very succinct synthesis of a CSR. In addition to seeking CSRs, we decided to read and review regulatory documentation. The FDA in particular (and the EMA to a far lesser extent) makes many of its scientific reviews available on its website. Unlike Cochrane review authors, regulators can have access to the whole data set and their comments can provide useful insight, helping to achieve a better understanding of trial programmes.

Clinical study reports generally remain hidden from public view and are not readily available for wider scientific scrutiny, despite the wealth of information that they contain for those willing and able to spend the time reading them and despite calls to make all relevant trial data public,^{11,40} as well as the known problems with reporting biases.^{41,42}

Implications

This modified approach to a Cochrane review aims to provide patients, clinicians and policy-makers with the most transparent and independent information possible about NIs for influenza. In addition, it should contribute to improving a European regulatory and pharmacovigilance legal framework, which commentators consider weak.^{40,43} We believe that as NIs have become public health drugs, recommended and stockpiled globally, independent scrutiny of all of the evidence relating to harms and effects on complications is necessary to provide patients, policy-makers and physicians with a complete and unbiased view of their risks and benefits.

Implication for A/H1N1 (2009) influenza

In response to our 2010 review,^{14,31} some have argued that its findings cannot be applied to the 2009 A/H1N1, suggesting that it is a new virus and that, we thus need new evidence.^{44–48} Novel A/H1N1 is a new strain of a subtype that has been circulating since 1977, but it also resembles the A/H1N1 strain that has been circulating since before 1957⁴⁹ or before the 1918 pandemic.⁵⁰ Influenza subtype A/H1N1 was indeed circulating at the time when the clinical trials, included in our previous reviews, were recruiting. In addition, oseltamivir and zanamivir were approved by regulators worldwide for the treatment and prevention of influenza types A and B, not specific subtypes or strains of influenza A and B. The expectation of regulatory approval is thus that the effects of these drugs demonstrated in clinical trials will apply to future strains of influenza A and B. Use of these drugs during the pandemic was not off-label. It was approved use on the assumption that the clinical trial evidence underpinning regulatory approval applied to novel A/H1N1. We reviewed the clinical trial evidence with the expectation that our results, similar to regulators, will apply to all influenza viruses.

Wider implications

The modified approach in this Cochrane review developed from the realisation that prior methods used to review NIs were inadequate. There is little reason to think that the lessons learned are limited to these particular drugs.^{40,42,51–53} On this basis, our independent scrutiny, using all possible trial information, may inform both the wider debate on the adequacy of existing regulatory frameworks in the adoption of new drugs and the question of whether or not other systematic reviews should move to this new, more rigorous, approach, which focuses on trial programmes rather than single trials^{54,55} (see *Appendix 1, Glossary*). Although there is substantial evidence for the effects of reporting bias in estimates of effectiveness, less is known of its impact on the evidence of harms.⁵⁶ We decided to quantify the additional resources required to follow our modified methodological approach to assess the feasibility of other systematic reviews proceeding in a similar fashion.

Objective

To describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all CSRs of published and unpublished randomised, placebo-controlled trials and regulatory comments.

Methods

Criteria for considering studies for this review

Types of studies

We included evidence from RCTs testing the effects of NIs for prophylaxis, post-exposure prophylaxis (PEP) and treatment of influenza. Prophylaxis is the mode of use of NIs when there is expectation of possible near-future exposure to influenza.

Post-exposure prophylaxis is the use of NIs following probable exposure to influenza but before symptoms develop. Treatment is the use of NIs in persons showing probable signs of influenza.

Owing to discrepancies between published and unpublished reports of the same trials, we included only those trials for which we had unabridged CSRs (e.g. with consecutively numbered pages), even though they may be parts of CSRs (i.e. module 1 only) and information on reports of trials that were considered 'pivotal' (i.e. first- or second-line evidence to regulators in support of the registration application).

Types of participants

We included previously healthy people (children and adults). 'Previously healthy' includes people with chronic illness (such as asthma, diabetes, hypertension), but excludes people with illnesses with more significant effects on the immune system (such as malignancy or human immunodeficiency virus infection). We included only trials on people who were exposed to naturally occurring influenza with or without symptoms. We targeted the ITT and safety populations, as our prior review discovered compelling evidence that the intention-to-treat-influenza-infected (ITTI) subpopulation – the subpopulation deemed to be influenza-infected – was not balanced between treatment groups in the Roche oseltamivir trials. In addition, estimates from the ITT population will be more generalisable to clinical practice, where routine testing for influenza is not common in many countries (and even where it is used is of variable accuracy).

Types of interventions

Neuraminidase inhibitors administered by any route compared with placebo during the period in which medication was assumed and during the follow-up (on- and off-treatment) periods.

Types of outcome measures

Primary outcomes

Primary outcome measures for treatment studies

1. Symptom relief.
2. Hospitalisation and complications.
3. Harms.

Primary outcome measures for prophylaxis studies

1. Influenza (symptomatic and asymptomatic, always with laboratory confirmation) and ILI.
2. Hospitalisation and complications.
3. Interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts).
4. Harms.

Secondary outcomes

Secondary outcome measures for treatment studies

1. Symptom relapse after finishing treatment.
2. Drug resistance.
3. Viral excretion.
4. Mortality.

Secondary outcome measures for prophylaxis studies

1. Drug resistance.
2. Viral excretion.
3. Mortality.

Although overall symptom reduction is well documented, our interest was particularly focused on complications and adverse events, as this is where evidence is currently scarce or inconclusive.^{31,32} Our preliminary examination of some regulatory documents and some published versions of the studies had identified that some symptoms and sequelae of influenza (such as pneumonia) had been classified as either a 'complication of influenza' or as an 'adverse event of the treatment', or both. This is somewhat confusing and we intended to analyse 'compliharms' (see *Appendix 1, Glossary*) irrespective of the classification as a 'complication of influenza' or as an 'adverse event of the treatment' (see *Appendix 2*) in oseltamivir trials. Complications of particular interest included pneumonia, bronchitis, otitis media and sinusitis, as these were the secondary illnesses often collected in the Roche oseltamivir trials and we agreed that these events are clinically important. Initially, we constructed a table to illustrate the design methodology that was used for each complication by study (*Table 1*). The table included the following variables: definition of which events are termed complications; where complications are first defined in the CSR; diagnosis method; and availability of data. We then stratified our analysis by method of diagnosis with three possible criteria: (1) laboratory-confirmed diagnosis (e.g. based on radiologically or microbiologically confirmed evidence of infection); (2) clinical diagnosis without laboratory confirmation (diagnosed by a doctor after a clinical examination); and (3) other type of diagnosis, such as self-reported by patient. We conducted analysis of any complication (pneumonia, bronchitis, otitis media and sinusitis) that was classified as serious or led to study withdrawal.

In all cases of influenza complications reporting (pneumonia, bronchitis, sinusitis, otitis media) there is a variable degree of participant self-reporting, of investigator mediation (e.g. in writing down the details in the CRF) and lack of verification with investigations, such as culture or imaging. The 'self-reported, investigator-mediated, unverified' title is relevant to all complications but for brevity we use it as sparingly as possible.

For harms, we were limited by the frequency of occurrence of the adverse events collected in the trials. Consequently, we meta-analysed (1) all serious adverse events; (2) all adverse events leading to study withdrawal; (3) all withdrawals; (4) all adverse events within a CSR's defined body system; and (5) a small group of common adverse events as defined in the FDA drug label for oseltamivir. There were too few events to meta-analyse: (1) deaths; (2) serious adverse events by body system; and (3) any events that had an overall incidence of < 0.5%. We did not meta-analyse outcomes with fewer than 10 events in total. We conducted analyses separately for on-treatment and off-treatment periods. However, in two cases for which (on-treatment) treatment effects were borderline statistically significant (prophylaxis with oseltamivir: renal body system on-treatment and psychiatric body system on-treatment), we conducted additional analysis combining on- and off-treatment periods to maximise statistical power. We conducted dose-response harms analysis for two treatment trials^{8,58} combined and one prophylaxis study,⁵⁹ as these trials investigated the active agent at multiple doses. These studies^{8,58,59} included standard-dose and

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
M7600 ¹³⁶	1167	Yes/no answer to question: 'Is this event a secondary illness related to influenza?' Secondary illness is defined: sinusitis, otitis, bronchitis, pneumonia plus other chest infections that are not diagnosed as bronchitis and/or pneumonia	Investigator	In form for 'Adverse events or intercurrent illness'	No	Px
NV16871 ⁵⁷	361, 389	Form states: Have there been any changes in the patient's health, including any new conditions or worsening of existing conditions since day 1 (please include secondary illnesses)? Yes/no: If 'Yes', please record the details on the 'Adverse events or secondary illness' form in the Additional Forms section of the CRF on p. 30.0. All serious adverse events must be reported within 1 working day of occurrence to Roche Page 30.0 of CRF (PDF p. 389) defines secondary illnesses as sinusitis, otitis media, bronchitis and pneumonia, and asks additional questions such as relationship to test drug and outcome, and leaves space for investigator's comments on the adverse event	Investigator	Secondary illness not listed as efficacy outcomes Recording of secondary illnesses was to occur in a form titled 'Adverse event or secondary illness'	No	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15670 ⁸	732, 754, 791, 832	CRF (PDF p. 732) states: secondary illness reminder: has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? Yes [] Complete secondary illness page (not the adverse event page) No [] Secondary illness page CRF (PDF p. 754) requests information on date of onset, date resolved, whether or not treatment was given and, if so, what treatment or medical procedures, total daily dose, and start/end date of treatment or medical procedure In addition, participants could fill in information related to a secondary illness in their diary card in the free-text box called 'Notes', which prompts participants: 'Please can you record below any extra information about your flu which may be of interest to us, (for example: did your flu symptoms re-occur, and if so when?), and have you taken any other treatments? If so please record the treatment name and the dates you took it.' (PDF p. 791)	Participant, mediated through investigator	For investigators, on 'Secondary illness' form For participants, on 'Notes' section of diary card	No	

continued

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials (*continued*)

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15671 ⁵⁸	740, 889, 1018	CRF (PDF p. 740) states: Secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? Yes ☐ Complete secondary illness page (not the adverse event page) No ☐ Secondary illness page CRF (PDF p. 889) requests information on date of onset, date resolved, whether or not treatment was given and, if so, what treatment or medical procedures, total daily dose and start/end date of treatment or medical procedure Secondary illnesses are listed as sinusitis, otitis, bronchitis, pneumonia and other chest infections that are not diagnosed as bronchitis and/or pneumonia	Participant, mediated through investigator	Mentioned in module 1 and RAP, as tertiary outcomes not mentioned in protocol	No	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WW15673/ WW15697 ⁵⁹	From 483	In addition, participants could fill in information related to a secondary illness in their diary card in the free-text box called 'Notes', which prompts participants: 'Please can you record below any extra information about your flu which may be of interest to us, (for example: did your flu symptoms re-occur, and if so when?), and have you taken any other treatments? If so please record the treatment name and the dates you took it.' (PDF p. 1018) No mention of pneumonia, secondary illness, complications in the CRFs	Unclear	Secondary illnesses not listed in protocol as end points. They are listed as safety end points in the RAP, which states that 'pre-defined' secondary illnesses were 'sinusitis, otitis, bronchitis, pneumonia, and other chest infections that are not diagnosed as bronchitis and/or pneumonia, plus recurrence of symptoms from the diary card once alleviation had occurred.' (PDF p. 479)		
continued						

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials (*continued*)

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV1570 ⁶⁰	From 98	Page 117: secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? Yes [] Complete secondary illness page (not the adverse event page) No [] Page 131: diagnostic procedures 1. Were there any diagnostic procedures or tests carried out since day 1 as a result of influenza or secondary illness that were not scheduled as part of protocol? Yes Type of diagnostic procedure or test: 1. Chest X-rays 2. ECG 3. Bacterial culture 4. Bronchoscopy 5. Pulmonary function test	Participant, mediated through investigator	Mentioned in RAP as tertiary end points, pp. 57–8	Yes	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15708 ⁶¹		6. Viral culture (other than influenza)				
		7. Blood tests (other than antibody sample)				
		8 Other specify No				
		Secondary illness p. CRF (PDF p. 158) requests information on date of onset, date resolved, whether or not treatment was given and, if so, what treatment or medical procedures, total daily dose and start/end date of treatment or medical procedure				
	From 460	Secondary illness reminder, p. 474:	Participant, mediated through investigator	Secondary illness not mentioned in protocol	No	Px
		Has the patient reported any new episodes of sinusitis, otitis, bronchitis, other chest infection or pneumonia since screening?				
		Yes [] . . . Complete adverse event page				
		No []				
		'Adverse events' CRF collected data on date of onset, initial intensity, test drug adjustment, whether or not treatment was given (if so, what), most extreme intensity, relationship to test drug, outcome, whether or not it led to hospitalisation and a free-text line for recording				
		'Comments on AE' (e.g. PDF p. 479)				
						continued

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials (*continued*)

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15730 ⁶²	From 340	Secondary illness reminder:	Participant, mediated through investigator	Listed as tertiary end points in RAP, p. 297	No	Px
		Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline?				
		Yes [] ... Complete secondary illness page (not the adverse event page)				
		No []				
WV15758 ⁶³	From 637	The secondary illness page is descriptive of dates and Px	Participant, mediated through investigator	Listed as secondary illnesses in core report modules 1 and 2, p. 36	Yes	Px
		Has the patient reported any new adverse events or symptoms (including intercurrent illnesses and secondary illnesses)?				
		Yes [] record in the adverse events/intercurrent illness section of the case				
		No [] report form				
		Diagnostic confirmation of otitis media from p. 648 onwards				

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15759/ WV15871 ⁶⁴	From 665	Has the subject reported any adverse events including secondary and intercurrent illnesses?	Participant, mediated through investigator	Secondary illnesses not mentioned in protocol, but secondary outcome in core report Note: worth looking at comparisons 1.49 to 1.51 in RM5. No effect but in bronchitis this study has a more conservative effect than NV16871, which has no definitions and no diagnostics	Yes	Px
WV15799 ⁶⁵	From 642	Secondary illness defined as in M76001. ³⁶ There is a generic physical examination form at p. 704, including 'lungs' normal/abnormal specify At p. 709, has the patient reported any new AE, including intercurrent or secondary illnesses? Yes/no. If yes, record the adverse events/intercurrent illness section of the CRF (noted at p. 746 on the back of the CRF) with full history, physical examination and diagnostic work up questions for BRON ± PNIUM ± LRTI ± SIN ± OM including questions about CXR, MRI, sputum, etc.	Investigator	Proportion of contacts who are classified as having a secondary illness subsequent to a confirmed episode of influenza listed as tertiary end points	Yes	Px

continued

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials (*continued*)

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15812/ WV15872 ⁶⁶	From 285	Has the patient reported any new adverse events or symptoms (including intercurrent illnesses and secondary illnesses)? Yes [] record in the adverse events/intercurrent illness section of the case No [] report form	Participant mediated through investigator	Listed as secondary tertiary in protocol at p. 252	Yes	Px
WV15819/ WV15978/ WV15876 ⁶⁷	From 412	At pp. 450–74 is diagnosis of secondary illness page, which is very similar to the one at serial 10 Exhaustive list of diagnostic procedures Page 437 (adverse event reminder): Has the patient reported any new adverse events or symptoms (including intercurrent illnesses)? Yes [] record in the adverse events/intercurrent illness section of the case No [] report form In CRF p. 447 and p. 443, usual secondary illness reminder	Participant, mediated through investigator	Secondary illness listed as secondary (required antibiotics) and tertiary outcomes in core report and as an addition in protocol amendment at p. 21	Yes	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
		From p. 471, diagnosis of secondary illness. This is a one-page list of diagnostics similar to that at serial 10. The question is: 'Were there any diagnostic procedures or tests carried out since day 1 as a result of influenza or secondary illness that were not scheduled as part of protocol?' If yes, list per serial 10 From p. 486 is a list of diagnostic tests				
WV15825 ⁶⁸	From 389	There is a usual note: please go to diagnosis of secondary illness at back of CRF, p. 487 Is this event a secondary illness related to influenza? Diagnosis of secondary illness From pp. 510–40 with exhaustive list of diagnostics as per serial 10	Participant, mediated through investigator	Secondary illness listed as secondary outcomes in protocol p. 346 Secondary illnesses recorded on 'Adverse events' CRF	Yes	Px
WV16277 ⁶⁹	From 415	Not found	Not found	Secondary illness not listed as efficacy outcomes		

AE, adverse event; BRON, bronchitis; CXR, chest radiography; ECG, electrocardiography; LRTI, lower respiratory tract infection; MRI, magnetic resonance imaging; OM, otitis media; PNUM, pneumonia; Px, prognosis; RAP, reporting analysis plan; SIN, sinusitis.

high-dose oseltamivir arms. For these analyses we used logistic regression, adjusting for study effects if appropriate (i.e. for the two treatment trials^{8,58}) and testing for trend using a likelihood ratio test. We tested the hypothesis that increased dose of drug leads to increased incidence of adverse effects.

Search methods for identification of studies

To identify trials in the manufacturer-funded clinical trial programmes for NIs, as well as non-manufacturer-funded clinical trials of NIs, we used a variety of methods that were applied to a variety of sources from the literature, manufacturers and regulatory bodies. These methods, as well as our methodology for identifying and obtaining relevant CSRs, are detailed in *Appendices 1, 4 and 5*.

Electronic searches

We used electronic searches to identify trials that were not identified by the methods outlined in *Appendix 1*, particularly for non-manufacturer-funded clinical trials (see *Appendix 3* for details). For the 2012 review, we updated our searches of the electronic databases of published studies that were previously carried out for the Cochrane reviews on NIs in children³⁵ and healthy adults,¹⁴ and then updated the searches again on 22 July 2013.

Searching other resources

For the description of our searches for regulatory information (FDA, EMA, Roche, GSK, the Japanese Pharmaceuticals and Medical Devices Agency), see *Appendix 4*.

Data collection and analysis

Collection and inventory of the evidence base was facilitated by the tools that were specifically developed for the review (see *Appendix 5*). The overall risk of bias is presented graphically in *Figure 1* and summarised in *Figure 2*.

Selection of studies

For this 2013 review, two authors (PD and TJ) reapplied the inclusion criteria for the oseltamivir CSRs and resolved disagreements by discussion. Two review authors (ES and IO) applied the criteria for the zanamivir CSRs, whereas one review author (CH) arbitrated.

For the procedures followed in the 2012 review, see *Appendix 7*.

Data extraction and management

The sizeable quantity of available data led us to subdivide the extraction, appraisal and analysis of the data into a two-stage exercise. In stage 1 we assessed the reliability and completeness of the identified trial

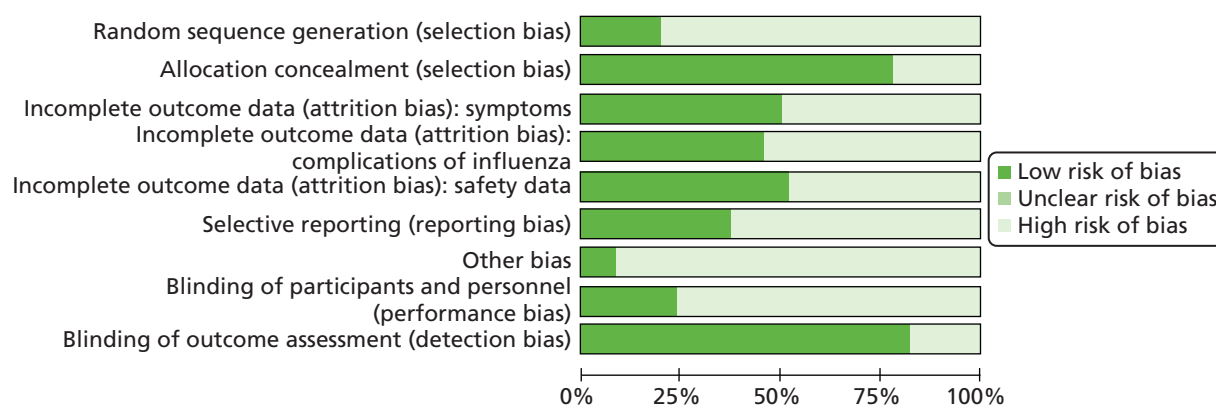


FIGURE 1 Risk-of-bias graph: review of authors' judgements about each risk-of-bias item, presented as percentages across all included studies. 'Other bias' includes potentially active placebos.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias): symptoms	Incomplete outcome data (attrition bias): complications of influenza	Incomplete outcome data (attrition bias): safety data	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
167-101 ⁷⁰	-	+	-	-	-	-	-	+	+
JNAI-01 ⁷¹	-	+	-	-	-	-	-	+	+
JNAI-04 ⁷²	-	+	-	-	-	-	-	-	-
JNAI-07 ⁷³	-	-	-	-	-	-	-	-	-
JV15823 ⁷⁴	-	-	-	-	-	-	-	-	-
JV15824 ⁷⁵	-	-	+	+	-	-	-	-	-
M76001 ³⁶	+	+	-	-	-	-	-	-	+
ML16369 ⁷⁶	-	+	+	-	+	+	-	+	-
NAI30008 ⁷⁷	-	+	+	+	+	+	+	-	+
NAI30009 ⁷⁸	-	+	+	+	+	+	-	-	+
NAI30010 ⁷⁹	-	+	+	+	+	+	-	-	+
NAI30011 ⁸⁰	-	+	+	+	+	+	-	-	+
NAI30012 ⁸¹	-	+	+	+	+	+	-	-	+
NAI30015 ⁸²	-	+	+	+	+	-	+	-	+
NAI30020 ⁸³	-	-	-	-	-	-	-	-	-
NAI30028 ⁸⁴	+	+	-	-	-	-	+	-	+
NAI30031 ⁸⁵	-	+	+	+	+	-	-	-	+
NAI30034 ⁸⁶	-	+	+	+	+	+	-	-	+
NAIA/B2008 ⁸⁷	-	+	+	+	+	-	-	-	+
NAIA/B2009 ⁸⁸	-	+	+	+	+	+	-	-	+
NAIA2005 ⁸⁹	-	+	+	+	+	+	-	-	+
NAIA2006 ⁹⁰	-	+	+	+	+	+	-	-	+
NAIA3002 ⁹¹	-	+	+	+	+	+	+	-	+
NAIA3003 ⁹²	-	+	+	+	+	+	-	-	+
NAIA3004 ⁹³	-	+	+	+	+	+	-	-	+
NAIA3005 ⁹⁴	-	+	+	+	+	+	-	-	+
NAIB2005 ⁹⁵	-	+	+	+	+	+	-	-	+
NAIB2006 ⁹⁶	-	+	-	-	-	+	-	-	+
NAIB2007 ⁹⁷	-	+	+	+	+	-	-	-	+
NAIB3001 ⁹⁸	-	+	+	+	+	+	-	-	+
NAIB3002 ⁹⁹	-	+	+	+	+	+	-	-	+
NV16871 ⁵⁷	+	+	-	-	-	-	-	-	+
PE-01 ¹⁰⁰	-	-	-	-	-	-	-	-	-
WV15670 ⁸	-	+	-	-	+	-	-	+	+
WV15671 ⁵⁸	+	-	-	-	-	-	-	+	+
WV15673/WV15697 ⁵⁹	-	-	-	-	-	-	-	-	+
WV15707 ⁶⁰	+	+	-	-	-	-	-	+	+
WV15708 ⁶¹	-	-	-	-	-	-	-	-	+
WV15730 ⁶²	-	+	-	-	-	-	-	+	+
WV15758 ⁶³	-	+	-	-	-	-	-	+	+
WV15759/WV15871 ⁶⁴	-	+	-	-	-	-	-	+	+
WV15799 ⁶⁵	+	+	-	-	+	-	-	+	+
WV15812/WV15872 ⁶⁶	+	+	-	-	-	-	-	-	+
WV15819/WV15876/WV15978 ⁶⁷	+	+	-	-	-	-	-	+	+
WV15825 ⁶⁸	-	-	-	-	-	-	-	-	+
WV16277 ⁶⁹	+	-	+	-	+	-	-	-	-

FIGURE 2 Risk-of-bias summary: review of authors' judgements about each risk-of-bias item for each included study. 'Other bias' includes potentially active placebos. +, low risk of bias; -, high risk of bias.

data. We decided to include in stage 2 of the review (full analysis following standard Cochrane methods) only data that satisfied the following three criteria:

1. *Completeness* CSRs/unpublished reports include both identifiable CONSORT (Consolidated Standards of Reporting Trials) statement-specified methods to enable replication of the study. Identifiable CONSORT statement-specified results (primary outcomes, tables, appendices) must be available.
2. *Internal consistency* All parts (e.g. denominators) of the same CSRs/unpublished report are broadly consistent.
3. *External consistency* Consistency of data as reported in regulatory documents, other versions of the same CSRs/unpublished reports and other references, to be established by cross-checking.

This was a different approach to that used in the previous version of the current review,⁹ as we had only incomplete information at that time and applied only the second and third criteria.

Stage 1

For details of the use of the CONSORT-based extraction template and the assessment for stage 1 inclusion in the A159 review,⁹ see *Appendix 5*. In this review, assessment for inclusion in stage 1 was part of the inclusion procedure.

Stage 2

In stage 2, one review author extracted data and a second review author checked it. We extracted data on to standard forms, checked and recorded it.

Use of regulatory information

We used regulatory information to assess the possible correlation between citation frequency of oseltamivir treatment trials in the FDA regulatory documents and trial size.

Post-protocol analyses

After publication of the A159 protocol in December 2010, but before validation of our CONSORT-based extractions in the spring of 2011, we decided to carry out analyses (which we called post-protocol analyses) to test five null hypotheses that we had formulated while reading, summarising and reconstructing the CSRs. The hypotheses originated from our observations of discrepancies and other unexpected observations in the CSRs' data, and were informed by reading regulatory information. *Appendix 8* reports the rationale, methods to formulate and test, and the results of the hypotheses.

The hypotheses reflect the uncertainty prevailing in the evidence base at a time when full CSRs were not available for all studies.

Assessment of risk of bias in included studies

Previous studies comparing regulatory with published or internal company sources of evidence have reported a variety of different biases that affect medical knowledge.^{41,42,56,101} We will report in detail elsewhere our comments on using the Cochrane risk-of-bias tool¹⁰² to appraise CSRs and for trial programmes, and our efforts to construct an instrument for assessing risk of bias in complete CSRs. A full description of the methods used to quantify biases will be published in another paper.

Measures of treatment effect

To estimate treatment effects we first calculated the risk ratios (RRs) and used the average (mean) control event rate and the pooled RRs reported in the figures to calculate the RDs. For consistency, we adopted this method for both the 'Summary of findings' tables and for the RDs reported in the text. For the analysis we chose to report the RRs, as they are more consistent across the studies, and we have reported the heterogeneity for the pooled RR. We reinterpreted the results using the RD, as this result is applicable to clinical decision-making. We calculated MDs for time to first alleviation of symptoms. For time to first alleviation of symptoms we also estimated the treatment effect as the percentage reduction in the average time to first alleviation of symptoms in the placebo group. Most zanamivir CSRs stated treatment effects only in terms of medians in each treatment

group, as well as p -values from a hypothesis test comparing the time-to-event distributions. These data are insufficient for conducting a meta-analysis. However, often sufficient time-to-event data were reported to allow us to estimate restricted means and standard deviations. Restricted means are based on the maximum time reported where alleviation occurred. There were some patients for whom alleviation was censored at the maximum follow-up time; therefore, restricted means are underestimates of the true means. However, the proportion of patients who were censored was generally low and similar in both treatment arms, hence this limitation is unlikely to have led to bias. The length of follow-up varied across trials and this has led to high variation in the estimated means and standard deviations across trials.

A post hoc analysis was undertaken after we discovered seven zanamivir trials that provided data on time to first alleviation of symptoms with and without relief medication. Each patient in the studies may or may not have taken relief medication [e.g. paracetamol (acetaminophen)] during the trial. Alleviation of symptoms may have occurred while the patient was taking relief medication and the 'standard' comparison was made using this scenario. However, an additional analysis used a stricter definition, for which alleviation of symptoms could be achieved only without the use of relief medication. For example, a patient may have achieved alleviation using relief medication after 5 days but took 7 days to achieve alleviation without the use of relief medication. The comparison we reported is for all patients for whom we used the stricter definition for the zanamivir group (alleviation without relief medication) and the less-strict definition for the placebo group (alleviation with relief medication).

We planned to use the tridimensional dose-relatedness, timing and patient susceptibility methodology to assess the likelihood of harms causality,¹⁰³ but the quality of the data available did not allow for this.

Unit of analysis issues

Problems with unit of analysis are described in 'Post-protocol hypotheses' (see *Appendix 8*).

Dealing with missing data

We developed a comprehensive strategy for dealing with data that we know are missing at the trial level, that is, unpublished trials (see *Search methods for identification of studies*, above, and *Appendices 1, 4 and 5*) and unreliable published records, which are a very concentrated summary of CSRs. For example, in the oseltamivir trial programme, some trials' CSRs (e.g. WP16263¹⁰⁴) consist of 8545 pages. This has a 1000-fold greater length than its published version,¹⁰⁵ which consists of seven pages. The purpose of this review is to provide as complete a picture as possible of trial programmes, without reliance on the published literature. *Appendix 9* reports an example of the content of a typical Roche CSR.

Assessment of heterogeneity

We used tau-squared (inverse variance method) and the I^2 statistic to estimate between-study variance as measures of the level of statistical heterogeneity, and the chi-squared test to test for heterogeneity.

Assessment of reporting biases

We carried out assessment of reporting biases (comparing CSR with the relevant publication) only in the first publication of A159.¹⁰⁶ For this version, as we had complete CSRs for the trial programmes of the two drugs, we expected to find all of the relevant information in these documents and adopted a binary assessment (high risk, low risk or unclear bias).

Data synthesis

We used the random-effects approach of DerSimonian and Laird¹⁰⁷ based on MDs for analysis of time to first alleviation of symptoms. For all of the other outcomes we used the random-effects approach for binary data of DerSimonian and Laird¹⁰⁷ where tau-squared was estimated using the inverse variance method.

Although overall symptom reduction is well documented, our interest was particularly focused on complications and adverse events, as this is where evidence is currently scarce or inconclusive.^{31,32,35} Our preliminary examination of CSRs identified that some symptoms and sequelae of influenza (such as 'pneumonia') had been classified as either a 'complication of influenza' or as an 'adverse event of the treatment', or both. We called this somewhat confusing classification 'compliharms'. We decided to deal with compliharms as follows. We identified complications of particular clinical interest as 'pneumonia', bronchitis, otitis media and sinusitis. We tabulated the type of data capture used for each complication ('secondary illness') by study, including the following variables: definition of what events are termed complications; which part of the CSR captured data on complications; who reported and captured the data; which diagnostic method was used; whether or not, and where, the diagnostic pathway was (usually a form); and whether or not prescriptions for treatment were captured. We then aimed to stratify our analysis by method of diagnosis with three possible criteria: (1) laboratory-confirmed diagnosis (e.g. based on radiologically or microbiologically confirmed evidence of infection); (2) clinical diagnosis without laboratory confirmation (diagnosed by a doctor/investigator after a clinical examination); and (3) other type of diagnosis, such as self-reported by patient. We also conducted analysis of any complication (such as 'pneumonia', bronchitis, otitis media and sinusitis) that was classified as serious or led to study withdrawal.

We tested the effects of oseltamivir in prophylaxis of influenza and ILI. However, the CSRs of prophylaxis trials do not define ILI but report eight different definitions for influenza with laboratory confirmation (see web extra influenza definitions, *Appendix 11*).

This is a complex and confusing set of definitions, in which, for example, the definition for upper respiratory tract infection with systemic disturbance is the same as one of the definitions for asymptomatic influenza. After discovering the absence of a definition for ILI, and the complex and confusing definitions for laboratory-confirmed influenza, we classified ILI as having two or more symptoms from the following: nasal congestion, headache, chills/sweats, sore throat, cough, fatigue, myalgia and fever. These were the symptoms reported in the efficacy listing of individual patients in module 3 of the prophylaxis trials CSRs.

In two oseltamivir treatment trials^{8,58} and one prophylaxis study⁵⁹ there were three treatment arms comparing placebo, standard dose and high dose. For time to first alleviation of symptoms, we restricted comparison to placebo against standard dose (as this is how it was reported in the original report). However, for all other outcomes we combined the standard and high-dose treatment arms. There was little apparent difference in the incidence of outcomes between the standard- and high-dose arms, and combining the arms did not appear to cause heterogeneity. However, in two cases there was some evidence of a dose-response effect. These cases are described more fully below (see *Results, Analysis of harms*).

The majority of zanamivir trials compared placebo with inhaled zanamivir. However, some trials also included an intranasal zanamivir treatment arm and a combined arm of inhaled and intranasal treatment. The multiple zanamivir arms were generally combined for meta-analysis, as effects appeared similar and did not appear to cause heterogeneity.

Subgroup analysis and investigation of heterogeneity

We investigated the robustness of complications outcomes using subgroup analysis by method of diagnosis. We investigated high estimates of heterogeneity, where possible, using subgroup analysis. For example, we conducted a subgroup analysis of time to first alleviation of symptoms in studies of oseltamivir treatment in children by partitioning studies into those of otherwise healthy children and those of children with chronic illness (asthma). Based on a referee's comment, we conducted a subgroup analysis on time to first alleviation of symptoms by infection status for zanamivir. We could not do a similar analysis for oseltamivir because we did not have data on the non-influenza-infected patients, and we could not correctly identify the patients with influenza infection as a result of the effect of oseltamivir on antibodies.

In the trial programmes for both oseltamivir and zanamivir there was large variation in treatment effects for pneumonia across the populations studied (i.e. adults and children, as well as treatment and prophylaxis), hence we conducted a metaregression to investigate this heterogeneity. We included all of the studies that reported pneumonia (32 studies in total) and investigated the four binary factors: age group (adults vs. children), drug (oseltamivir vs. zanamivir): indication (treatment vs. prophylaxis) and method of diagnosis. For oseltamivir studies, the method of diagnosis was based on either data collected on non-specific adverse events or secondary/intercurrent illness forms, or data collected on specific 'diagnosis of secondary illness' forms that included objective criteria such as X-ray confirmation. For zanamivir, two trials included X-ray confirmation of pneumonia. We conducted the metaregression in Stata/SE, version 13 for Windows (StataCorp LP, College Station, TX, USA) using the *metareg* command. There were some studies where one treatment group had zero events, therefore we added 0.5 events to all treatment groups for all studies prior to analysis. The dependent variable in the regression was log-relative risk. A further post hoc analysis was undertaken after we discovered that seven trials provided data on time to first alleviation of symptoms with and without relief medication. Each patient in the studies may or may not have taken relief medication during the trial. Alleviation of symptoms may have occurred while the patient was taking relief medication, and the 'standard' comparison was made using this scenario. However, an additional analysis used a stricter definition, for which alleviation of symptoms could be achieved only without the use of relief medication. For example, a patient may have achieved alleviation using relief medication after 5 days but took 7 days to achieve alleviation without the use of relief medication. The comparison we reported is for all patients, for which we used the stricter definition for the zanamivir group (alleviation without relief medication) and the less strict definition for the placebo group (alleviation with relief medication).

Sensitivity analysis

Sensitivity analyses applicable to our post-protocol analyses have been covered above (see *Methods*). We used the fixed-effect method of Mantel and Haenszel as a sensitivity analysis to supplement our primary analyses using the random-effects method of DerSimonian and Laird.¹⁰⁷ Random-effects meta-analysis is known to be overly conservative with sparse data. Hence, we conducted sensitivity analysis using Peto's method on two occasions for which we had sparse data and borderline statistically significant results (prophylaxis with oseltamivir: renal body system on-treatment and psychiatric body system on-treatment).

Results

Description of studies

We searched trial registries, electronic databases and regulatory archives, and corresponded with manufacturers to identify all trials and requested CSRs. Although this review focuses on the primary data sources of manufacturers, we checked that there were no published RCTs from non-manufacturer sources by running electronic searches in the following databases: CENTRAL 2013, Issue 6, limited to year published 2010–13 (20 search results); MEDLINE (January 2011 to July week 2, 2013) (56 search results) and MEDLINE (via Ovid) from 1 January 2011 to July week 2, 2013 (56 search results); EMBASE (January 2011 to July 2013) (90 search results) and EMBASE.com from 1 January 2011 to July 2013 (90 search results); and PubMed (not MEDLINE) with no date limit (21 records). We searched PubMed to identify publisher-submitted records that will never be indexed in MEDLINE and the most recently added records not yet indexed in MEDLINE. To identify reviews that may possibly have referenced further trials we searched DARE 2013, Issue 2 of 4 April (four search results); NHS EED, Issue 2 of 4 April 2013 (two search results); both resources parts of The Cochrane Library (accessed 22 July 2013); and HEED (searched 22 July 2013) (three search results).

Results of the search

Use of regulatory information

We were able to download 2673 pages from the FDA website. The table of contents (TOC) is provided in *Tables 2–5*. We used these pages to identify all of the trials that had been conducted within a drug's trial programme. There was no correlation between citation frequency of oseltamivir treatment trials in the

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
113502			
113625			
113678			
114045			
NAI108166			
105934			
NAI106784			
107485			
108127			
112311			
112312			
113268			
GCP/95/045			
NAI10901	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	15.15	
NAI10902			
NAI30008 ⁷⁷	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	15	Seven documents with 14 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	13	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	19, 19, 20	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	1, 1, 3, 4, 4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/21036ltr.pdf	2	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_MEDR.pdf	33	
NAI30009 ⁷⁸	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	1.2	Seven documents with 110 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P1.pdf	10, 10, 12, 13, 13, 14, 14, 17, 29, 42, 61, 62, 64, 64, 65, 65, 68	

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAI30010 ⁷⁹	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P2.pdf	33, 34, 36, 43, 43, 43, 43, 52, 52, 52, 53, 53, 56, 57	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 5, 6, 6, 8, 8	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_MEDR.pdf	3, 3, 3, 3, 3, 3, 3, 4, 4, 5, 8, 9, 9, 10, 10, 11, 11, 11, 14, 14, 15, 16, 17, 19, 19, 19, 20, 20, 22, 23, 23, 23, 24, 24, 24, 25, 25, 25, 25, 25, 26, 26, 26, 27, 27, 28, 28, 28, 29, 29, 31, 31, 31, 31	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_MICROBR.pdf	3, 3, 4, 4, 4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_STATR.pdf	2, 2, 2, 4, 7, 12, 18, 18, 18, 19	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P1.pdf	31.56	One document with two instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	1.2	Six documents with 65 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P1.pdf	10, 12, 13, 14, 14, 15, 17, 62, 62, 62, 64	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P2.pdf	34, 34, 36, 43, 53	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 6, 6	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_MEDR.pdf	3, 3, 3, 3, 3, 4, 5, 18, 19, 21, 21, 22, 23, 23, 23, 23, 24, 25, 25, 25, 26, 26, 26, 26, 27, 27, 27, 28, 28, 29, 29, 29, 30, 31, 31, 31, 32	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_STATR.pdf	2, 2, 13, 13, 13, 19	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	6	One document with one instance

continued

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAI30012 ⁸¹	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	1	One document with one instance
NAI30015 ⁸²			
NAI30020 ⁸³			
NAI30028 ⁸⁴			
NAI30034 ⁸⁶			
NAI40012			
NAIA1009	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P1.pdf	56	Four documents with 17 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P2.pdf	1, 1, 1, 48, 49, 52	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 6	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_MEDR.pdf	3, 3, 6, 7, 20, 31, 31	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	18	Five documents with five instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	9	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P2.pdf	52	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	11	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_STATR.pdf	2	
NAIA3002 ⁹¹	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Thirteen documents with 122 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	6, 6, 7, 7, 14, 15, 22, 22, 23	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	1, 4, 4, 12, 12, 12, 12, 17	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	4, 14, 14, 14, 14, 14, 15, 15, 15, 15, 16	

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview2.pdf	1, 2, 3, 4, 4, 5, 6, 6, 6, 8, 8, 9, 9, 9, 12, 12, 15, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview3.pdf	5, 5, 6, 6, 6, 7, 7, 7, 8, 8, 9, 9, 9, 10, 11, 12, 13, 13, 14, 15, 15, 17, 18, 18, 19, 20, 21	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	1, 1, 1, 1, 2, 6	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	4, 5, 10, 12	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	1, 1, 2, 2, 2, 2, 3, 3, 4, 4, 5, 5, 7, 8, 10, 11, 12, 14, 16, 16, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	2, 2, 6, 6, 8, 8, 9, 10	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	10	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-stats.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	15	One document with one instance
NAIA3003 ⁹²	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	17, 17, 18	Three documents with six instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	4.4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	22	
NAIA3004 ⁹³	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	14	Four documents with eight instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	7	

continued

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAIA3005 ⁹⁴	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	18, 18, 19	Five documents with 12 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	4, 4, 4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	14	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	12, 12, 12, 13, 14, 15, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	14.15	
NAIB1002	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCORRES_P2.pdf	38	
NAIB3002 ⁹⁹	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Fourteen documents with 99 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	14, 15, 15, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	11.12	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	4, 14, 14, 14, 14, 14, 14, 14, 14	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview2.pdf	9, 9, 9, 9, 9, 9, 10, 11, 12, 12, 12, 12, 13, 13, 13, 14, 14, 14, 15, 15, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview3.pdf	4, 5, 6, 6, 6, 7, 7, 7, 8, 8, 8, 9, 9, 11, 12, 12, 13, 13, 14, 15, 17, 18, 18, 19, 20, 21	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	1, 1, 1, 1, 2	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	4, 5, 10, 12	

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	2, 3, 3, 7, 8, 10, 11, 14, 15, 16, 16, 16	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	7, 8, 8, 8, 9, 9	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	10.2	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-stats.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5.5	
NAI30011 ⁸⁰			
NAIB2007 ⁹⁷	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Seven documents with 18 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	14, 15, 15, 16, 16, 17, 17, 17, 18	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	3	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	8, 10, 10, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	2	
NAIA2006 ⁹⁰			
NAIB2006 ⁹⁶			
NAIB1007			
C94-009	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	17	One document with one instance

continued

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
C94-085	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	17	Two documents with two instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	22	
NAIB1001	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	17	One document with one instance
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	6	
NAIA2005 ⁸⁹	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Ten documents with 44 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	7, 17, 10	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	2.4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	4.5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	2, 2, 3, 3, 3, 3, 5, 6, 6, 6, 6, 8, 8, 8, 9, 11, 12, 12, 13, 14, 14, 14, 14, 14, 15, 18	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	3.4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	2, 5, 9, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	10	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-microbiology.pdf	21	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	
NAIB2005 ⁹⁵	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Nine documents with 43 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	17, 20, 20, 22, 23	

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	5.5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	3, 3, 3, 7, 8, 8, 8, 9, 10, 11, 11, 11, 11, 11, 12, 12, 12, 13, 14, 14, 14, 14, 14, 14, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	3.4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	2, 9, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	2	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-microbiology.pdf	21	
NAIA/B2008 ⁷⁸	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	4	One document with one instance
NAIA2010	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	16	One document with one instance
NAIA/B2009 ⁸⁸			
167-02			
167-03			
167-05			
167-04			
JNAI-03			
JNAI-02			
JNAI-01 ⁷¹			
JNAI-07 ⁷³			
JNAI-04 ⁷²			
PE-01 ¹⁰⁰			
167-101 ⁷⁰			
167T3-11			

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
NP15717	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	46.46	Six documents with 13 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	14, 15, 15	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Admindocs_P2.pdf	2	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_BioPharmr.pdf	5, 8, 10, 13, 31	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
NP15718	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	17	One document with one instance
NP15728	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	16.35	Three documents with six instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	11	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	45, 46, 47	
NP15757	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21–087SE1–002_review.pdf	92, 93, 104, 122, 126, 131, 144, 144, 145	One document with nine instances
NP15826	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	47	Nine documents with 26 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Admindocs_P2.pdf	2	

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
NP15827	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_BioPharmr.pdf	4, 5, 5, 8, 8, 8, 10, 17, 29, 30, 30, 30, 30, 30, 31, 31	Two documents with seven instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Medr.pdf	9.1	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Statr.pdf	9.1	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
NP15827	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	10.12	Two documents with seven instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	16, 16, 17, 17, 17	
WP15525	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	21, 25, 26, 27, 27, 27, 27, 42, 42, 44	Three document with 13 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Admindocs_P2.pdf	2.2	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_BioPharmr.pdf	29	
WP15647	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	24, 27, 27	Two documents with four instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	44	
WP15648	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	39	Three documents with eight instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	44.44	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21–087SE1–002_review.pdf	94, 128, 153, 153, 154	

continued

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
WP15676	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	28.33	Three documents with four instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	11	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	45	
WV15670 ⁸	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	2, 44, 44	Six documents with 45 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6, 19, 37, 38, 39, 39, 39, 39, 40, 41, 41, 42, 43, 44, 48, 48, 49, 49	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1, 25, 25, 35, 35, 39, 39, 47	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Statr.pdf	3, 3, 4, 4, 5, 5, 5, 8, 9, 10, 17, 17, 21, 22	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21–087SE1–002_review.pdf	189	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
WV15671 ⁵⁸	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	2, 44, 44	Seven documents with 50 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6, 16, 19, 24, 24, 25, 25, 26, 27, 27, 28, 32, 34, 35, 36, 37, 38, 39, 39, 39, 40, 41, 46, 49, 49	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1, 25, 25, 35, 38, 47	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Statr.pdf	3, 4, 4, 5, 5, 5, 9, 10, 10, 15, 17, 21	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21–087SE1–002_review.pdf	189	

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
WV15673 ⁵⁹	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	Three documents with 50 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	18, 18, 18, 20, 21, 21, 21, 22, 39	
WV15697 ⁵⁹	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21-087SE1-002_review.pdf	58, 59, 71, 71, 71, 71, 71, 72, 72, 73, 73, 76, 76, 76, 76, 77, 77, 79, 82, 83, 83, 84, 122, 124, 125, 126, 128, 131, 131, 132, 133, 134, 134, 145, 145, 156, 169, 177, 189	Two documents with 40 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	39	
WV15708 ⁶¹	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21-087SE1-002_review.pdf	58, 59, 71, 71, 71, 71, 71, 72, 72, 73, 73, 76, 76, 76, 76, 77, 77, 79, 82, 83, 83, 84, 122, 126, 128, 131, 131, 131, 132, 133, 134, 145, 145, 152, 153, 156, 162, 189	Three documents with 39 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	23, 35, 39, 41	
WV15708D	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21-087SE1-002_review.pdf	71, 71, 71, 71, 71, 72, 72, 72, 72, 75, 75, 75, 75, 77, 77, 78, 79, 79, 82, 82, 122, 125, 125, 126, 131, 134, 134, 135, 135, 149, 151, 152, 152, 153	Two documents with three instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	23.35	

continued

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
WV15730 ⁶²	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	44.44	Five documents with 15 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6, 9, 19, 49, 50, 50	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1, 1, 25, 25, 27	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21-087SE1-002_review.pdf	189	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
WV15731	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	17	Four documents with nine instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5, 30, 37	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	5.6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5, 30, 37	
WV157588 ⁶³	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P1.pdf	12, 19, 19, 36	Nine documents with 92 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	2, 8, 17, 39, 39, 57, 57	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_BioPharmr.pdf	3, 4, 5, 5, 5, 8, 10, 17, 27, 30	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Corres.pdf	6.9	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5, 5, 9, 9, 10, 11, 12, 12, 16, 18, 18, 18, 19, 19, 31, 31, 31, 33, 33, 35, 36, 37, 37, 37, 37, 37, 37, 37, 40, 43	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	2, 4, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5, 5, 9, 9, 10, 11, 12, 12, 16, 18, 18, 18, 19, 19, 31, 31, 31, 33, 33, 35, 36, 37, 37, 37, 37, 37, 37, 37, 40, 43	

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
WV15759 ⁶⁴	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6, 6, 8	Seven documents with 44 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	2.3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P1.pdf	12.13	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P2.pdf	39	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	5, 10, 30, 30, 30, 30, 31, 32, 32, 33, 34, 37, 37, 37, 40, 44	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Microbr.pdf	2, 4, 4, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	5, 10, 30, 30, 30, 30, 31, 32, 32, 33, 34, 37, 37, 37, 40, 44	
WV15799 ⁶⁵	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6, 6, 9	Four documents with 89 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	2	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	28, 28, 28, 28, 28, 29, 29, 30, 30, 30, 30, 31, 31, 31, 31, 32, 32, 32, 32, 33, 33, 34, 34, 35, 35, 35, 36, 37, 37, 37, 37, 37, 38, 38, 38, 39, 39, 40, 40, 40, 40, 40, 58, 60, 71, 71, 71, 71, 71, 71, 72, 72, 73, 76, 76, 76, 77, 78, 79, 84, 85, 122, 125, 125, 126, 126, 128, 131, 140, 140, 140, 143, 147, 149, 156, 162, 169, 175, 187, 203, 208, 208	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	10.11	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	10.11	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6.7	

continued

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
WV15812 ⁶⁶	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3, 6, 10, 12	Two documents with nine instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	6, 8, 10, 25, 35	
WV15819 ⁶⁷	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6, 10, 12, 15	Two documents with eight instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	2, 6, 6, 39	
WV15825 ⁶⁸	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/21–087SE1–002_review.pdf	41, 41, 41, 41, 42, 42, 42, 42, 42, 42, 43, 44, 58, 59, 71, 71, 71, 71, 72, 72, 72, 72, 73, 73, 75, 75, 77, 77, 78, 79, 79, 79, 80, 80, 80, 81, 82, 85, 125, 125, 126, 126, 128, 131, 134, 134, 135, 135, 137, 137, 138, 145, 150, 151, 152, 152, 155, 156, 162, 169, 180, 204, 211	One document with 64 instances
WV15871 ⁶⁴	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Admindocs_P1.pdf	12.13	Seven documents with 42 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Admindocs_P2.pdf	39	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Medr.pdf	5, 11, 30, 31, 31, 32, 32, 32, 33, 34, 37, 37, 37, 37, 37, 37, 40	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Microbr.pdf	2, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Statr.pdf	5, 11, 30, 31, 31, 32, 32, 32, 33, 34, 37, 37, 37, 37, 37, 37, 40	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	2	
WV15872 ⁶⁶	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Medr.pdf	11.33	Two documents with four instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/21–246_Tamiflu_Statr.pdf	11.33	

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAI106784			
107485			
108127			
112311			
112312			
113268			
GCP/95/045			
NAI10901			
NAI10902			
NAI30008	Relenza treatment submission executive summary.pdf	4	Three documents with 10 instances
	Relenza treatment submission full document.pdf	5, 26, 26, 26, 146	
	Relenza treatment submission main text.pdf	5, 26, 26, 26	
NAI30009	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	Seven documents with 461 instances
	NAI30009 study report pdf\CSR30009.pdf		
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf		
	NAI30009 study report pdf\suptables.pdf		
	NAI30009 study report pdf\tables.pdf		
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 18, 19, 27, 30, 31	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 18, 19, 27, 30, 31, 76, 128, 130, 132, 134, 144	
NAI30010	NAI30010 study report\Final NAI30010 for sign-off.pdf		Seven documents with 399 instances
	NAI30010 study report pdf\NAI30010 HO final FSR.pdf		
	NAI30010 study report pdf\suptables.pdf		
	NAI30010 study report pdf\tables.pdf		
	Relenza prophylaxis submission.pdf	2, 5, 8, 11, 12, 19, 20, 21, 23, 24	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 27, 30, 31, 76, 135, 137, 139, 141, 143, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 27, 30, 31	

continued

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAI30012	Relenza treatment submission executive summary.pdf	4	Three documents with eight instances
NAI30012	Relenza treatment submission full document.pdf	5, 26, 26, 146	
NAI30012	Relenza treatment submission main text.pdf	5, 26, 26	
NAI30015	Relenza treatment submission full document.pdf	146	One document with one instance
NAI30020			
NAI30028			
NAI30031			
NAI30034			
NAI40012			
NAIA1009	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	101	Two documents with three instances
	NAI30009 study report pdf\CSR30009.pdf	28.34	
NAIA3002 ⁹¹	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	Nine documents with 513 instances
	NAI30009 study report pdf\CSR30009.pdf	34.95	
	NAI30009 study report pdf\NAI30009 HO final FSR.pdf	22	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf		
	NAIA3002 study report pdf\NAIA3002 supporting tables 2.pdf		
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 47, 49	
	Relenza treatment submission full document.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31, 63, 63, 63, 76, 106, 106, 107, 107, 109, 109, 112, 112, 114, 114, 115, 115, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31	
NAIA3003	Relenza prophylaxis submission.pdf	10	One document with one instance
NAIA3004	Relenza prophylaxis submission.pdf	10	One document with one instance

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAIA3005	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	36, 94, 94, 94, 95, 96, 96, 101	Five documents with 310 instances
	NAI30010 study report pdf\NAI30010 HO FSR.pdf	6.18	
	NAIA3005 study report pdf\VA3005cr01.pdf		
	NAIA3005 study report pdf\TABS.pdf		
	Relenza prophylaxis submission.pdf	2, 5, 6, 12, 13, 13, 15, 15, 16, 16, 17, 17, 18, 18	
NAIB1002			
NAIB3001	NAI30009 study report pdf\CSR30009.pdf	34, 50, 95	Eleven documents with 374 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10.22	
	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	
	NAI30010 study report pdf\NAI30010 HO FSR.pdf	17.17	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	
	NAIA3005 study report pdf\VA3005cr01.pdf	25	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf		
	NAIB3001 study report pdf\NAIB3001 supporting tables 1.pdf		
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 18, 27, 30, 31, 32, 63, 63, 63, 76, 99, 99, 101, 101, 103, 103, 105, 105, 144, 162	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 18, 27, 30, 31, 32	
NAIB3002	NAI30009 study report pdf\CSR30009.pdf	34.95	Ten documents with 579 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	22	
	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 48, 50	
	NAIA3005 study report pdf\VA3005cr01.pdf	25	

continued

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	NAIB3002 study report pdf\NAIB3002 full study report.pdf		
	NAIB3002 study report pdf NAIB3002supporting tables 1.pdf		
	NAIB3002 study report pdf NAIB3002supporting tables 2.pdf		
	Relenza treatment submission full document.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31, 63, 63, 63, 76, 117, 117, 117, 118, 118, 120, 120, 122, 122, 124, 124, 125, 125, 127, 127, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31	
NAI30011	Relenza treatment submission full document.pdf	146	One document with one instance
NAIB2007	NAI30009 study report pdf\CSR30009.pdf	95	10 documents with 379 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 29	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2007 study report pdf\b2007cr.pdf		
	NAIB2007 study report pdf\TABLES.pdf		
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25.26	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 29	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 19, 27, 30, 31, 76, 91, 91, 92, 92, 94, 94, 96, 96, 98, 98, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 19, 27, 30, 31	
NAIA2006	NAIA2005 study report pdf\A2005cr.pdf	38, 73, 74	Four documents with six instances
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	
	NAIA3005 study report pdf A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAIB2006	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	Three documents with three instances
	NAIA3005 study report pdf \A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
NAIB1007			
C94-009			
C94-085			
NAIB1001			
NAIB_1001			
NAIA2005	NAI30009 study report pdf\CSR30009.pdf	95	Twelve documents with 895 instances
	NAIA2005 study report pdf\A2005cr.pdf		
	NAIA2005 study report pdf\APPS_ALL.pdf		
	NAIA2005 study report pdf\TBS_ALL.pdf		
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 48, 48	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2005 study report pdf\b2005cr.pdf	7, 7, 22, 25, 26, 34, 34, 42, 71, 72, 72	
	NAIB2007 study report pdf\b2007cr.pdf	76	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 47, 47	
NAIB2005	Relenza treatment submission full document.pdf	16, 16, 16, 16, 17, 18, 27, 30, 76, 77, 77, 77, 79, 79, 79, 80, 80, 82, 82, 84, 84, 85, 144, 144	
	Relenza treatment submission main text.pdf	16, 16, 16, 16, 17, 18, 27, 30	
NAIB2005	NAI30009 study report pdf\CSR30009.pdf	95	Twelve documents with 838 instances
	NAIA2005 study report pdf\A2005cr.pdf	7, 8, 8, 24, 24, 25, 43, 70, 74, 74	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 48, 48	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2005 study report pdf\APPSNEW.pdf		
	NAIB2005 study report pdf\b2005cr.pdf		
	NAIB2005 study report pdf\TBS_ALL.pdf		

continued

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	NAIB2007 study report pdf\B2007cr.pdf	76	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 47, 47	
	Relenza treatment submission full document.pdf	16, 16, 16, 16, 17, 18, 27, 30, 76, 77, 79, 79, 85, 85, 85, 86, 86, 88, 88, 90, 90, 144, 144	
	Relenza treatment submission main text.pdf	16, 16, 16, 16, 17, 18, 27, 30	
NAIA/B2008	NAI30009 study report pdf\CSR30009.pdf	95	Six documents with 16 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 29, 29	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25, 26, 26, 26, 77	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 29, 29	
NAIA2010	NAIA3005 study report pdf\A3005cr01.pdf	25	One document with one instance
NAIA/B2009 ⁸⁸	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	Three documents with three instances
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
167-02			
167-03			
167-05			
167-04			
JNAI-03			
JNAI-02			
JNAI-01			
JNAI-07			
JNAI-04			
PE-01 ¹⁰⁰			
167-101 ⁷⁰			
167T3-11			

NICE, National Institute for Health and Care Excellence.

TABLE 5 Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK)

Referenced study	File name volume ^a	Pages where study is mentioned (separated by commas)	Note
GS97-802			
133312			
GS-97-801			
JP15734			
JP15735			
JV15823 ⁷⁴			
JV15824 ⁷⁵			
JV16284			
M76001 ³⁶	1	33, 36, 37, 37, 38, 38, 39, 67, 68, 94, 95, 224	One document with 12 instances
M76006			
ML20910			
ML22789			
ML22879			
MV21118			
MV22841			
NCT00298233			
NCT00555893			
NCT00707941			
NCT00799760			
NCT00830323			
ML25018			
NCT00867139			
NCT00873886			
NCT01002729			
NP15717	6	32, 75, 76, 77	Two documents with five instances
	8	68	
	6	73.98	One document with two instances
NP15718			
NP15728			

continued

TABLE 5 Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*continued*)

Referenced study	File name volume ^a	Pages where study is mentioned (separated by commas)	Note
NP15757	8	68	One document with one instance
NP15826	6	32, 75, 75, 75, 76, 76, 77, 78, 79, 80, 98	One document with 11 instances
NP15827	8	68	One document with one instance
NP22770			
NP25138			
NP25139			
NV16871			
NV20234			
NV20235			
NV20236			
NV20237			
NV22155			
NV25118			
NV25182			
PP16351			
WP15517	1	185.245	One document with two instances
WP15525	1	185.245	One document with two instances
WP15647			
WP15648			
WP15676			
WP15901			
WP22849			
WV144181			
WV15670 ⁸	1	33, 36, 37, 37, 38, 38, 39, 47, 48, 48, 49, 49, 50, 53, 54, 54, 55, 163, 171, 188, 207, 209, 224, 245, 245, 252, 253, 253	Seven documents with 1193 instances
	10	7, 36, 37, 37	
	2		
	3		
	4	90	
	6	35.98	
	8	65	
	2	20, 20, 20, 20, 20	One document with five instances

TABLE 5 Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*continued*)

Referenced study	File name volume ^a	Pages where study is mentioned (separated by commas)	Note
WV15671 ⁵⁸	1	33, 36, 37, 37, 38, 38, 39, 47, 48, 49, 49, 50, 53, 54, 54, 55, 163, 171, 188, 207, 209, 224, 245, 245	Seven documents with 1222 instances
	10	7, 36, 37, 37	
	2	82	
	4		
	5		
	6	35.98	
	8	66	
WV15673 ⁵⁹	8	66	One document with one instance
WV15673D	8	66	One document with one instance
WV15697 ⁵⁹	8		One document with one instance
WV15697D	8		One document with one instance
WV15707 ⁶⁰	1	33, 36, 37, 37, 38, 67, 68, 224, 245, 245, 245, 246	One document with 12 instances
WV15708 ⁶¹			
WV15708D			
WV15730 ⁶²	1	33, 36, 37, 37, 38, 38, 39, 47, 53, 54, 55, 186, 207, 224, 245, 245, 246	Four documents with 22 instances
	10	7, 36, 37	
	2	82	
	4	90	
WV15731	6	98	One document with one instance
WV15758 ⁶³	1	36, 37, 82, 83, 84, 85, 86, 92, 94, 95, 97, 106, 224, 246	Four documents with 424 instances
	6		
	7		
	8	68	
WV15759 ⁶⁴	1	36, 37, 94, 95, 95, 109, 113, 114, 121, 122, 224, 246	One document with 12 instances
WV15799 ⁶⁵	1	137, 139, 139, 232, 233	Three documents with 499 instances
	8		
	9		

continued

TABLE 5 Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*continued*)

Referenced study	File name volume ^a	Pages where study is mentioned (separated by commas)	Note
WV15812 ⁶⁶	1	36, 37, 37, 38, 38, 39, 67, 68, 68, 107, 107, 107, 108, 108, 121, 121, 122, 123, 224, 246	Two documents with 197 instances
	10		
WV15819 ⁶⁷	1	33, 36, 37, 37, 38, 58, 58, 59, 59, 60, 61, 62, 62, 65, 65, 67, 68, 224, 246	Two documents with 173 instances
	10		
WV15825 ⁶⁸	8	66, 66	One document with two instances
WV15871 ⁶⁴	1	109, 246	One document with two instances
WV15872 ⁶⁶	1	36, 37, 37, 38, 38, 39, 67, 68, 68, 107, 107, 108, 108, 121, 121, 122, 123, 224	One document with 18 instances
WV15876 ⁶⁷	1	246, 246	One document with two instances
WV15978 ⁶⁷	1	67, 70, 175, 246, 246	One document with five instances
WV16193			
ML16369 ⁷⁶			

NICE, National Institute for Health and Care Excellence.

a Number of the volume of the Tamiflu NICE submission.

Notes

Oseltamivir trials citation by trial ID and source NICE file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which file. Blank spaces indicate no citation for known trials.

All of the studies have been searched in the folder 'Roche submission'.

When there is the number of the volume but no pages are mentioned, it means that the code of the study is cited more than 100 times.

FDA regulatory documents and trial size. The biggest treatment trial³⁶ is cited only four times in three documents, whereas other contemporary treatment trials are cited far more.^{8,58,60,62,66} One trial,⁸ for example, is cited 46 times in the FDA documents. However, the combined enrolled denominator of the four treatment trials completed at the time^{8,58,60,62} was 1442, smaller than 1459.³⁶ This suggested that the FDA's regulatory evaluation of Roche's New Drug Application (NDA) was based predominantly on what Roche had presented to them as 'pivotal', or trials that best demonstrated the properties of oseltamivir, not the complete evidence base of all oseltamivir trials. One possible alternative explanation for this observation could have been the interval between trial completion, generation of the report and NDA submission. This explanation is supported by the relatively brief interval between completion of the M76001 trial³⁶ (19 February 1999) and submission (on 30 April 1999) of NDA 021087 to the FDA. However, the core part of the submission (the clinical development programme) contains data from two (at the time of writing) ongoing trials.^{66,67}

The basis of the selection of trials to regulators is therefore unclear but appears to be dictated by criteria other than availability and size. The importance of trials (to manufacturers and possibly to regulators) may not be based on the same criteria that systematic reviewers would use (i.e. the capability of the trial to answer questions).

Owing to the vast size of FDA documents, sometimes hundreds of pages long, it was difficult to determine important emerging themes solely by reading. To identify items of interest in the FDA comments we used word clouds.¹⁰⁸ Word clouds give greater prominence to words that appear more frequently in the source document. The resulting graphic representation showed words such as 'diary' and 'baseline' to be heavily mentioned in the relevant (abridged) text from the FDA's Medical Officer Review.¹⁰⁹ Examining the 'diary' entry in more detail, we found the following FDA comment:

The majority of subjects participating in the treatment trials had only used the first diary card. The second diary card was issued in 15% to 20% of participants. In response to FDA's request, the applicant provided a summary of diary card dispensing in the 8/6/99 submission. It became apparent that instructions on when to start a second diary card were not uniformly followed in three trials.^{8,58,62} There were examples of patients who had alleviated symptoms yet also received a second diary card. Conversely, there were also examples of patients who did not alleviate all symptoms but did not receive a second diary card. Thus the second diary card was used inconsistently which is viewed as a flaw of these trials. The lack of consistency in collecting symptom information after alleviation precluded a complete documentation of symptom fluctuation. Also missing second diary cards in subjects who had not alleviated symptoms were responsible for the majority of censored data which may have potentially influenced the results of efficacy analysis. In order to address the impact of censoring, the applicant performed several sensitivity analyses, which will be summarized in the Integrated Summary of Efficacy.

This comment highlights problems with the follow-up procedure of treatments trials, which may have impaired the regulator's ability to draw conclusions on the duration of effect of oseltamivir. It also provides a good example of how graphic methods can help to identify crucial comments in vast regulatory files.

Several other experiments with text from the same FDA document showed that the choice of text to be represented as a word cloud heavily influenced cloud construction, visibility of words and hence our ability to detect important comments. It is for this reason that we decided to adopt a mixed approach: mapping citations while reading FDA comments and integrating such comments in our appraisal of the evidence. Regulatory comments were all the more important because, at the time that we developed this method, we had few CSRs, and comments helped to identify the gaps in our knowledge of the trial programmes.

Once the TOC had been constructed, we postulated that, given the huge work involved in reviewing lots of regulatory files, our new instrument could also help us by indicating which parts were more important than others, thus focusing our efforts. We experimented with a variety of methods, which are reported above (see *Data collection and analysis*).

Clinical study reports

After prolonged correspondence and media pressure (see *Appendix 1*), we were able to access the trial programmes for both oseltamivir and zanamivir without clauses restricting their accessibility to third parties.

Electronic searches

Two review authors (CDM and MT) independently scanned the titles and abstracts of the electronic searches. Three identified studies^{110–112} were published versions of trials that were possibly unknown to us. We wrote to the first trial author to ask for CSRs, or equivalent, on 12 November 2013, and the author confirmed that the trials had not been completed.

Included studies

The absence of documentation of trial programmes for both drugs, listing all sponsored trials completed or under way, meant that we had to rely on a variety of sources for the reconstruction of the trial programmes and identification of relevant CSRs. This complexity is reflected in the flow chart presented in *Figure 3*, illustrating the study selection process for this review. The two main pathways were the

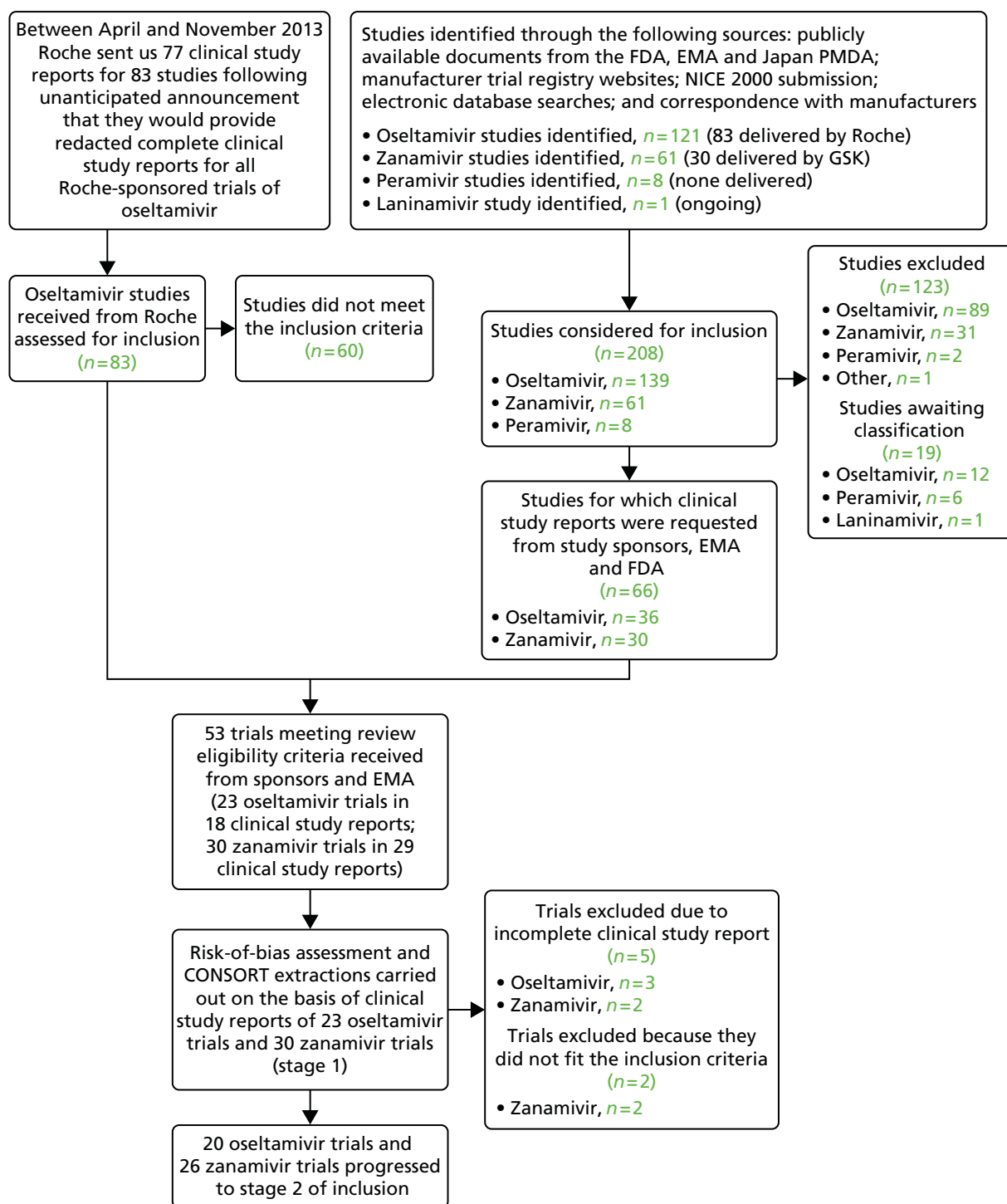


FIGURE 3 Flow diagram describing the number of studies identified, inclusion, exclusion and progression from identification to stage 1 to stage 2 of the review. PMDA, Japanese Pharmaceuticals and Medical Devices Agency.

spontaneous release of 77 full CSRs by Roche and the requests to regulatory authorities and GSK for all of the relevant reports.

We carried out the inclusion into stage 1 using the CSRs, titles, abstracts and any other relevant information. Through this process we identified 208 potentially relevant studies (139 oseltamivir trials, 61 zanamivir trials and eight peramivir trials). We excluded 123 studies (see *Appendix 10*, listed in the 'characteristics of excluded studies' table) as clearly ineligible. A further 19 studies are awaiting classification (*Table 6*). We requested 66 trials from study sponsors, the EMA and the FDA. From these

TABLE 6 Characteristics of studies awaiting assessment (ordered by study ID)

JPRN-JapicCTI-111647	
Methods	A randomised, double-blind, placebo-controlled study to confirm the efficacy in the prevention of influenza virus infection (Phase 3 study)
Duration of the study	1 October 2011 to 30 June 2012
Sponsor	Daiichi Sankyo Co., Ltd
Participants	–
Interventions	Laninamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
ML20589	
Methods	Economic and social benefits of treating and preventing influenza in aged care facilities
Sponsor	The University of Sydney, Australia
	anzctr.org.au number ACTRN12606000278538
Participants	–
Interventions	Oseltamivir, three different regimens
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
ML20910	
Methods	A study of Tamiflu (oseltamivir) treatment in laboratory-confirmed influenza
Sponsor	Hoffmann-La Roche, NCT00436124
Participants	–
Interventions	Oseltamivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
ML21776	
Methods	Study to evaluate nosocomial transmission of influenza
Sponsor	University Hospitals, Leicester
NCT00798421	
Participants	–
Interventions	–
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
MV21118	
Methods	Early oseltamivir treatment of influenza in children aged 1–3 years
Sponsor	Hospital District of Southwestern Finland
NCT00593502	
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study

continued

TABLE 6 Characteristics of studies awaiting assessment (ordered by study ID) (*continued*)

MV21737	
Methods	Long-term influenza prophylaxis with inhaled zanamivir or oral oseltamivir
Sponsor	University of Oxford
NCT00980109	
Participants	–
Interventions	Oseltamivir, zanamivir, placebo
Outcomes	–
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study
MV21879	
Methods	Oseltamivir randomised controlled efficacy trial
Sponsor	International Centre for Diarrhoeal Disease Research, Bangladesh
NCT00707941	
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
MV22841	
Methods	An observational clinical trial of influenza A/H1N1 2009 resistance under standard-duration oseltamivir treatment
Sponsor	Not known
Participants	–
Interventions	Oseltamivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
MV22940	
Methods	A randomised controlled trial on the effect of post-exposure oseltamivir prophylaxis on influenza transmission in nursing homes
Sponsor	National Institute for Public Health and the Environment (RIVM), The Netherlands
NCT01053377	
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00419263	
Methods	Evaluation of the efficacy and safety of peramivir in subjects with uncomplicated acute influenza
Sponsor	BioCryst Pharmaceuticals
Participants	–
Interventions	Peramivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study

TABLE 6 Characteristics of studies awaiting assessment (ordered by study ID) (*continued*)

NCT00453999	
Methods	Evaluation of the efficacy and safety of peramivir in adults with acute serious or potentially life-threatening influenza
Sponsor	BioCryst Pharmaceuticals
Participants	–
Interventions	Peramivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00486980	
Methods	Intramuscular peramivir for the treatment of uncomplicated influenza
Sponsor	BioCryst Pharmaceuticals
Participants	–
Interventions	Peramivir
Outcomes	–
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study
NCT00555893	
Methods	Efficacy study of early versus late oseltamivir administration for treating and preventing influenza
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00610935	
Methods	Intramuscular peramivir in subjects with uncomplicated acute influenza
Sponsor	Marshfield Clinic Research Foundation
Participants	–
Interventions	Peramivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00705406	
Methods	A Phase II, multicentre, randomised, placebo-controlled, study to evaluate the efficacy and safety of intramuscular peramivir 600 mg in subjects with uncomplicated acute influenza
Sponsor	BioCryst Pharmaceuticals
Participants	–
Interventions	Peramivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
continued	

TABLE 6 Characteristics of studies awaiting assessment (ordered by study ID) (*continued*)

NCT00958776	
Methods	A study to evaluate the efficacy and safety of IV peramivir in addition to standard of care compared to standard of care alone in adults and adolescents who are hospitalised due to influenza
Sponsor	BioCryst Pharmaceuticals
Participants	Peramivir
Interventions	–
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00980109	
Methods	Long-term influenza prophylaxis with inhaled zanamivir or oral oseltamivir
Sponsor	University of Oxford
Participants	–
Interventions	Oseltamivir, zanamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT01032837	
Methods	A study of Tamiflu (oseltamivir) for treatment of influenza with a focus on (H1N1) 2009 flu strain
Sponsor	Hoffmann-La Roche
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NV20236	
Methods	A study of Tamiflu (oseltamivir) for seasonal prophylaxis of influenza in children
Sponsor	Hoffmann-La Roche
NCT00412555	
Participants	–
Interventions	Oseltamivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study

different methods, the total number of trials available for assessment for inclusion in our review at stage 1 was 53.

Twenty-three studies of oseltamivir^{8,36,57–69,74–76} and 28 of zanamivir^{70–73,77–100} were included in stage 1. It was not uncommon for more than one trial to be reported in the same CSRs. This was either because of the amalgamation of two or more trials due to low influenza virus circulation and difficulties in recruitment (e.g. WV15812/WV15872⁶⁶) or because the trials bore different ID numbers when, in reality, they followed the same protocol, albeit in two different hemispheres (e.g. WV15759/WV15871⁶⁴).

We also identified six completed or ongoing studies of peramivir in dose–response or placebo-controlled studies.^{113–118}

The included trials were predominantly conducted in adults during influenza seasons in both hemispheres. A small number of studies were conducted in older people who were residing in care homes and in people with underlying respiratory diseases. All trials were sponsored by the manufacturers.

Oseltamivir

Of the 23 oseltamivir trials in stage 1, 15 were multicentre trials conducted in both the northern and southern hemispheres, whereas eight were carried out in only one country (USA, five; Japan, two; China, one). In total, 9623 participants were included (6574 in treatment trials and 3049 in prophylaxis trials). The age of the participants ranged from 1 to 82 years and the duration of follow-up varied from 6 to 42 days.

Two of the trials were conducted within nursing homes; 20 were within free-living populations; and one was performed in inpatient and outpatient departments. Three trials were conducted in children (two of the trials were among children with chronic asthma, $n = 660$; one trial was performed among otherwise healthy children, $n = 669$), whereas participants in 20 trials were adults. In some trials the eligible population included participants who were at increased risk of influenza complications, or with diagnoses of asthma or chronic obstructive pulmonary disease, but the majority included only otherwise healthy adults. In one trial,⁶² participants were stratified by smoking status, whereas those in another trial were stratified by the presence or absence of otitis media.⁶³

All trials compared orally administered oseltamivir (either as capsules or reconstituted powder) with placebo.

Of the 23 trials, we included 20 RCTs for the analysis examining the use of oseltamivir compared with placebo. Two RCTs were excluded from the meta-analysis because they were only synopsis reports^{74,75} and another because it was not a full CSR.⁷⁶

We finally included 20 oseltamivir trials into stage 2: 11 on treatment in adults,^{8,36,57,58,60–62,66,67,69,74–76,108–112} four in children^{57,63,64} and five on prophylaxis:^{51,61,65,68} two in adults,⁵¹ two in the elderly^{61,68} and one in households.⁶⁵ Of the 15 included treatment trials of oseltamivir, only three^{8,36,63} were successful in recruiting the a priori planned sample size.

Zanamivir

Of the 28 included zanamivir trials, 18 were multicentre trials that were conducted in both the northern and southern hemispheres and 10 were carried out in only one country (Japan, five; USA, three; Finland, one; Germany, one). In total 14,628 participants were included (7678 in treatment trials and 6950 in prophylaxis trials). Participants' age ranged from 5 to 12 years to > 65 years, and duration of follow-up varied from 5 to 35 days.

Two of the trials were performed within nursing homes; several were within free-living populations; one was performed within a university student population. In some trials the eligible population included

participants at increased risk of influenza complications, or with diagnoses of asthma or chronic obstructive pulmonary disease, but the majority included only adults who were otherwise healthy.

Zanamivir was administered as an intranasal spray, an inhalation or a combination of both, and placebos were designed to match. Administration was by the participant in the majority of trials and by nursing staff in the trials within nursing homes. Twenty-two trials compared inhaled zanamivir with placebo and six trials compared inhaled zanamivir, or intranasal zanamivir, with placebo or usual care.

Of the 28 trials,^{70–73,77–100} we included 26 RCTs^{70–73,77–82,84–91,93–100} for the analysis, examining the use of zanamivir compared with placebo. Two trials^{83,92} were excluded from the meta-analysis because one was only a synopsis⁸³ and one compared zanamivir to usual care and not placebo.⁹²

We finally included 26 zanamivir trials: 14 on treatment in adults,^{71–73,77,80–82,87,89,91,95,97–99} two in children^{78,84} and 10 trials in prophylaxis.^{70,79,85,86,88,90,93,94,96,100}

Our attempt at collecting sufficient information from regulatory files to reconstruct missing CSRs also failed because the information appeared to be insufficient for a reliable reconstruction.

Excluded studies

We excluded 123 studies from entering stage 1 for various reasons. Some were pharmacokinetic studies, had an active comparator, compared higher-dose schedules with lower-dose schedules or were ongoing trials. A further 19 trials are awaiting assessment (see *Table 6*).

Risk of bias in included studies

Study-level assessments are reported in the risk-of-bias tables (see *Figure 2*). To address the problem of reporting bias, we ignored published trial reports and directed our attention to CSRs and regulatory information. Our problems in reviewing the copious material at our disposal were how to identify and analyse important details in the midst of thousands of pages of information and how to construct a coherent appraisal of large and complex trial programmes.

In addition, as we gained unrestricted access to the full CSRs (apart from personal de-identifying redactions) we took the view that all information needed to judge risk of bias should be present. Therefore, when this information was not available, we judged the corresponding risk-of-bias element as at 'high' risk of bias. For example, when details of the random sequence generation are missing from journal publications of clinical trials, it is customary to record this as 'unknown' risk of bias. This judgement usually carries the assumption that the random sequence generation details are available in more detailed reports. But when these details were still missing, even in full CSRs, we chose to rate this risk-of-bias element at 'high' risk of bias.

In the following paragraphs we report some of the salient findings using the current Cochrane format but applying the logic of reviewing regulatory data.

Allocation (selection bias)

In 10 of the 20 oseltamivir studies included in stage 2, the description of random sequence generation is missing. All of the zanamivir trials but one⁸⁴ had reporting bias due to the absence of description of random sequence generation.

Blinding (performance bias and detection bias)

The placebo and active drug capsule cap were not identical in 11 of the 20 trials of oseltamivir. This may have compromised blinding of participants. For all but one of the zanamivir trials we did not have the certificates of analysis to enable us to reconstruct the appearance, taste and texture of the two principles.

Incomplete outcome data (attrition bias)

In addition to the missing diary cards in three treatment trials (see *Results of the search*, above), we were unable to identify all of the data for all of the outcomes in all of the oseltamivir trials and in eight of the zanamivir trials. For example, hospitalisations were not reported in zanamivir trials and inconsistently reported in oseltamivir trials. The relevant data in this review come from a table of hospitalisations sent to us by Roche in late 2013. In addition, in some trials we were unable to track individual participants through tables, narratives and individual listings. The issue of compliharms impeded the ascertainment of harms in oseltamivir treatment trials (see *Appendix 1*). We had difficulty in following the logic of compliharms, even with access to full CSRs. The definition of adverse events in the RCTs of oseltamivir and zanamivir is different from the ordinary definition of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E2D guideline, which is as follows: 'An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product' [www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Ste p4/E2D_Guideline.pdf (accessed 27 December 2013)].

As an example, the definition of adverse events in one study⁵⁸ is as follows: 'following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event, however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness) and therefore do not appear as adverse events' (p. 35)⁵⁸ and: '*any adverse change from the subject's baseline (pre-treatment) condition, which occurred during the course of the study after treatment had started, whether considered related to treatment or not*'. Treatment included *all* investigational agents (including placebo and comparative agents) administered during the course of the study)' (our emphasis).⁸ As a consequence, adverse events that are similar to the symptoms of influenza (such as headache and mild gastrointestinal adverse events) tend to be excluded from the treatment trials.

We identified a report of a site inspection for one adult prophylaxis trial.⁵⁹ The FDA carried out the inspection in September 2000 at various trial sites in the USA, including the West Virginia site (which was responsible for enrolling many hundreds of participants). A FDA official letter reported several violations, including failure to report serious harms to the sponsor (Roche) as the protocol required and in addition stated: '... we view the statement in the payment section of the consent form used in the study that subjects ... will receive \$300.00 for participating in and completing the study. No payment will be made to you if you withdraw from the study for personal reasons ... to be an improper procedure. When subjects are to be paid for participating in a study, the payment should be prorated for the subject's actual participation in the study in order to avoid the possibility of coercion' (p. 177).¹¹⁹ However, the FDA allowed the data (which had been published 1 year earlier in a prime journal) to stand in support of Roche's application for the prophylaxis indication. We do not know whether or not the participant contract was standard (i.e. whether or not the observation of possible improper procedures could be generalised to other sites and other trials) but the document cited by the FDA inspector is the subject of one of our (as yet unfulfilled) FOI requests. The possibility of financial pressure, if confirmed, could seriously confound dropout rates because of harms or any other causes in prophylaxis trials.

The significantly higher incidence of diarrhoea in placebo recipients of treatment trial WV15671⁵⁸ was identified by the FDA reviewers who remarked 'Diarrhea was reported more frequently among subjects receiving placebo than among subjects receiving Ro 64-0796 [oseltamivir]. Diarrhoea, although not specified as an inclusion criterion, has been documented to be a clinical manifestation of influenza infection. The reduction in the incidence of diarrhoea for the treatment groups compared with the placebo group could be considered as a possible treatment effect of Ro 64-0796'.¹⁰⁹ However, according to the Japanese Summary Basis for Approval of oseltamivir capsules for prophylaxis, diarrhoea was reported more frequently in the oseltamivir arm (49/986) than in the placebo group (38/973) in the summarised table of adverse events from three trials.^{59,61,68} Our findings are inconsistent with the explanation by the FDA.

Selective reporting (reporting bias)

All of the oseltamivir trials and almost half of the zanamivir trials had selected reporting. The oseltamivir trials showed a consistent trend of missing original protocols (except for one trial³⁶), changing outcome definitions while the trial was running, protocol amendments even after the trial had been completed, inconsistent approaches to outcome data collection, missing SAPs, missing date of unblinding and the use of self-reported outcomes such as pneumonia.^{8,36,47,60,68,69} This represents 55% of pneumonia event data. As an example, in trial WV15670,⁸ secondary illnesses were patient reported. The body of the CSR states that complications requiring antibiotic treatment were specified a priori, but, even in the final version of the protocol, for which we have the full text, there is no predefined list of secondary illnesses (i.e. no mention of pneumonia, bronchitis, sinusitis or otitis in the protocol); complications did not have anything to do with antibiotic treatment according to the protocol; and the CRF did not mention specific secondary illnesses by name. Zanamivir trials reported outcomes that were not specified in the protocol provided.

We found evidence of possible selective reporting bias when we analysed the Japanese Summary Basis for Approval data on prophylaxis. The regulatory data report tables for individual trials, as well as 10 pages of summarised tables for three trials of prophylaxis.^{59,61,70} Tables for individual trials include data for high-dose arms but report few psychiatric adverse events overall. However, the summarised tables list a variety of psychiatric adverse events, including psychotic and suicidal adverse events, but not adverse events from the high-dose group. As a preliminary exploratory analysis, we combined the following suspected serious adverse events collectively: hallucination and delusion, which are classified grade 3 (serious) by the National Cancer Institute-Common Toxicity Criteria Version 2.0 (NCI-CTC V2.0); psychosis (hallucination and delusion are the two major symptoms of this disease); suicidal attempt, which is classified grade 3 (serious) by the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE V4.0); and hostility, which includes aggression, hostility, violence and murder, commonly considered as serious events although not listed in the NCI-CTC V2.0 or CTCAE V4.0. Numbers of suspected serious psychotic/suicidal adverse events (including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide) were five in the oseltamivir group and zero in the placebo group during the on-treatment period; when the off-treatment period data are added, the total was eight compared with one. The prophylaxis programme is crucial in understanding the harms profile of the drug, as the potential for harms witnessed to be confounded by the apparently numerous symptoms and signs of influenza infection is far less, as many participants do not become infected with influenza. This makes a causality assessment more straightforward.

Other potential sources of bias

All but three of the oseltamivir treatment trials were under-recruited. Several of the zanamivir trials were also under-recruited. We noted the use of different relief medication across different centres within the same trial, and in one zanamivir trial,⁸⁵ according to the protocol, participants receiving antibiotics for bacterial respiratory tract infection should have been excluded but in the trial this did not happen. In the zanamivir trial,⁸⁶ the definition of 'confirmed influenza' was amended after protocol closure.

We also noted several other items that were not included in all full CSRs:

- Study protocols dated prior to participant enrolment (missing for many oseltamivir trials).
- Certificates of analysis for the intervention/placebo preparations.
- Patient enrolment dates explicitly reported (only trial inception and cessation dates are given; in zanamivir trials these are partially redacted).
- Explicitly reported date of trial unblinding. We frequently noted the statement 'the database was authorised on xxxx' to identify the unblinding date but an explicit date is important to report. In some cases, the date of unblinding was reported, but the actual date within the month was redacted. This practice also applied to zanamivir protocol amendments.
- Authorship and accountability for the writing of the CSRs.

- SAPs in some cases.
- Patient consent forms (missing from most zanamivir trials).
- Patient information form (missing from most zanamivir trials).
- List of randomisation codes (variably included).
- CRF templates in zanamivir trials do not allow for determining who completes the form (patient or clinician).
- Core data sheet.

Other important documents that we did not have included:

- study manual of procedures
- minutes of safety data monitoring committee meetings.

The placebo interventions in both sets of trials may have contained active substances. The placebo for zanamivir trials contained lactose powder, which can potentially cause bronchospasm, whereas the placebo for oseltamivir trials contained dehydrocholic acid and dibasic calcium phosphate dehydrate, which can cause gastrointestinal symptoms.

Data on participants by influenza-infected status (in treatment trials) and for participants with ILI (in prophylaxis trials) were not reported in the oseltamivir CSRs.

Finally, data on the effects of rescue or relief medication (mainly paracetamol/acetaminophen) were incomplete in CSRs of oseltamivir trials and not reported separately in all of the zanamivir trials.

Effects of interventions

Analysis of time to first symptom alleviation

In adult treatment, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% CI 8.4 to 25.1 hours; I^2 statistic = 0%), representing a 10% reduction from 7 days to 6.3 days (*Figure 4*). There was no significant effect in asthmatic children: increased by 5.2 hours (95% CI 11.1 hours lower to 21.4 hours higher; I^2 statistic = 0%). But there was an effect in otherwise healthy children, based on one trial (29 hours, 95% CI 12 to 47 hours; $p = 0.001$) (see *Table 9*). Zanamivir reduced time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days; I^2 statistic = 9%), which equates to a 14.4-hour (10%) reduction in symptoms from 6.6 days to 6.0 days (*Figure 5*). There was no significant effect in children: time to first alleviation of symptoms was 1.08 days lower in the zanamivir group (95% CI 2.32 lower to 0.15 days higher; I^2 statistic = 72%).

In eight zanamivir trials that reported on use of relief medication, in all of the participants the median days to alleviation in both the placebo and the treatment arms was less than those who did not use relief medications (*Table 7*). In seven zanamivir trials, time to first alleviation of symptoms was also reported with and without rescue medication. Using these data we were able to compare zanamivir without rescue medication with placebo with rescue medication. Overall, there was a non-significant 0.41-day decrease (95% CI 0.47 days lower to 1.29 days higher; I^2 statistic = 67%) in time to first alleviation of symptoms in the placebo with rescue medication group, suggesting that zanamivir itself is no better than rescue medication, and possibly even less effective, although the varying levels of use of rescue medication in the seven trials did give rise to large heterogeneity (*Figure 6*).

In a subgroup analysis of time to first alleviation of symptoms in adults by infection status, we found no evidence of a difference in treatment effect for zanamivir on the influenza-infected subgroup compared with the non-influenza-infected subgroup ($p = 0.53$). The treatment effect was 0.67 days (95% CI 0.35 to 0.99 days; I^2 statistic = 17%) for influenza-infected patients and 0.52 days (95% CI 0.18 to 0.86 days; I^2 statistic = 0%) for non-influenza-infected patients.

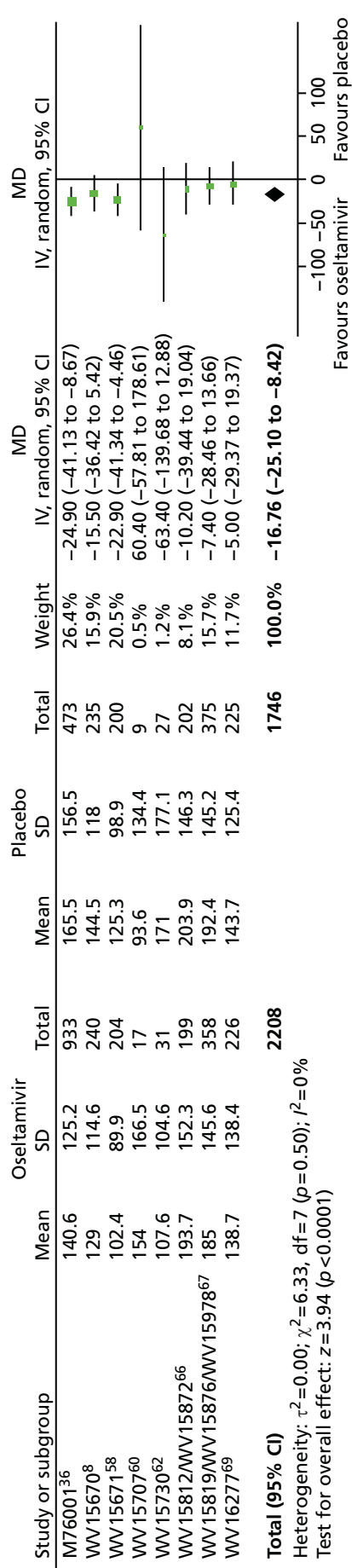


FIGURE 4 Oseltamivir vs. placebo for treatment. Time (hours) to first alleviation of symptoms in adult treatment (ITT population). df, degrees of freedom; IV, inverse variance; SD, standard deviation.

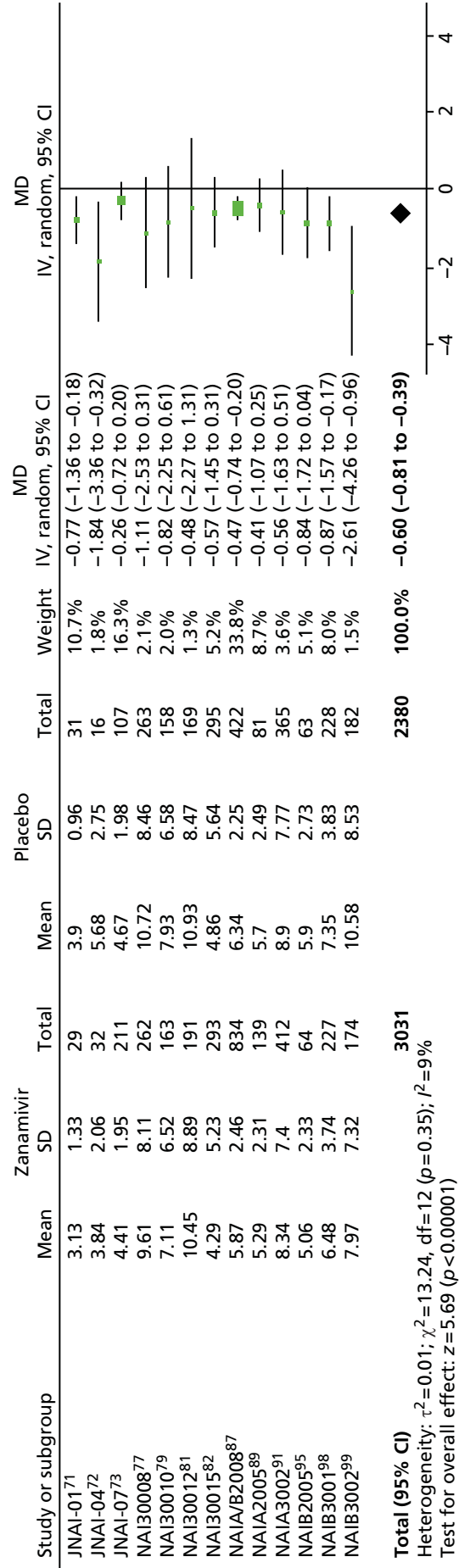
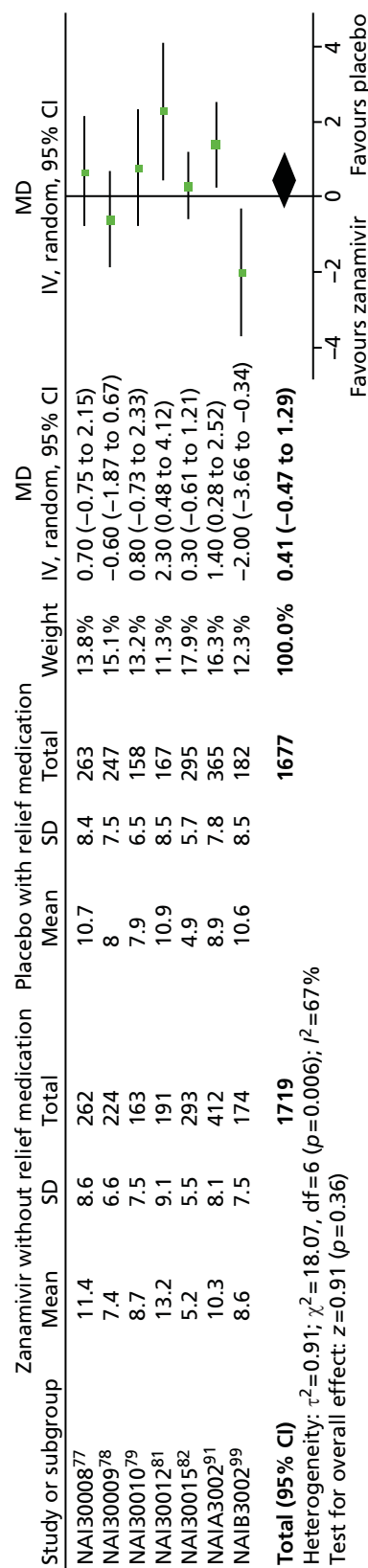


FIGURE 5 Zanamivir vs. placebo for treatment. Time (days) to first alleviation of symptoms in adult treatment. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

TABLE 7 Time to alleviation^a of clinically significant symptoms of ILI (in all participants and participants with no use of relief medication)

Study	Sample size (n)		Median days to alleviation for all participants		Difference in days (p-value)	Median days to alleviation and no use of relief medication		Difference in days (p-value)
	Zanamivir	Placebo	Zanamivir	Placebo		Zanamivir	Placebo	
NAI30008 ⁷⁷	262	263	6.0	7.0	1.0 (0.123)	8.0	10.0	2.0 (0.037)
NAI30009 ⁷⁸	224	247	4.5	5.0	0.5 (0.011)	5.0	6.0	1.0 (0.002)
NAI30010 ⁷⁹	76	81	4.5	5.5	1.0 (0.033)	5.5	6.75	1.25 (0.150)
NAI30011 ⁸⁰	237	229	4.50	5.00	0.50 (0.495)	7.0	7.0	0.0 (0.623)
NAI30012 ⁸¹	191	167	6.5	7.5	1.0 (0.159)	9.0	10.0	1.0 (0.131)
NAI30015 ⁸²	293	295	2.17	2.67	0.5 (0.166)	3.17	3.83	0.66 (0.058)
NAIA3002 ⁹¹	412	365	5.5	6.0	0.5 (0.228)	7.0	8.0	1.0 (0.054)
NAIB3002 ⁹⁹	174	182	5.0	7.5	2.5 (< 0.001)	5.5	8.25	2.75 (< 0.001)

^a Alleviation defined as no fever (temperature of < 37.8°C), cough recorded as none or mild, and muscle/joint aches and pains, sore throat, feverishness/chills and headache recorded as absent/minimal.

**FIGURE 6** Zanamivir vs. placebo for treatment. Time (days) to first alleviation of symptoms in adults with/without relief medication. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Analysis of hospitalisations

In oseltamivir treatment of adults, there was no significant difference in hospitalisation rate between treatment groups (RR 0.92, 95% CI 0.57 to 1.50; I^2 statistic = 0%) or in treatment of children (RR 1.92, 95% CI 0.70 to 5.23; I^2 statistic = 0%), with wide CIs; or in prophylaxis (RR 1.14, 95% CI 0.66 to 1.94; I^2 statistic = 0%). Data on hospitalisations for the zanamivir studies were not reported.

Analysis of influenza complications

Pneumonia

In adult treatment trials, oseltamivir significantly reduced self-reported, investigator-mediated, unverified pneumonia (RR 0.55, 95% CI 0.33 to 0.90; I^2 statistic = 0%; RD 1.00%, 95% CI 0.22% to 1.49%; NNTB 100, 95% CI 67 to 451) in the treated population. The effect was significant in the six trials that collected data on non-specific adverse events or secondary/intercurrent illness forms (RR 0.44, 95% CI 0.22 to 0.88; I^2 statistic = 0%; RD 0.99%, 95% CI 0.21% to 1.38%; NNTB 101, 95% CI 73 to 470). However, it was not significant in the five trials (two CSRs) that used more detailed diagnostic data collection forms, and in no studies that reported on radiological confirmation of pneumonia (*Figure 7*). There was no significant effect on pneumonia in children (RR 1.06, 95% CI 0.62 to 1.83; I^2 statistic = 0%). In two zanamivir adult trials,^{81,82} pneumonia reporting was based on a stricter definition of X-ray confirmation and there was also no significant treatment effect (RR 1.02, 95% CI 0.35 to 3.02; I^2 statistic = 39%). In nine zanamivir trials,^{77,79,80,87,89,91,97-99} pneumonia was a self-reported, investigator-mediated, unverified outcome (see *Figures 8* and *9*). Overall, there was no significant effect of zanamivir on mixed verified and unverified pneumonia in adult treatment (RR 0.90, 95% CI 0.58 to 1.40; I^2 statistic = 0%). In prophylaxis trials, zanamivir reduced the risk of self-reported, investigator-mediated, unverified pneumonia in adults (RR 0.30, 95% CI 0.11 to 0.80; I^2 statistic = 0%; RD 0.32%, 95% CI 0.09% to 0.41%; NNTB 311, 95% CI 244 to 1086).

In a metaregression of 'pneumonia' based on 32 studies, treatment effects were not statistically different by age group ($p = 0.22$), drug ($p = 0.89$) or indication ($p = 0.14$). However, treatment effects were statistically different by method of diagnosis ($p = 0.025$). For unclear objective diagnosis of pneumonia, the treatment effect was RR 0.51 (95% CI 0.35 to 0.75; I^2 statistic = 0%), whereas for objective diagnosis data collection of pneumonia, the treatment effect was 1.01 (95% CI 0.69 to 1.47; I^2 statistic = 0%).

Serious complications and study withdrawals

In oseltamivir trials, treatment did not significantly affect complications classified as serious or those that led to withdrawal from the trial in adults (RR 0.91, 95% CI 0.40 to 2.06; I^2 statistic = 0%) or in children (RR 1.98, 95% CI 0.58 to 6.72; I^2 statistic = 0%). This outcome could not be assessed in oseltamivir prophylaxis because of an insufficient number of events. There was no significant effect of zanamivir, in adult treatment, in reducing the risk of any complication classified as serious or which led to study withdrawal (RR 1.10, 95% CI 0.46 to 2.63; I^2 statistic = 0%) or in prophylaxis (RR 1.09, 95% CI 0.36 to 3.26; I^2 statistic = 0%). This outcome could not be assessed in children because of an insufficient number of events.

Bronchitis, sinusitis and otitis media

Neither zanamivir nor oseltamivir significantly reduced the risk of bronchitis or sinusitis in prophylaxis trials. In adults, treatment with oseltamivir did not significantly reduce the risk of bronchitis (RR 0.75, 95% CI 0.56 to 1.01; I^2 statistic = 36%), sinusitis (RR 1.03, 95% CI 0.76 to 1.40; I^2 statistic = 0%) or otitis media (RR 1.11, 95% CI 0.57 to 2.15; I^2 statistic = 0%). The result for bronchitis was sensitive to the methods used, as a fixed-effects analysis showed a significant effect ($p = 0.02$). Oseltamivir did not significantly affect complications in treatment of children, including otitis media (RR 0.80, 95% CI 0.62 to 1.02; I^2 statistic = 0%).

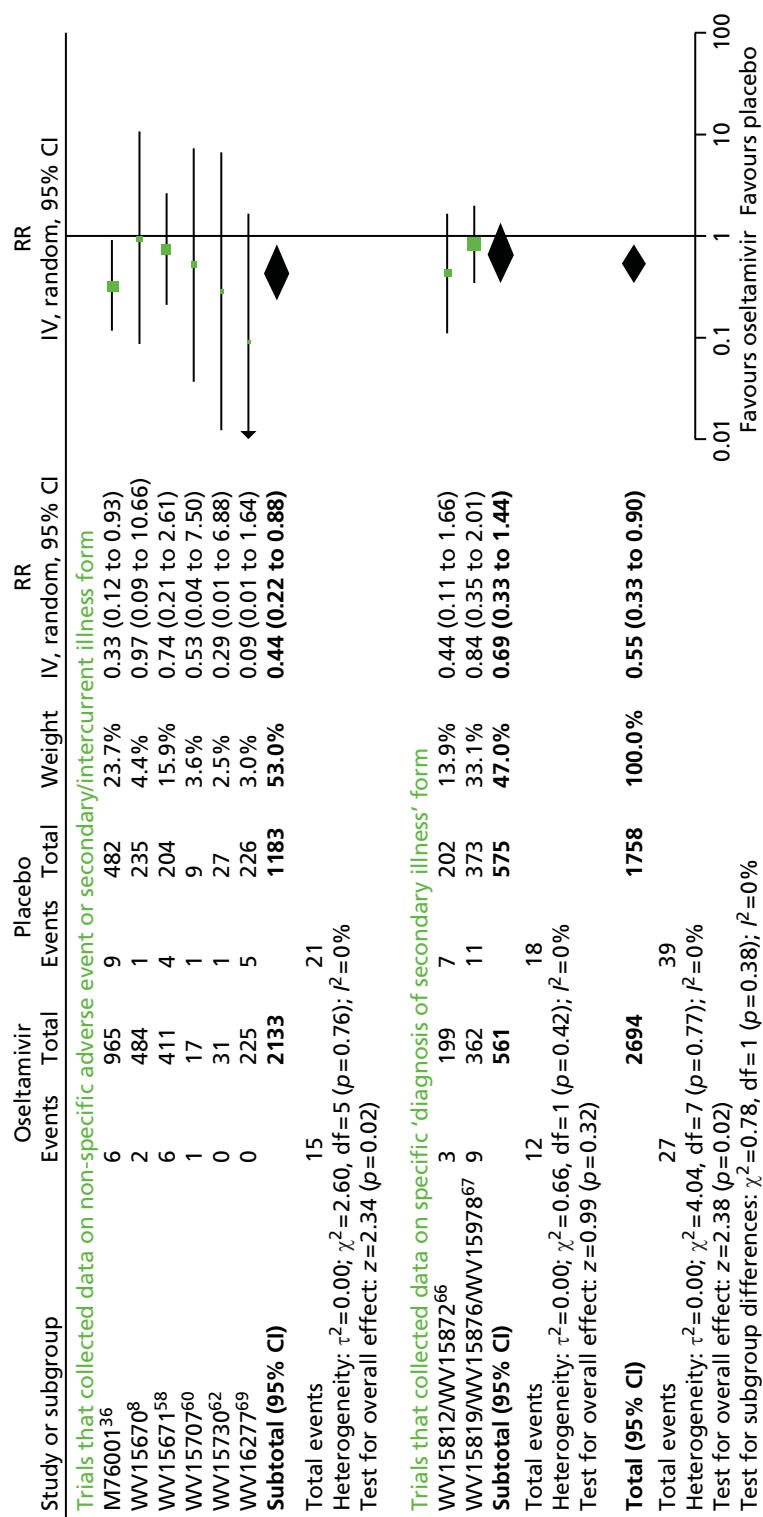


FIGURE 7 Osetamivir vs. placebo for treatment complications: pneumonia in adult treatment. df, degrees of freedom; IV, inverse variance.

Treatment with zanamivir significantly reduced the risk of bronchitis in adults (RR 0.75, 95% CI 0.61 to 0.91; P statistic = 0%; RD 1.80%, 95% CI 0.65% to 2.80%; NNTB 56, 95% CI 36 to 155), but did not reduce the risk of sinusitis or otitis media. In children, zanamivir treatment did not significantly reduce the risk of sinusitis (RR 0.87, 95% CI 0.12 to 6.45; P statistic = 40%) or otitis media (RR 1.00, 95% CI 0.59 to 1.72; P statistic = 0%).

See *Table 1* for a summary of the methodology used for collecting and assessing complications in oseltamivir treatment trials. For the overall results for oseltamivir in adults see *Table 8* and for children see *Table 9*. *Table 10* shows the overall results for zanamivir in adults and *Table 11* shows the results for children.

Analysis of influenza outcomes in prophylaxis studies

Symptomatic influenza was lower in the oseltamivir arms than the placebo arms in studies of prophylaxis (RR 0.45, 95% CI 0.30 to 0.67; P statistic = 0%; RD 3.05%, 95% CI 1.83% to 3.88%; NNTB 33, 95% CI 26 to 55), but there were no differences for all other influenza outcomes, including overall ILI reported as an adverse event on-treatment. In household prophylaxis, one small study with missing outcome data and selective reporting, including 405 participants, showed a significant reduction of symptomatic influenza in the oseltamivir arm compared with placebo (RR 0.20, 95% CI 0.09 to 0.44; RD 13.6%, 95% CI 9.52% to 15.47%), but in the same study there was no significant reduction in asymptomatic influenza (RR 1.14, 95% CI 0.39 to 3.33). Asymptomatic influenza was not significantly reduced and there was no non-influenza ILI reported throughout the study period.

In prophylaxis trials we could not analyse effects on ILI because of a lack of definition in the CSRs. However, using our definition (see *Methods*), oseltamivir did not reduce ILI in participants (RR 0.95, 95% CI 0.86 to 1.06). See *Appendix 11* for further analysis of symptomatic ILI.

The Roche trial programme assessing the effects of oseltamivir in PEP, submitted to the FDA on 22 May 2000, consisted of two trials.^{65,120} We included only one trial⁶⁵ because the other¹²⁰ was not placebo controlled. WV15799⁶⁵ was a double-blind, cluster-randomised trial in which contact clusters of index cases were randomised to oseltamivir 75 mg a day or placebo for 7 days. The manufacturer concluded that the trial proved that oseltamivir could prevent influenza in contacts by interrupting transmission from index cases. Interruption of transmission has two components: reduction of viral spread from index cases (measured by nasal shedding of influenza viruses) and prevention of onset of influenza in contacts measured with a mixture of symptoms and signs and 'laboratory confirmation' (i.e. viral culture from the upper airways and/or at least a fourfold rise in antibody titres measured between baseline and 2–3 weeks later). The design of the WV15799⁶⁵ is weak. All index cases were left untreated except for a paracetamol rescue pack, making it impossible to assess the effect of oseltamivir on nasal voidance of index cases. Nasal viral voidance was measured only in symptomatic participants thereby missing out on potential asymptomatic infected people.

TABLE 8 Oseltamivir vs. placebo for treating influenza in adults

<i>Patient or population:</i> healthy adults with influenza <i>Settings:</i> community, nursing homes <i>Intervention:</i> oseltamivir vs. placebo for treatment						
Illustrative comparative risks, ^a study population (95% CI)						
Outcomes	Assumed risk		Corresponding risk		Relative effect (95% CI)	Number of participants (studies)
	Placebo		Oseltamivir vs. placebo for treatment			
Time to first alleviation of symptoms in adult treatment (ITT population) (hours)			The mean time (hours) to first alleviation of symptoms adults in the intervention groups was 16.76 lower		16.8 hours (8.4 to 25.1)	3954 (8)
Adverse events: nausea in adult treatment (on-treatment)	64 per 1000		101 per 1000 (73 to 138)		RR 1.57 (1.14 to 2.15)	4452 (8)
Adverse events: vomiting in adult treatment (on-treatment)	32 per 1000		77 per 1000 (56 to 108)		RR 2.43 (1.75 to 3.38)	4452 (8)
Adverse events: diarrhoea in adult treatment (on-treatment)	71 per 1000		47 per 1000 (32 to 69)		RR 0.67 (0.46 to 0.98)	4452 (8)
Complications: self reported, investigator-mediated, unverified pneumonia in adult treatment	22 per 1000		12 per 1000 (7 to 20)		RR 0.55 (0.33 to 0.90)	4452 (8)
Adverse events: cardiac body system in adult treatment (on-treatment)	13 per 1000		7 per 1000 (3 to 13)		RR 0.49 (0.25 to 0.97)	3943 (6)
Adverse events: hospital admission in adult treatment	18 per 1000		17 per 1000 (11 to 28)		RR 0.92 (0.57 to 1.50)	4394 (7)
					0.15 (−0.78 to 0.91)	NNTB 687 (NNTB 110 to ∞ to NNTB 128)
N/A, not applicable.						
^a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.						

TABLE 9 Oseltamivir vs. placebo for treating influenza in children

Patient or population: healthy children with influenza						
Settings: community						
Intervention: oseltamivir vs. placebo for treatment						
Outcomes	Illustrative comparative risks, ^a study population (95% CI)		Number of participants (studies)	Relative effect (95% CI)	RD, % (95% CI)	NNTB or NNTH (95% CI)
	Assumed risk	Corresponding risk				
	Placebo	Oseltamivir vs. placebo for treatment				
Time to first alleviation of symptoms in child treatment (hours)		The mean time (hours) to first alleviation of symptoms in children in the intervention groups was 8.04 lower (33.34 lower to 17.26 higher)	1329 (3)			Not significant
Hospital admission in child treatment (safety population)	9 per 1000	17 per 1000 (6 to 46)	1359 (3)	RR 1.92 (0.7 to 5.23)	-0.81 (-3.72 to 0.26)	NNTH 124 (NNTB 379 to ∞ to NNTH 27)
Complications: bronchitis in child treatment	31 per 1000	20 per 1000 (8 to 48)	1359 (3)	RR 0.65 (0.27 to 1.55)	1.08 (-1.69 to 2.25)	NNTB 93 (NNTB 45 to ∞ to NNTH 59)
Complications: otitis media in child treatment	163 per 1000	130 per 1000 (101 to 166)	1359 (3)	RR 0.8 (0.62 to 1.02)	3.26 (-0.33 to 6.18)	NNTB 31 (NNTB 17 to ∞ to NNTH 308)
Complications: pneumonia in child treatment	37 per 1000	39 per 1000 (23 to 68)	1359 (3)	RR 1.06 (0.62 to 1.83)	-0.22 (-3.07 to 1.41)	NNTH 450 (NNTB 71 to ∞ to NNTH 33)
Adverse events: diarrhoea in child treatment (on-treatment)	72 per 1000	63 per 1000 (42 to 92)	1358 (3)	RR 0.87 (0.58 to 1.28)	0.93 (-2.01 to 3.02)	NNTB 108 (NNTB 34 to ∞ to NNTH 50)
Adverse events: vomiting in child treatment (on-treatment)	76 per 1000	130 per 1000 (94 to 179)	1358 (3)	RR 1.7 (1.23 to 2.35)	5.34 (1.75 to 10.29)	NNTH 19 (10 to 57)
a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.						

^a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

TABLE 10 Zanamivir vs. placebo for treating influenza in adults

<i>Patient or population:</i> healthy adults with influenza						
<i>Settings:</i> community, nursing homes						
<i>Intervention:</i> zanamivir vs. placebo for treatment						
Outcomes	Illustrative comparative risks, ^a study population (95% CI)		Number of participants (studies)	Relative effect (95% CI)	RD, % (95% CI)	NNTB or NNTH (95% CI)
	Assumed risk	Corresponding risk				
	Placebo	Zanamivir vs. placebo for treatment				
Time to first alleviation of symptoms in adult treatment (days)		The mean time (days) to first alleviation of symptoms in adults in the intervention groups was 0.60 lower		0.60 days (0.39 to 0.81)	N/A	N/A
Complications: pneumonia confirmed with X-ray in adult treatment	32 per 1000	33 per 1000 (11 to 98)	946 (2)	RR 1.02 (0.35 to 3.02)	-0.06 (-6.56 to 2.11)	NNTH 1540 (NNTB 48 to ∞ to NNTH 16)
Adverse events: nausea/vomiting in adult treatment (on-treatment)	41 per 1000	24 per 1000 (16 to 38)	6553 (15)	RR 0.6 (0.39 to 0.94)	1.63 (0.24 to 2.48)	NNTB 62 (41 to 411)
Adverse events: psychiatric body system in adult treatment (on-treatment)	6 per 1000	6 per 1000 (3 to 13)	4732 (10)	RR 1.16 (0.57 to 2.38)	-0.09 (-0.76 to 0.24)	NNTH 1132 (NNTB 421 to ∞ to NNTH 132)
Complications: bronchitis in adult treatment	72 per 1000	54 per 1000 (44 to 65)	6072 (12)	RR 0.75 (0.61 to 0.91)	1.80 (0.65 to 2.80)	NNTB 56 (36 to 155)
N/A, not applicable.						
^a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.						

TABLE 11 Zanamivir vs. placebo for treating influenza in children

<i>Patient or population:</i> healthy children with influenza						
<i>Settings:</i> community						
<i>Intervention:</i> zanamivir vs. placebo for treatment						
Outcomes	Illustrative comparative risks, ^a study population (95% CI)			Relative effect (95% CI)	Number of participants (studies)	RD, % (95% CI)
	Assumed risk		Corresponding risk			
	Placebo	Zanamivir vs. placebo for treatment				
Time to first alleviation of symptoms in children (days)			The mean time (days) to first alleviation of symptoms in children in the intervention groups was 1.08 lower (2.32 lower to 0.15 higher)		723 (2)	N/A
Complications: sinusitis in child treatment	15 per 1000		13 per 1000 (2 to 96)	RR 0.87 (0.12 to 6.45)	737 (2)	0.19 (−8.09 to 1.31)
Complications: otitis media in child treatment	71 per 1000		71 per 1000 (42 to 122)	RR 1.0 (0.59 to 1.72)	737 (2)	0.00 (−5.13 to 2.92)
N/A, not applicable.						
^a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.						

Zanamivir similarly significantly reduced the risk of symptomatic influenza for individuals (RR 0.39, 95% CI 0.22 to 0.70; I^2 statistic = 45%; RD 1.98%, 95% CI 0.98% to 2.54%; NNTB 51, 95% CI 40 to 103), as well as households (RR 0.33, 95% CI 0.18 to 0.58; I^2 statistic = 40%; RD 14.84%, 95% CI 12.18% to 16.55%; NNTB 7, 95% CI 6 to 9). However, it did not reduce the risk of asymptomatic influenza in the prophylaxis of individuals (RR 0.97, 0.76 to 1.24; I^2 statistic = 0%) or asymptomatic individuals in PEP of households (RR 0.88, 95% CI 0.65 to 1.20; I^2 statistic = 0%). See *Table 10* for the overall results for zanamivir in adults and *Table 11* for results in children. See *Tables 12* and *13* for the overall results for zanamivir in adults.

Analysis of harms

Oseltamivir treatment

Nausea, vomiting and diarrhoea Oseltamivir in the treatment of adults is associated with increased risk of nausea (RR 1.57, 95% CI 1.14 to 2.15; I^2 statistic = 43%; RD 3.66%, 95% CI 0.90% to 7.39%; NNTH 28, 95% CI 14 to 112) and vomiting (RR 2.43, 95% CI 1.75 to 3.38; I^2 statistic = 12%; RD 4.56%, 95% CI 2.39% to 7.58%; NNTH 22, 95% CI 14 to 42). It is associated with a decreased risk of diarrhoea (RR 0.67, 95% CI 0.46 to 0.98; I^2 statistic = 44%; RD 2.33%, 95% CI 0.14% to 3.81%; NNTB 43, 95% CI 27 to 709) compared with placebo during on-treatment periods. Both nausea and vomiting were associated with significant heterogeneity, when treatment effects appeared larger in otherwise healthy adults than in the elderly and the chronically ill. However, one trial of otherwise healthy adults⁶⁹ also showed smaller effects. Vomiting was more common in those children on oseltamivir treatment than in those on placebo treatment (RR 1.70, 95% CI 1.23 to 2.35; I^2 statistic = 0%; RD 5.34%, 95% CI 1.75% to 10.29%; NNTH 19, 95% CI 10 to 57).

Cardiac effects The cardiac effects of oseltamivir are unclear. Exposure to oseltamivir may reduce cardiac general events compared with placebo (RR 0.49, 95% CI 0.25 to 0.97; I^2 statistic = 0%; RD 0.68%, 95% CI 0.04% to 1.00%; NNTB 148, 95% CI 101 to 2509), excluding one trial⁷⁰ in which electrocardiography was included in the safety parameters. However, exposure to oseltamivir may increase corrected QT interval prolongation (including borderline) as reported in trial WV16277⁷⁰ (RD 4.0%, 95% CI 0.71% to 7.30%; NNTH 25, 95% CI 14 to 140) compared with placebo during on-treatment periods.

Psychiatric effects In treatment trials, there was no significant increase in risk between oseltamivir and on-treatment psychiatric adverse events overall (RR 0.93, 95% CI 0.43 to 2.03; I^2 statistic = 0%). However, there was a dose–response effect in the two ‘pivotal’ treatment trials.^{8,58} In the identically designed trials^{8,58} there were two active treatment groups: 150 mg (standard dose) and 300 mg (high dose) oseltamivir per day. In the dose–response analysis there was an increased risk of psychiatric body system adverse events over the entire follow-up period ($p = 0.038$, based on likelihood ratio test). In one trial,⁸ the event rates were 1 of 204, 1 of 206 and 4 of 205 in the placebo, 75-mg and 150-mg arms, respectively, whereas the second trial⁵⁸ had rates of 2 of 235, 0 of 242 and 5 of 242, respectively.

Effect on antibodies (post-protocol hypotheses) The proportion of patients being diagnosed as influenza infected in oseltamivir treatment of adults was significantly lower in the treated group than in the control group (RR 0.95, 95% CI 0.91 to 0.99; I^2 statistic = 0%). The proportion of patients with fourfold increases in antibody titre was significantly lower in the treated group than in the control group (RR 0.92, 95% CI 0.86 to 0.97; I^2 statistic = 0%). This represents an absolute difference of 5% between treatment groups. There was a lower proportion of children on oseltamivir with a fourfold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00; I^2 statistic = 0%).

TABLE 12 Zanamivir vs. placebo for preventing influenza in adults

<i>Patient or population:</i> healthy adults without influenza <i>Settings:</i> community, nursing homes <i>Intervention:</i> zanamivir vs. placebo for prophylaxis						
Outcomes	Illustrative comparative risks, ^a study population (95% CI)		Relative effect (95% CI)	Number of participants (studies)	RD, % (95% CI)	NNTB or NNTH (95% CI)
	Assumed risk	Corresponding risk				
	Placebo	Zanamivir vs. placebo for prophylaxis				
Symptomatic influenza in prophylaxis of individuals	33 per 1000	13 per 1000 (7 to 23)	RR 0.39 (0.22 to 0.70)	5275 (4)	1.98 (0.98 to 2.54)	NNTB 51 (40 to 103)
Asymptomatic influenza in prophylaxis of individuals	50 per 1000	48 per 1000 (38 to 60)	RR 0.97 (0.76 to 1.24)	5275 (4)	0.14 (-1.1 to 1.1)	NNTB 729 (NNTB 91 to ∞ to NNTH 91)
Symptomatic influenza in household prophylaxis	190 per 1000	42 per 1000 (25 to 68)	RR 0.22 (0.13 to 0.36)	824 (2)	14.84 (12.18 to 16.55)	NNTB 7 (6 to 9)
Asymptomatic influenza in household prophylaxis	107 per 1000	97 per 1000 (64 to 145)	RR 0.90 (0.6 to 1.35)	824 (2)	1.32 (-2.2 to 3.84)	NNTB 76 (NNTB 26 to ∞ to NNTH 46)
Complications: pneumonia in adult prophylaxis	5 per 1000	1.5 per 1000 (1 to 4)	RR 0.30 (0.11 to 0.8)	7662 (6)	0.32 (0.09 to 0.41)	NNTB 311 (244 to 1086)
Complications: bronchitis in adult prophylaxis	15 per 1000	8 per 1000 (3 to 18)	RR 0.49 (0.02 to 1.19)	7662 (6)	0.79 (-0.29 to 1.24)	NNTB 127 (to NNTB 81 to ∞ to NNTH 341)

^a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

TABLE 13 Oseltamivir vs. placebo for preventing influenza in adults

<i>Patient or population:</i> healthy adults without influenza		<i>Settings:</i> community, nursing homes		<i>Intervention:</i> oseltamivir vs. placebo for prophylaxis			
		Illustrative comparative risks, ^a study population (95% CI)					
		Assumed risk	Corresponding risk				
		Placebo	Oseltamivir vs. placebo for prophylaxis	Relative effect (95% CI)	Number of participants (studies)	RD, % (95% CI)	NNTB or NNTH (95% CI)
Outcomes							
Symptomatic influenza in adult prophylaxis of individuals		55 per 1000	25 per 1000 (17 to 37)	RR 0.45 (0.30 to 0.67)	2479 (3)	3.05 (1.83 to 3.88)	NNTB 33 (26 to 55)
Symptomatic influenza in household prophylaxis		170 per 1000	34 per 1000 (15 to 75)	RR 0.2 (0.09 to 0.44)	405 (1)	13.6 (9.52 to 15.47)	NNTB 7 (6 to 11)
Adverse events: psychiatric body systems in adult prophylaxis (all events on- and off-treatment)		13 per 1000	23 per 1000 (14 to 40)	RR 1.80 (1.05 to 3.08)	3434 (4)	-1.06 (-2.76 to -0.07)	NNTH 94 (36 to 1538)
Adverse events: headache in adult prophylaxis (on-treatment)		175 per 1000	207 per 1000 (184 to 233)	RR 1.18 (1.05 to 1.33)	3434 (4)	-3.15 (-5.78 to -0.88)	NNTH 32 (18 to 115)
Adverse events: nausea in adult prophylaxis (on-treatment)		43 per 1000	85 per 1000 (52 to 138)	RR 1.96 (1.2 to 3.2)	3434 (4)	-4.15 (-9.51 to -0.86)	NNTH 25 (11 to 116)
Adverse events: vomiting in adult prophylaxis (on-treatment)		10 per 1000	20 per 1000 (7 to 55)	RR 1.91 (0.7 to 5.22)	3434 (4)	-0.95 (-4.41 to 0.31)	NNTH 106 (NNTB 319 to ∞ to NNTH 23)
Adverse events: headache in adult prophylaxis (off-treatment)		37 per 1000	33 per 1000 (23 to 46)	RR 0.88 (0.63 to 1.24)	3434 (4)	0.44 (-0.89 to 1.37)	NNTB 226 (NNTB 74 to ∞ to NNTH 113)

^a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

Oseltamivir prophylaxis

Headaches and nausea In oseltamivir prophylaxis, there was an increased risk of headaches on-treatment (RR 1.18, 95% CI 1.05 to 1.33; I^2 statistic = 0%; RD 3.15%, 95% CI 0.88% to 5.78%; NNTH 32, 95% CI 18 to 115) (Figure 8) and nausea on-treatment (RR 1.96, 95% CI 1.20 to 3.20; I^2 statistic = 49%; RD 4.15%, 95% CI 0.86% to 9.51%; NNTH 25, 95% CI 11 to 116). There was also a dose-response effect for headaches in study⁵² ($p = 0.013$, based on likelihood ratio test), for which on-treatment rates were 202 of 519, 225 of 520 and 242 of 520 in the placebo, standard-dose and high-dose arms, respectively.

Psychiatric effects Figure 9 shows that in prophylaxis trials of oseltamivir there was a significant increase in patients with psychiatric adverse events over the on- and off-treatment periods (RR 1.80, 95% CI 1.05 to 3.08; I^2 statistic = 0%; RD 1.06%, 95% CI 0.07% to 2.76%; NNTH 94, 95% CI 36 to 1538). Initial analysis of patients with psychiatric adverse events in the on-treatment period showed a borderline statistically significant result ($p = 0.06$), hence we conducted sensitivity analysis using Peto's method ($p = 0.05$) as well as the analysis reported in Figure 9.

Table 14 shows a summary of all of the psychiatric adverse events in oseltamivir prophylaxis trials. Of particular note was an oseltamivir patient in one study⁶⁸ who had severe confusion on day 27 and was hospitalised. On day 28 the patient was taken off medication and the event resolved. On day 29 the patient was discharged from hospital and subsequently resumed medication. However, confusion reappeared on day 32. The initial event was misclassified in the CSR as 'mental impairment' but has since been corrected in an erratum published in the same journal that published the original trial manuscript.^{37,38}

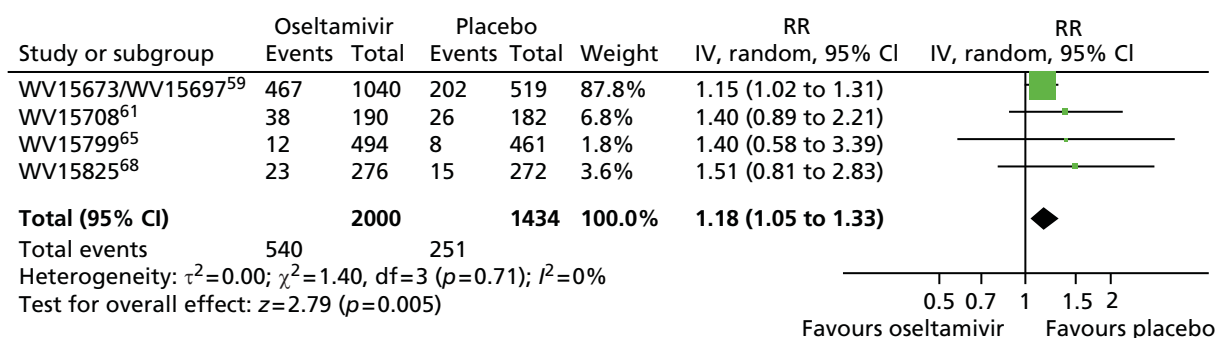


FIGURE 8 Oseltamivir vs. placebo for prophylaxis, outcome: adverse events – headache in adult prophylaxis (on-treatment). df, degree of freedom; IV, inverse variance.

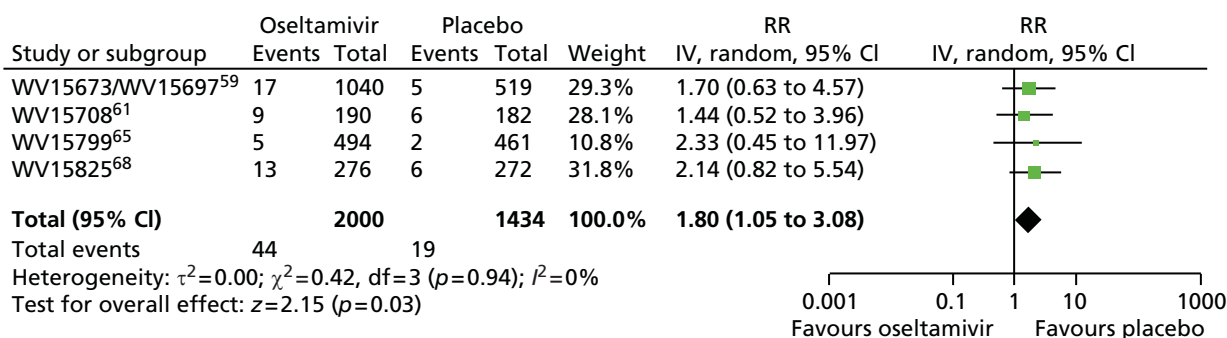


FIGURE 9 Oseltamivir vs. placebo for prophylaxis: adverse events – psychiatric body system in adult prophylaxis (on- and off-treatment). df, degree of freedom; IV, inverse variance.

TABLE 14 Psychiatric adverse events in oseltamivir prophylaxis trials

Event type	Oseltamivir		Placebo		Total	
	Number of events	%	Number of events	%	Number of events	%
Confusion	5	0.25	1	0.07	6	0.17
Depression	14	0.7	6	0.42	20	0.58
Hallucinations	2	0.1	0	0.00	2	0.06
Anxiety	7	0.35	8	0.56	15	0.44
Psychosis	2	0.1	1	0.07	3	0.09
Schizophrenia	1	0.05	0	0.00	1	0.03
Bipolar disorder	0	0	1	0.07	1	0.03
Sleeping disorder	2	0.1	0	0.00	2	0.06
Aggression	1	0.05	0	0.00	1	0.03
Stress symptoms	3	0.15	0	0.00	3	0.09
Restlessness	1	0.05	0	0.00	1	0.03
Nervousness	1	0.05	0	0.00	1	0.03
Suicide ideation	1	0.05	0	0.00	1	0.03
Paranoia	1	0.05	0	0.00	1	0.03
Alcohol related	6	0.3	2	0.14	8	0.23
Total	47	2.35	19	1.32	66	1.92

Renal effects There was a non-significant increase in renal events on-treatment (RR 3.17, 95% CI 0.96 to 10.49; I^2 statistic = 0; RD 0.67%, 95% CI -0.01% to 2.93%; NNTH 150, 95% CI NNTH 35 to ∞ to NNTB > 1000). However, in sensitivity analysis using Peto's method the result for renal events was statistically significant ($p = 0.02$).

Zanamivir

Serious adverse events There was no significant effect on serious adverse events in adult treatment trials (RR 0.86, 95% CI 0.49 to 1.50; I^2 statistic = 0%).

Nausea, vomiting and diarrhoea In treatment trials, there was no significant effect on diarrhoea in adults (RR 0.87, 95% CI 0.66 to 1.14; I^2 statistic = 5%) or headache (RR 0.84, 95% CI 0.60 to 1.18; I^2 statistic = 0). However, during the on-treatment phase, nausea and vomiting were significantly less frequent in the zanamivir arm (RR 0.60, 95% CI 0.39 to 0.94; I^2 statistic = 0%; RD 1.63%, 95% CI 0.24% to 2.48%; NNTB 62, 95% CI 41 to 411).

Renal, psychiatric and other harms There was no significant effect observed on the renal system (RR 0.84, 95% CI 0.41 to 1.72; I^2 statistic = 0%) or the psychiatric system (RR 1.16, 95% CI 0.57 to 2.38; I^2 statistic = 0%). In adult treatment trials of zanamivir, there was no significantly increased risk of any other reported adverse events, and there was no significant increase in adverse effects observed in prophylaxis trials, including psychiatric (RR 1.05, 95% CI 0.48 to 2.29; I^2 statistic = 25%) and renal effects (RR 0.67, 95% CI 0.35 to 1.26; I^2 statistic = 0%) on-treatment. There was no significant increase in harms associated with zanamivir treatment of children but data were sparse.

Effect on antibodies There was no significant effect of zanamivir treatment on influenza diagnosis (RR 1.02, 95% CI 0.98 to 1.06; P statistic = 0%) or probability of a fourfold increase in antibody titre (RR 1.06, 95% CI 0.96 to 1.06; P statistic = 0%).

Deaths

In oseltamivir treatment trials, there was one death overall. This event occurred as a result of acute respiratory syndrome in a placebo patient without influenza in study.⁶⁶ In prophylaxis trials, there were four deaths in total, all in elderly patients, with two in the placebo group and two in the oseltamivir group. Causes of death were reported as two cancers, one myocardial infarction and one intestinal perforation. However, for both deaths in the oseltamivir arms the participants experienced acute renal failure on-treatment prior to death.

There were eight deaths in total in the zanamivir trials. Six of the deaths were caused by neoplasias or cardiovascular events in elderly patients with multiple pathologies. However, two deaths were reported as being due to influenza A pneumonia. One participant was on inhaled rimantadine plus placebo and the other on zanamivir.

The results of post-protocol hypotheses are in *Appendix 8*.

Discussion

Oseltamivir and zanamivir have small, non-specific effects on reducing time to alleviation of ILI symptoms in adults but not in asthmatic children. Using either drug as prophylaxis reduces the risk of developing symptomatic influenza. Treatment trials with oseltamivir or zanamivir do not settle the question of whether or not complications of influenza, such as pneumonia, are reduced, because of a lack of diagnostic definitions. Use of oseltamivir increases the risk of adverse effects such as nausea, vomiting, psychiatric effects and renal events in adults, and the risk of vomiting in children. The lower bioavailability may explain the lower toxicity of zanamivir than that of oseltamivir. The influenza virus-specific mechanism of action proposed by the producers does not fit the clinical evidence, which shows no such effects.

Reconstructing trial lists and indexing regulatory comments

Calls for incorporating unpublished data to supplement published trial data in systematic reviews and meta-analyses highlight deficiencies in the current methods for obtaining the most complete understanding of a drug's effects.¹²¹ Our methodological approach entailed comprehensive searching of unpublished sources, with a particular emphasis on obtaining unpublished and internal reports from drug manufacturers, intended for regulatory submission, and comments from national regulatory bodies. Our decision not to use published evidence as a basis for trial appraisal and data extraction meant that we had to reconcile and synthesise information from multiple unpublished sources. We had to devise a new method of searching, indexing, retrieving and reviewing trial data, and to combine this understanding with regulatory comments to produce an informative review. The first step in this process entailed the need to develop our own reconstruction of the trial programme without initial help from outside sources. The reconstructed list of trials and then programmes took a whole-time equivalent researcher 20 days to compile. Owing to the complexity of the task, we suggest that, in the future, some of the essential phases, such as checking the trial identification number across multiple documents and databases, be conducted in pairs.

One of the comments received on our protocol suggested that discrepancies between published and unpublished versions of the same data set could be due to mistakes in the non-peer reviewed, unedited CSRs (which may be corrected by the time of publication). Our experience, especially with the non-reporting of serious adverse events, points to the opposite being the case.¹²² Considering the fact that unintentional errors can occur, we believe that the response should not be a resort to published papers as 'most accurate' and best unit of analysis, but rather that CSRs – as by far the most comprehensive record of a trial – remain the key unit of analysis, with the expectation that they be amended and kept as accurate as possible over

time, with complete documentation of reasons for any amendments. We believed that the results of our review would be undermined without accessing a more complete body of evidence that we knew to be outside the public domain.

In theory, trial registers would be expected to provide a comprehensive picture of a drug's trial programme. However, registers were not our primary instruments to reconstruct zanamivir and oseltamivir trial programmes. Both drugs' programmes were mainly run in the late 1990s, before trial registration became the norm. In addition, registers may suffer from some of the problems that we were trying to address. Bourgeois *et al.*¹²³ audited entries for 546 trials of five major classes of drugs on ClinicalTrials.gov, the biggest prospective register of clinical trials, and found evidence of risk of reporting bias and delay in reporting of results. Another review of 152 trials found that the description of 123 (or 81%) of the trials in the sample had been changed in at least one key element in the time between registration and publication. The most frequent changes regarded outcomes.¹²⁴ Despite the current limits of registers, both specifically to this review and in the way they are run and updated, we believe that registers are an obvious first choice to start reconstruction of trials programmes. Searching for unpublished material has not yet become standard practice in conducting Cochrane reviews,¹²⁵ and is currently variably reported.¹²⁶

The indexing and review of regulatory files was also a very laborious task. It took a whole-time equivalent researcher 3 days to review the FDA regulator's comments and gain a basic understanding of the content. Four additional days were needed to read and annotate the FDA zanamivir files and 28 days for reading and annotating the oseltamivir files and building the table of contents-evidence (see *Appendix 11*). The exercise had to be repeated several times to cross-check content and expand annotations. Construction of the TOC was laborious. A first attempt at electronic mapping the TOC content took 12 and 8 hours, respectively, for the FDA and National Institute for Health and Care Excellence (NICE) regulatory documents. This was carried out using the Adobe Acrobat (Adobe Systems; <https://acrobat.adobe.com/us/en/acrobat/how-to/ocr-software-convert-pdf-to-text.htm>) optical character recognition search facility, which enabled mapping of citation counts by document and by trial ID. Initially, we used the trial prefix followed by the serial number ('WV15670') as ID. This procedure, however, had one major drawback linked to the nature of regulatory documents. As regulatory documents consist of notes, correspondence and reviews, the same trial is cited in a non-standardised way. For example, trial WV15670⁸ is cited as 'WV15670' 15 times, as 'WV_15670' 12 times and simply as '15670' 19 times. Thorough searches must be conducted using all of the different terms. As this can be very time-consuming, we decided to compare an Acrobat search with a Boolean string strategy containing all of the possible citation formats (e.g. WV15758 OR WV 15758 OR Trial 15758 OR Trial15758 OR Trials 15758 OR Trials15758 OR 15758 OR study 15758 OR study15758) (this is logically equivalent to 'WV 15758 OR WV 15758') with a term-by-term search (i.e. separately searching for WV15758 and then for WV 15758 and so on). We reasoned that if the yield were comparable, the Boolean strategy would have been faster. The yield of citations of the two strategies was the same for six of seven 'tracker' studies, but use of a Boolean string was considerably faster (an average of 3 vs. 14 hours) than the term-by-term strategy. The NICE submission citations took 2 hours to list in a TOC using a Boolean strategy. We adopted the Boolean search strategy to construct our TOC. Ultimately, it is possible that a search with the trial numerals ('15670') may be sufficient to identify the vast majority of citations. To validate this method of searching further, our methods should be repeated on other sets of regulatory documents.

Once we had reconstructed the trial programmes, we submitted the results to GSK and Roche for their input. We received detailed feedback from both but, into 2011, Roche's list of trials was still incomplete. Despite the laboriousness of the methods, we believe that we ended up with a far more comprehensive and less biased set of evidence than that available through the current system of journal-based publications. This shift in our data synthesis paradigm was made necessary by the numerous and documented discrepancies between regulatory and published evidence and by the sizeable risk of publication bias of the oseltamivir trial programme. The importance of reconstructing the trial programme by first generating a complete trial list was further reinforced upon discovering bias and oversights in regulators' handling of the trial programme. Regulators focus on a few mutually agreed 'pivotal' trials, the data analyses of which are replicated by the FDA but not by the EMA. Both largely ignored trial M76001,³⁶ the largest oseltamivir

treatment trial that was conducted prior to initial registration of the drug (and still unpublished). Although the manufacturer may not have offered it as a 'pivotal' trial, far smaller and even ongoing studies were included in the evidence base to support Roche's year 1999 NDA number 021087 (treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than 2 days). The history of the EMA scrutiny is harder to assess as we could find no reports of trial site visits or of data analysis replication, but we identified a pooled analysis of treatment trials, very similar to the Kaiser 2003 analysis,⁴ which formed the basis for the EMA conclusion that oseltamivir affected complications reported, for example on EMA's 4 October 2012 Summary of Product Characteristics (www.bmj.com/tamiflu/ema). We requested modules 3–5 (individual listings, demographic data and the statistical analysis report) from the EMA. However, for most oseltamivir trials, the EMA does not have the relevant documents and neither apparently does the National Competent Authorities (e-mail from the EMA, 24 May 2011; e-mail from Dutch regulator Medicines Evaluation Board, 20 July 2011). This means that the modules do not appear to have been either submitted to or requested by regulators, raising questions as to the extent of scrutiny of the clinical trials during the regulatory review of oseltamivir in Europe.

Our new method

Reviewing large quantities of complicated data and linked comments is a very difficult and delicate process. The main problem is not so much the appraisal following standard rules and possible synthesis of data (as when we review published information), but the reconstructions and logical threading of a trial programme generating huge amounts of data needing appraisal. Also the manufacturer's full regulatory submission, which may have even more information than a full CSR, remains confidential. Most of the essential data required are available in CSRs, together with masses of less important data, but, as we have explained, even in this case there may be important omissions, such as mislaid diary cards (*Figures 10 and 11*) for follow-up. Manufacturers are under obligation to provide regulators with all of the data requested to enable them to reach a decision: in doing so they produce vast submissions. None of the authors (all experienced systematic reviewers) had any experience of reviewing regulatory information, but we could not find any workable shortcuts. We believe that providing a critical overview of a trial programme rather than minute dissection of each trial is necessary. This can be done by identifying the important topics in the trial programme (such as the effects of the drug on symptoms, infection, complications, transmission and well-being) and following them throughout the programme, putting the evidence together coherently. This includes carrying out a high-level overview of the mode of action of the drug in different populations for different indications. Understanding a drug's mode of action underpins correct reporting of its strengths and limitations. In addition, a large part of the regulatory submission is made up of chemistry, microbiological, animal model pharmacodynamic and pharmacokinetic studies, which are important for shedding light on the trial programme but which seldom feature in systematic reviews. We are unsure whether or not this information could be considered as core information, but an exhaustive review of a trial programme should include reviews dedicated to such topics.

These methods revealed possible problems in trial conduct and validity, including the lack of comparability between arms induced by subset analysis and by the randomisation analysis fork, high positivity rate of influenza, high gastrointestinal events in the placebo arms, possibly active placebo content and possible procedural breaches in several trials. The ideal option is to carry out analyses on the basis of the ITT population, in which units of randomisation and analysis are the same and many of the potential problems listed are either not present or minimised. We are continuing to develop further methods for using such data.

1

FIGURE 10 Example diary card from CRF for zanamivir trial (1).

12

FIGURE 11 Example diary card from CRF for zanamivir trial (2).

Regulatory comments

Reviewing regulatory comments was essential to expand our understanding of the trial programme. We expected that detailed reading of regulatory material would allow us to understand discrepancies between US and European regulators' conclusions regarding the effects of oseltamivir, particularly (but not limited to) their putative effect on complications.⁸ We were interested in what led the FDA to have far more cautious and conservative statements – as witnessed in the Tamiflu product label and FDA letters – in comparison with European regulators. Our access to huge amounts of FDA regulatory data allowed for many insights but gave us little visibility of manufacturers' responses.

Some of the statements (such as NIs reduce bacterial complications) made by the manufacturer in the CSRs, and, subsequently, in contemporaneous publications and advertisements, appeared unsupported by the evidence provided at the time. The FDA drug regulatory reviewers' comments, although laborious to summarise and contextualise (because of the non-availability of the whole pharmaceutical submission), were confirmed by our reading of the CSRs. However, we were unable to find a statement explaining how the FDA reviewed each NDA. FDA reviewing methods appeared to be a mixture of spot checks, re-run of statistical analyses and on-site inspections. A FDA methods volume or standard operational procedure may be among the documents not available from the web but accessible through a FOI request. Neither the FDA nor the EMA have inventories of held documents, making it very difficult to know what to ask for under FOI rules. We concentrated on downloading or asking for specific CSRs and related documents or reviewers' comments on a particular NDA. The quantity of information held by regulators is likely to be large. For example, NDA 21–246, regarding the use of Tamiflu in the treatment of influenza in children, submitted to the FDA on 15 June 2000, consisted of 137 volumes of study documents and possibly several electronic files. Although we do not know exactly how long a volume was, we have seen references to up to hundreds of pages in each volume.

Requesting specific documents and packages of information is especially important to allow a more efficient and timely reviewing process when confronted with a large volume of evidence, most of which could be of peripheral value. A request for a specific document is likely to be dealt with far more efficiently than a generic request for 'all documentation relating to oseltamivir'. This is one of the reasons why developing a TOC for any drug or family of drugs (no matter how time-consuming) is an absolute prerequisite for any serious attempt at reviewing regulatory evidence. This introduces another very difficult problem: how to handle huge quantities of structured information and the ethics of drawing conclusions from what is still a fragmentary (albeit sizeable) evidence base.

Overall, the FDA assessment of the performance of oseltamivir was 'modest'. This adjective appears six times in a 50-page review document.¹⁰⁹ For example, in the Division Director Memorandum dated 25 October 1999, under the heading 'Public health role of antiviral treatment' the FDA¹⁰⁹ states: 'The clinical relevance of the modest treatment benefit is a highly subjective question' (p. 3). The FDA refused to accept claims of oseltamivir's effects on influenza complications as 'false or misleading' statements in promotional materials.¹²² A FDA warning letter seems to imply, for example, that oseltamivir's mode of action is 'proposed' or 'possibly' (that proposed by the manufacturers) (i.e. not certain).¹²⁷ However, FDA reviewers appear to have missed important problems in Roche's clinical trials (such as the imbalance in the numbers of individuals classified as influenza infected in oseltamivir treatment trials). Importantly, there appears to have been no investigation into the coherence of the evidence with the proposed mode of action of the drug.

Summary of main results

For the first time, a Cochrane review is based on all relevant full CSRs of a class of drugs integrated by regulatory comments. Also for the first time, all CSRs of trials in a manufacturer's programme (regardless of their relevance to the review) are available to readers without any restriction (apart from minimal redactions to protect anonymity further). The role of Roche and GSK in making this possible should be recognised, as well as that of the BMJ, which kept the issue in the public eye until it was resolved.

The evidence we have presented and synthesised shows that both of the NIs in this review have symptom-relieving effects, especially for self-reported outcomes. They appear to have symptom-relieving properties that make people with ILI and self-reported, investigator-mediated, unverified pneumonia feel better by shortening symptom duration and reducing the frequency of symptoms, such as cough. For oseltamivir, this effect perhaps extends to cardiac symptoms, despite the short duration of treatment (5 days). We are unsure what to make of this finding but we think it deserves further investigation.

The issue which triggered our change of evidence-seeking methods is partly resolved: no definitions of secondary illnesses were given anywhere in the CSRs [e.g. 'pneumonia' was defined as 'pneumonia' in the CRFs (see *Table 1*) and diagnostic criteria were not given]; clinical diagnosis in the absence of criteria and without X-ray has only a moderate chance of being correct.

We could not decide the level of diagnostic ascertainment of diagnosis of pneumonia and other complications, as it is unclear from the CSRs. Definitions of pneumonia were not given and the algorithm for classification of an event as pneumonia was not supplied. In oseltamivir trials, the CRF trigger for recording of adverse events and secondary illness was a question to the participant posed by the investigator. A typical phrasing is as follows: 'Secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline?' This was followed by a yes/no box to be ticked and an additional form was to be filled out by the investigator for collecting details on the secondary illness. A record of medications outside trial allocation was elicited in addition to the participant's diary card. The original and Medical Dictionary for Regulatory Activities terms suggest diagnoses for all secondary illnesses and adverse events but there is no indication as to how the original and preferred terms were assigned. We therefore considered these outcomes to be 'self-reported, investigator-mediated, unverified' outcomes. For a subset of trials, secondary/intercurrent illness and adverse event data were collected on a single, one-page form. In our meta-analyses, we called this subanalysis 'Trials which collected data on non-specific adverse events or secondary/intercurrent illness form'. For a different subset of trials, CRFs contained space to record diagnostic tests, such as chest X-rays, tympanometry and sinus X-rays for all secondary illness but there was no reporting of such variables in the CSRs (*Figures 12–15*). In our meta-analyses, we called this subanalysis 'Trials which collected data on specific "Diagnosis of Secondary Illness" form'. None of the complications was defined as primary outcomes in any trial, which may explain the poverty of data definition.

In a metaregression of all of the 32 included studies that reported on 'pneumonia', we found evidence that treatment effects for pneumonia are statistically different depending on the method of diagnosis. Unclear objective diagnosis was associated with an apparent 46% reduction in pneumonia as a result of treatment with NIs, whereas the use of objective criteria in the data collection showed no evidence of effect, with a RR of 1.0. Age group (adults vs. children), drug (oseltamivir vs. zanamivir) and indication (treatment vs. prophylaxis) showed no evidence of association with treatment effect.

Meaningful conclusions on the effect of either NI on complications of influenza are difficult to draw based on the trial evidence. In part, this was due to the lack of standardised definitions. In addition, meta-analyses of these outcomes that lacked definitions were based on few events and therefore not robust. Caution is therefore urged in interpreting the meta-analysis result, which suggests that 100 patients (95% CI 67 to 451 patients) need to be treated with oseltamivir for one less self-reported, investigator-mediated, unverified pneumonia. The same applies to the zanamivir treatment result, which suggests a reduced risk of self-reported, investigator-mediated, unverified bronchitis in adults (NNTB 56, 95% CI 36 to 155). The evidence suggested that oseltamivir had a similar effect, although the result was non-significant.

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PART IV - CLINICAL
DOCUMENTATION

Tamiflu® (oseltamivir phosphate) 

**Diagnosis of
secondary illness**

page 77

Date of diagnosis / /
mm day yr

Diagnostic confirmation: Pneumonia, LRTI, Bronchitis

Diagnosis: Pneumonia ☐
 Bronchitis ☐
 Lower respiratory tract infection ☐ → specify: _____

acute ☐
 chronic ☐

Which lung(s) are affected? right ☐
 left ☐
 bilateral ☐

Duration of respiratory
secondary illness Days¹

Symptoms

	present	absent	duration (days) ²
1. Cough	☐	☐	 / /
2. Chest pain	☐	☐	
3. Haemoptysis	☐	☐	
4. Tachypnea	☐	☐	
5. Dyspnea	☐	☐	
6. Purulent sputum	☐	☐	
7. Non-purulent sputum	☐	☐	
8. Rigors	☐	☐	
9. Convulsion	☐	☐	

Chest examination

	RIGHT		LEFT	
	anterior	posterior	anterior	posterior
10. Rates	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐
11. Rales	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐
12. Crepitations	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐
13. Bronchial breath sounds	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐
14. Pleural rub	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐

COP-60
24x6080 183x11.0 WV15978

FIGURE 14 Sample 'Diagnosis of secondary illness' form, page 1/2 (oseltamivir study WV15978⁶⁷).

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PART IV - CLINICAL
DOCUMENTATION

Tamiflu® (oseltamivir phosphate) 

**Diagnosis of
secondary illness**

page 78

Diagnostic confirmation: Pneumonia, LRTI, Bronchitis (continued)

Vital signs

Temperature¹ / / °F

Sitting measurement

Respiratory rate per minute

Chest X ray

Was chest X ray performed?
yes ☐
no ☐

Are there any clinically significant abnormalities noted in the chest X ray?

yes ☐ → Specify: _____ infiltrate ☐
 no ☐ consolidation ☐
 other ☐ → specify: _____

Microbiology

Was sputum gram stain performed?
yes ☐ → Specify below
 no ☐

epithelial cells cells/Lpf
 WBC cells/Lpf

organisms present ☐
 absent ☐

Was sputum culture performed?
yes ☐ → If organism/pathogen found specify below
 no ☐

organism/pathogen
 colony count cfu/Lpf

COP-60
24x6080 183x11.0 WV15978

FIGURE 15 Sample 'Diagnosis of secondary illness' form, page 2/2 (oseltamivir study WV15978⁶⁷).

As stated above, there is no evidence that definitions of complications in paediatric, elderly or adult trials were ever prepared and incorporated in the trials' design. Therefore, the reporting of cases of 'otitis media', 'pneumonia', 'sinusitis' or 'bronchitis' are of unclear significance and importance, making it impossible to attribute a cause and draw conclusions.¹²⁸ This is probably why the FDA-approved oseltamivir package insert, since 17 November 2000, has consistently stated: 'serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications'. The original product label did not contain such a statement but, on 14 April 2000, after oseltamivir was approved for sale in the USA, the FDA sent Roche an untitled letter about 'Misleading Efficacy Claims', which the FDA had noted in Roche's promotional materials (p. 3¹²⁹). One of the statements that Roche made was: 'Tamiflu reduces incidence of secondary complications (i.e. bacterial infections) by 45%'. The FDA commented: 'Further, you have claimed reductions in severity and incidence of secondary infections with Tamiflu that are misleading because they are not supported by substantial evidence' (p. 3¹²⁹). We do not know how Roche responded to the FDA but in subsequently available Roche promotional material information, Roche's statements were consistent with the FDA's demands.⁸

There is uncertainty in the 'complications' and 'secondary illnesses' outcome definition, therefore we carried out an analysis on the data from adult treatment trials on those complications classified as serious or those which led to study withdrawal. For oseltamivir, there was no evidence that treatment affected such complications (RD 0.07%, 95% CI -0.78% to 0.44%). This outcome could not be assessed in oseltamivir prophylaxis due to an insufficient number of events. For zanamivir, there was no significant evidence of a treatment effect on such complications (RD -0.04%, 95% CI -0.64% to 0.24%). This outcome could not be assessed in children because of an insufficient number of events.

Contrary to the FDA, the EMA's oseltamivir Summary of Product Characteristics states that oseltamivir significantly reduces the incidence of 'specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics' in individuals aged ≥ 13 years. This claim is based on 'a pooled analysis of all influenza-positive adults and adolescents ($N = 2413$) enrolled into treatment studies', of which 1063 were in the placebo group and 1350 were in the oseltamivir-treated population.¹³⁰ This statement appears in the EMA files as early as 2001.¹³¹ These exact denominators appear in the Kaiser *et al.*⁴ 2003 meta-analysis.

The design of the trials – as defined in the protocol with amendments, SAP and CRFs – does not allow any further inferences. The effect on outcomes that were originally considered of secondary or tertiary importance (such as bronchitis and pneumonia) would have been clarified with better clinical definitions and investigations, as were some of the serious adverse events. These benefited from a paragraph-length narrative, which reported most of the salient features of the event.

Our previous decision to analyse the effects of oseltamivir and zanamivir on the ITT population has been confirmed for oseltamivir, with the demonstration of the effect on antibody responses in participants in treatment trials, although no such effect is discernible for zanamivir. This effect leads to the introduction of selection bias, with a significantly reduced probability of being diagnosed with influenza and an imbalance in the two arms if the ITTI population is analysed. The effect of oseltamivir on antibodies appears to be carried over to children with ILI. Its finding contradicts statements made by the manufacturer.

The apparent incomparability between arms of the influenza-infected subpopulations in the oseltamivir trials raises the question of how an appropriate analysis should be conducted. If influenza-infected groups are comparable (as appears to be the case in zanamivir treatment trials) then an appropriate analysis strategy (based on Senn¹³²) would be to first determine the effect of treatment in the ITT population. If there is evidence of a treatment effect then treatment by infected status interaction could be tested. If there was evidence of an interaction then estimates of treatment effect could be derived separately for the influenza-infected and non-influenza-infected subpopulations. However, this analysis should be conducted on the ITT population using a single appropriate statistical model, obviating the need to conduct separate analysis on the influenza-infected subpopulation. Roche used geometric mean titres indicating antibody responses in the ITTI population to support their statement that oseltamivir does not affect antibody

responses (e.g. in *Table 15* and linked text of module 1 of trial WV15799⁶⁵). However, the use of such measures can be misleading. What are required for such an analysis are data on how many ITT population participants responded by arm, at what level of antibody response and how many were tested. Such data could not be identified with certainty. A further effect of choosing a subpopulation analysis (ITT in treatment trials and ITTIINAB (ITT influenza-infected index cases who had negative virology at baseline) in prophylaxis trials) as the primary analysis is the restriction of the generalisability of results. This is especially so in the case of design flaws (e.g. in the case of the PEP trial WV15799,⁶⁵ in which all index cases were not treated and around 55% of participants were dropped from the ITTIINAB analysis). In this cluster trial design, households should be included as random effects in the analysis to take account of within-household correlations.

A significant but slight reduction of the proportion with serum antibody (mostly haemagglutination inhibition antibody) titre rise by fourfold or more among those who were tested was shown in this review. This was consistent with the evidence from animal tests using a subclinical dose of oseltamivir in influenza A/H1N1-infected mice.¹³³ Takahashi *et al.*¹³³ reported a non-significant slight reduction of haemagglutinin-specific secretory immunoglobulin G antibody in the serum and spleen, whereas they reported about an 80% significant reduction of haemagglutinin-specific secretory immunoglobulin A antibody in the nasal wash and bronchoalveolar fluids on day 12. From this evidence, they warned that the risk of reinfection may increase in patients showing a low mucosal immunoglobulin A antibody response following oseltamivir administration. These experiments were done because they had the unexpected finding that patients with paediatric influenza who were treated orally with oseltamivir for 5 days had significantly low levels (about 60% reduction on day five) of anti-influenza secretory-immunoglobulin A nasopharyngeal fluids compared with levels in patients who were not treated with oseltamivir.¹³⁴ Their findings are consistent with our findings that serum haemagglutinin inhibition antibody response was decreased by oseltamivir administration, although secretory immunoglobulin G antibody could not be analysed in our study because the data were not reported in the CSRs.^{133,134} These findings are also consistent with the evidence on the mode of action of oseltamivir from animal models^{8,58,135} and from viral challenge, randomised, placebo-controlled studies in humans.²⁷

Pro-inflammatory cytokines, including interleukin 6, tumour necrosis factor alpha and interferon gamma, were completely suppressed by oseltamivir administered 28 hours after the experimental inoculation of influenza virus, whereas the reduction of viral titre in nasal lavages was partial.²⁷

There is decisive evidence that administration of oseltamivir in animals challenged by respiratory syncytial virus, which lacks a neuraminidase gene, showed a symptom-relieving effect (decreased weight loss) and inhibition of viral clearance.¹³⁶ These effects were accompanied by a decreased cluster of differentiation +8 T-cell surface sialoglycosphingolipid GM1 level, which is regulated by the endogenous sialidase/neuraminidase in response to viral challenge along with suppression of cytokine expression.¹³⁶ They are consistent with those findings from the pharmaceutical company and their investigators. The findings of the study by Moore *et al.*¹³⁶ suggest a risk of infection and exacerbation of infection by pathogens other than influenza virus despite the apparent reduction of symptoms from infection.

TABLE 15 Proportions of contacts with positive serology data (WV15799⁶⁵ ITTIINAB population)

Positive serology	Group		Total
	Placebo, <i>n</i> (%)	Tamiflu, <i>n</i> (%)	
No	166 (83.0)	192 (93.7)	358
Yes	34 (17.0)	13 (6.3)	47
Total	200	205	405
Chi-squared $p=0.001$.			

Sufficient plasma concentration of oseltamivir carboxylate from orally administered oseltamivir phosphate may act directly on the host endogenous neuraminidase to reduce (or suppress) the immune response even at the dose of 20 mg twice a day for 5 days. However, the bioavailability of inhaled zanamivir seems to be very broad: about 10–70%, as estimated by the area-under-the-curve data from the inhalation and intravenous study from the Japanese Summary Basis for Approval. The difference in peak concentration (C_{max}) was much larger (sixfold to 37-fold). This means that inhaled zanamivir could reach a high enough concentration to reduce the immune response, if it is administered at a high dose or for a long period, or if the patient is very susceptible. In fact, a double-blind, placebo-controlled trial¹³⁷ using healthy volunteers to investigate the effect of zanamivir treatment (20 mg/day for 14 days) on the humoral immune response to influenza vaccine showed that the zanamivir group responded with significantly lower antibody titres to the H1N1. Pro-inflammatory cytokines, including interleukin 6, tumour necrosis factor alpha, interferon gamma and other chemokines, were almost completely suppressed in the viral challenge RCT using a very high dose (600 mg) of intravenous zanamivir before inoculation of the influenza virus in human adults.¹³⁸

These findings all suggest that the low immune response, with a low level of pro-inflammatory cytokines, induced by the action of oseltamivir carboxylate, may reduce the symptoms of influenza irrespective of an inhibition of influenza virus replication, which is widely believed to be the main mode of action of NIs.

In addition, the potential hypothermic or antipyretic effect of oseltamivir (but not zanamivir) as a central nervous system depressant may also contribute to the apparent reduction of host symptoms.^{139,140}

Zanamivir had no effect on pneumonia symptoms in treatment trials, even when the diagnosis was supported by a chest radiograph, nor did it affect antibody responses, but it did affect bronchitis. We think that this shows a symptom-relieving effect of both drugs, which also applies to more severe, if undefined, syndromes. Both drugs relieve ILI symptoms by around 0.6–0.7% day's reduction although this is first relief and not necessarily complete relief. In the case of oseltamivir, the mix-up with the follow-up cards does not allow us to draw any conclusions on a possible length of the duration of symptom relief. Also of note is the fact that this important information came to light from the FDA reports and not from the CSRs of the relevant trials.^{8,58} This points to the incomplete nature of reporting in the CSRs and the important role of Summary Basis of Approval (SBA) regulatory information.

In a subgroup analysis we found no evidence of a difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza- and non-influenza-infected subgroups. Both subgroups showed strong evidence of treatment effect of 0.5–0.7% day's reduction in time to first alleviation of symptoms. This strongly supports our hypothesis that these drugs do not have an influenza-specific effect.

Oseltamivir relieves symptoms in otherwise healthy children, but no effect was noted with zanamivir, which may be because of the limited power of the two eligible trials, with just over 700 children in total. However, oseltamivir does not have any effect on asthmatic children with ILI, a population that should benefit most from its use. One explanation for this finding is in the nature of the young asthmatic population, which is well cared for and used to regular powerful medications and close follow-up. The incremental benefit of oseltamivir is thus likely to be undetectable in such a population. An alternative explanation could be the higher susceptibility of the immune system to suppression by oseltamivir carboxylate in asthmatic children compared with those in the placebo group. The finding that oseltamivir administered to asthmatic children reduces symptoms faster than in placebo recipients at the beginning of the study, but during the off-treatment period more recovered later than those administered placebo, gives some support to this explanation.

There is no evidence of an effect of oseltamivir on hospitalisations. Hospitalisations are an important but poorly defined outcome in the oseltamivir protocols, inconsistently reported in the CSRs and overlooked in the zanamivir protocols and reports.

The oseltamivir trials did not detect any influenza-related deaths, reflecting the relatively benign nature of influenza in the study populations. The zanamivir trials detected eight deaths, of which only two were likely to be caused by influenza and both occurred in the intervention arms. All of the trials were likely to be underpowered to detect differential effects on mortality, but the absence of deaths in placebo recipients again underlines the benign nature of influenza. In fact, mortality in Japan during the 2009A/H1N1 influenza outbreak was 198 among about 20 million patients with influenza (1 in 100,000 infected). Early deterioration leading to death was observed more frequently in oseltamivir recipients than in zanamivir recipients or no antiviral recipients.¹⁴¹

Overall, the two drugs have similar benefits but markedly different toxicity profiles. On average, for every 28 (95% CI 14 to 112) adults treated with oseltamivir there will be one more report of nausea and for every 22 (95% CI 14 to 42) adults and 19 (95% CI 10 to 57) children there will be one more report of vomiting. Oseltamivir seems to have an apparent protective effect on diarrhoea, contrary to the other evidence of gastrointestinal disturbance. This finding might be as an effect of a placebo containing dehydrocholic acid or it might be one of the results of the ILI symptom-relieving effects (similar to relief of tachycardia and palpitation). The other apparent gastrointestinal events, such as nausea and vomiting, may be the result of central nervous disorders indicated by 'only day 1 increase of vomiting' in treatment trials in children.

For every 62 (95% CI 41 to 411) adults exposed to zanamivir there will be one fewer case of nausea and vomiting, but no such effect was visible in children, probably because of a lack of power. Zanamivir does not appear to affect the frequency of bowel movements.

In the prophylaxis data set, 'influenza without laboratory confirmation' (i.e. ILI) was only partially reported in the oseltamivir CSRs and not reported in the zanamivir CSRs, except for one report,⁸⁶ in which no significant reduction was observed (zanamivir 9% vs. placebo 10%). As a consequence we are unable to report on that outcome. The size of the reduction in influenza symptoms in oseltamivir prophylactic trials is inferior in magnitude to that seen in hand washing to prevent severe acute respiratory syndrome, based on seven case-control studies [odds ratio (OR) 0.77, 95% CI 0.70 to 0.84; *P* statistic = 68%; RD -0.12, -0.16 to 0.08; *P* statistic = 26%], the NNTB being approximately '50' for prophylaxis with oseltamivir and '8' with handwashing.¹⁴²

There is a significant reduction in the proportion of patients with symptomatic influenza with both NIs. However, these findings do not reflect the true efficacy for prevention of influenza because they conceal the positivity of laboratory testing (measured through tests of viral shedding and fourfold antibody titre rise).

We found an apparent prophylactic effect of zanamivir on pneumonia (which was not defined in CRFs) when it was used for 14–28 days. However, we found no evidence of significant effects on other complications and no evidence of an effect of oseltamivir on complications or hospitalisations.

Oseltamivir induced nausea in people who were undergoing prophylaxis but there was insufficient evidence to show an association with vomiting.

On-treatment renal adverse events were three times more common in the oseltamivir arms than in the placebo arms, with 150 treated patients leading to one additional event. The two participants who died in the oseltamivir arms both experienced acute renal failure while on-treatment, although only one of those events was listed as an adverse event. The unlisted event was in a 91-year-old female who was 'withdrawn from the study on Study Day 15 because her estimated creatinine clearance was less than 30 ml/minute (WV15708, p. 44).⁶¹ The screening laboratory examinations, that were carried out 10 days before the start of study treatment, were normal'. Hyperglycaemic adverse events (aggravated diabetes mellitus or hyperglycaemia) were also more common in the oseltamivir arms, with eight events in total (one in WV15673/WV15697,⁵⁹ two in WV15708⁶¹ and five in WV15825⁶⁸) compared with none in the corresponding placebo arms. These data are only presented descriptively, as they are too few (< 10) to meta-analyse formally, as prespecified in our analysis plan.

Finally, oseltamivir caused headaches and psychiatric harms in adult prophylaxis trials. Headaches are one of the most prominent harms of oseltamivir. There is evidence of a dose–response effect in prophylaxis trials ($p = 0.013$),⁵⁹ in which headaches were observed in 202 of 519, 225 of 520 and 242 of 520 participants in the placebo, oseltamivir 75 mg once daily and twice daily arms, respectively.

In the psychiatric category, several rare and severe single events (nervousness, aggression, hallucinations, psychosis, suicide ideation and paranoia) were reported significantly more frequently in the intervention arm. Added to other more frequently reported but not significantly different events (such as depression and confusion), this gave a large effect and a relatively small NNTH of 94 (95% CI 36 to 1538). The importance of such a finding lies in the distribution of oseltamivir to large numbers of asymptomatic individuals following pandemic plans. There were no prophylaxis trials in children that met our inclusion criteria, therefore we cannot report on prophylaxis harms in this important population.

The question of why oseltamivir treatment trials failed to identify a clear association between oseltamivir and psychiatric harms, although a weak dose-dependent association was observed, is a moot point. It is possible that ILI and influenza symptoms masked the harms in those who were already symptomatic and therefore recruited in the treatment trials (and influenza-type symptoms were excluded as adverse events to be reported). The reporting issue of compliharms may have helped to mask such events. Alternatively, it could be that these events are rare in the populations studied and that there was insufficient power to detect an association. The CI was wide (0.43 to 2.03) and does not rule out a doubling in risk as a result of treatment, as was found in the prophylaxis trials. It is also possible that the risk of psychiatric harm increases with increasing dose (as the data from two trials^{8,58} suggest) and increasing duration of treatment (as the prophylaxis trials suggest).

Toovey *et al.*¹⁴³ assessed the issue and failed to find an association between neurological and psychiatric adverse events and oseltamivir exposure. The outcomes studied were not based on the a priori definition of psychiatric adverse events as defined in the CSRs. The definition was constructed post hoc, based on a selected group of adverse events taken from the psychiatric, neurological and injury body systems in the reports. The issues are described fully in another report¹⁴⁴ and Toovey's response.¹⁴⁵ Toovey *et al.*¹⁴³ reviewed only retrospective observational studies and did not review three prospective cohort studies conducted in Japan.

A meta-analysis of three prospective cohort studies of neuropsychiatric adverse events (NPAEs) in Japanese children show a pooled OR for abnormal behaviours due to oseltamivir exposure of 1.55 (95% CI 1.21 to 1.98; $p = 0.0005$) without significant heterogeneity.¹⁴⁶ In one prospective study¹⁴⁷ of several thousand children with influenza, carried out to test the hypothesis of a causal relation between oseltamivir and neuropsychiatric events, abnormal behaviour was observed more frequently in oseltamivir recipient children than in control subjects (RR 1.57, 95% CI 1.34 to 1.83). Abnormal behaviour was observed in 3.4 per 100 person-days (or 13.8%) in the oseltamivir group compared with 2.2 per 100 person-days (or 8.8%) in the control group. Reanalysis of this study population, focusing on delirium and unconsciousness, also showed a significant association between oseltamivir and neuropsychiatric events, especially in the very early phase of the illness within a day of commencement of fever.¹⁴⁸ These indicate that prospective and intentional collection with this scale of participants may be necessary in treatment RCTs.

Animal toxicity study results firmly support the effect of oseltamivir on the central nervous system. One of these is the hypothermic effect of oseltamivir (but not zanamivir) administered orally, intraperitoneally^{139,140} and intracerebroventricularly.¹⁴⁰ The other is that intraduodenal or intravenous administration of oseltamivir to mature rats induced respiratory arrest shortly followed by cardiac arrest. These studies clearly show central depressant effects of oseltamivir.¹⁴⁹ Moreover, in the post-marketing toxicology phase studies by Roche, many symptoms that the manufacturer considered 'item-related' were observed: alterations in respiration including decreased respiratory rate/gasping and altered mucous membrane/skin colour (pale) prior to death. Although the manufacturer denied the causality,¹⁵⁰ symptoms at 2 hours after administration that showed dose-related increase were lack of olfactory orientation, lack of cliff aversion and low/very low

arousal. Twenty-four of 52 pups that did not exhibit cliff aversion were later found dead. Fourteen of 17 animals with low or very low arousal died thereafter. These findings are consistent with the clinically observed psychiatric symptoms in the RCTs and post-marketing spontaneous reports.

Zanamivir was well tolerated. However, a potentially active placebo may have masked the occurrence of bronchospasm in zanamivir trials.

Treatment trials were mostly under-recruited and often their results pooled post hoc in two, or even three, trials, and yet they showed very high influenza positivity rates. One possible explanation for this lies in the intensive surveillance carried out in the predefined trial centre areas and the restricted time span of recruitment during high likelihood of positivity periods. This may be why many centres with low levels of recruitment are listed in the CSRs; this limits the generalisability of the results to everyday life.

In a primary or secondary prophylaxis indication the postulated central effect of oseltamivir is confined to suppressing symptoms, as infection was not prevented even when oseltamivir was administered prior to the inoculation of influenza virus both in animals¹³⁵ and in humans,²⁷ and the prophylaxis trials. However, the central problem remains the incompatibility of the two contrasting claims of its activity against antibody production. If, as reported in many documents, oseltamivir does not interfere with antibody production (e.g. see FDA¹⁵¹ and Roche Investigators' Guide¹⁵²), how is it possible that oseltamivir prevents cases of influenza when part of the definition of prevented cases in oseltamivir trials was based on the absence of antibody response?

The apparent ability of oseltamivir to interfere with antibody response calls into question the mode of action of the drug and puts in doubt the proposed effects of oseltamivir. One possibility in treatment trials is that oseltamivir administration, by interfering with antibody production, has the effect of selecting the strongest antibody responders in the ITTI subpopulation. These individuals are classified as influenza cases and are included in the oseltamivir arm of the ITTI population. This selected subpopulation probably represents the healthiest or those least likely to experience complications. An alternative consequence could be that interference with antibody production in the oseltamivir arm led to active arm participants being more likely to develop complications as a result of impaired immune function.

Evidence from prophylaxis and secondary prophylaxis trials suggests that in addition to the apparent similar mode of action as in the treatment studies, suppression of viral shedding in nasal swabs may be of importance. In the former, participants who become positive (i.e. who are subsequently classified as cases of influenza) in the oseltamivir arms are the few who mount a strong response despite oseltamivir interference. The remainder (who are significantly more than in the placebo arm) are classified as prevented or avoided cases. However, as prophylaxis CSRs do not report antibody responses and viral isolate results for the ITT populations either, it is impossible to tell whether or not this proposed mode of action fits all of the evidence. The effect of oseltamivir on nasal shedding is consistent with the proposed mode of action of NIs in preventing the virus from leaving the host respiratory epithelial cells, which are covered by a mucous layer. Compared with the rather small reduction of symptoms of ILI and reduction in antibody rise (up to 10%) by both oseltamivir and zanamivir, the extent of the reduction of symptomatic influenza is almost half. This may be as a result of reduction of influenza viruses in the nasal swab sample.

In prophylaxis there is no evidence that oseltamivir reduces symptomatic ILI. Oseltamivir reduces the number of prophylaxis participants testing positive (based on antibody rise and/or culture test). However, this finding is weakened by oseltamivir's interference with the viral replication on the swab and effect on antibody production. In addition oseltamivir does not affect asymptomatic influenza and there is no evidence that it interferes with person-to-person spread.

Similar to the FDA,^{109,153} because of the problems with the design of study WV15799⁶⁵ we could not draw any conclusions on the ability of oseltamivir to interrupt viral transmission.

This is important as the results of the trial⁶⁵ formed part of the WHO³ rationale for use of the drug to interrupt transmission from person to person, and allow time before the arrival of vaccines in the event of a pandemic furnishing a seemingly powerful rationale for stockpiling oseltamivir.

This shows the importance of availability of full CSRs, something the WHO did not have.

Antibody suppression seems stronger for oseltamivir than zanamivir, probably because of the difference in bioavailability. It may be that evidence of other effects, such as hyperglycaemia and renal impairment (though significance was marginal) in the prophylaxis trials may be due to inhibition of the host's endogenous neuraminidase, which impairs the cell function of various organs.¹⁵ Overall, the significance of oseltamivir for nasal shedding is unclear but problems with sampling and culture undermine any claims as to its secondary prophylactic properties, as the FDA made clear in its response.¹⁰⁹

The dose–response increase in psychiatric events in the ‘pivotal’ oseltamivir treatment trials and the increase in vomiting only on day 1 in treatment trials in children may be caused by the sudden onset of the central action of unchanged oseltamivir.¹⁵ Brain concentration of unchanged oseltamivir increases during the early phase of influenza in juvenile animals¹⁵⁰ as a result of a reduced or low function of *p*-glycoprotein, a major transporter of oseltamivir at the blood–brain barrier.^{15,149} The likely centrally mediated mode of action of oseltamivir is supported by the finding of adverse events in healthy people in prophylaxis trials. However, these effects may also be derived from a delayed action that is associated with host endogenous neuraminidase inhibition by oseltamivir,¹⁵ because this appeared after more than 1 week's exposure to the drug and lasted for > 2 weeks. Other effects, such as pain in the limbs, hyperglycaemia or diabetic events, reduction of antibody rise and reduction of cytokine induction, may also result from the suppression of the host's endogenous neuraminidase by oseltamivir.¹³⁶ Pain in the limbs and metabolic control events (mainly hyperglycaemia) were in excess in the oseltamivir arms, but we did not carry out a formal meta-analysis, as they were not prespecified in our analysis plan and the number of events was < 10 for metabolic events.

Statements made about the capacity of oseltamivir to interrupt viral transmission and reduce complications are not supported by any data that we have been able to access.

We have not reviewed other NIs, such as laninamivir and peramivir, or other antivirals, such as the adamantanes (amantadine and rimantadine) or antipyretic/anti-inflammatory agents. Laninamivir and peramivir may be more potent as NIs because their bioavailability is far higher than zanamivir and may affect the host's endogenous neuraminidase. Adamantanes are well known centrally active agents and may be more harmful than oseltamivir and zanamivir. Anti-inflammatory antipyretics (except paracetamol) may be more toxic than NIs.¹⁵ Hence, the other NIs, adamantanes and anti-inflammatory antipyretics may not be alternatives to oseltamivir and zanamivir.

Overall completeness and applicability of evidence

We used the Cochrane seven-domain risk-of-bias instrument to assess bias. The availability of partial or complete CSRs decreased the uncertainty and allowed definitive judgements to be made. Previous unclear risk of bias became certainty of bias or certainty of absence of bias. Certainty or low levels of uncertainty are due to our expectations regarding the complete CSRs. We were expecting to have all relevant and consistent information available for our reviews, but, when it was not, our judgements changed because we found gaps in the availability of information and inconsistent information. We are still uncertain as to whether or not the complete study reports represent an exhaustive and coherent source of trial narrative and data.

In the case of treatment trials, conclusions and generalisations are drawn from a subpopulation in which the two arms do not appear comparable as a result of the apparent ability of oseltamivir to interfere with influenza antibody production. The effect of oseltamivir on the gastrointestinal tract appears to be notable, although a definitive statement will be possible only once the mode of action and dosage of dibasic calcium phosphate dihydrate and dehydrocholic acid have been clarified. The high percentage of influenza infections appears to be in contrast with the need to pool or delay several trials and the small recruitment

size of others because of a lack of influenza circulation. In the case of PEP trials, the selection of the infected population has the effect of excluding from the analysis large percentages (in some cases > 50%) of participants. This brings the generalisability of the results of these trials into question.

Much has been made in the trial programmes of viral nasal voidance as a marker of effect. However, its measurement was unreliable in treatment trials, as this verbatim quote from the FDA review shows:

Duration of viral shedding was measured from treatment initiation to the time of the first negative virus culture with no subsequent positive cultures. Upon reviewing a list of viral shedding patterns provided by the applicant on 8/16/99, two problems emerged: (1) the pattern of virus shedding was fluctuating in at least 33 subjects (i.e. pos-neg-pos-neg, with or without a subsequent negative result). (2) In at least 100 subjects, the last virus shedding sample was the first negative sample in sequence, meaning there was not a subsequent negative confirmation. Given the fluctuating pattern of virus shedding, to estimate the duration of viral shedding based on the occurrence of a single first negative data poses a high level of uncertainty.

FDA, p. 14¹⁰⁹

In all of the programmes, the effect on complications was based on unclear and potentially unreliable definitions, often at the discretion of local clinicians, and confirmation (e.g. radiological confirmation of pneumonia) was not consistently reported when it did occur. In the ITT population, the correct population for analysis, there is no credible effect of oseltamivir against pneumonia as the significance of the term 'pneumonia' is not clarified.

In the case of PEP trial,⁶⁵ nasal voidance was measured only in symptomatic subjects, as an adjunct to the protocol version. However, this does not prevent the manufacturers from making claims of effect for all of these outcomes.

Other general requirements, such as presentation within 36–48 hours, raise questions about the generalisability of the research evidence. However, underlying all our doubts is the conflicting evidence on the mode of action of the drug.

Most of the trials were substantially under-recruited and so had insufficient power individually to answer the research question.

Quality of the evidence

We assessed all full CSRs of relevant trials. An example of the kind of detail available in complete CSRs and the importance of the trial timeline in assessing the presence of bias is the observation that of the CSRs for the included trials, only one contained a protocol that predated the beginning of participant enrolment, only two had SAPs that clearly predated participant enrolment and three had clearly dated protocol amendments. No oseltamivir CSR included a clear date of unblinding.

All reports in our review were sponsored by the manufacturers. It is known that published studies sponsored by the pharmaceutical industry are more likely to have outcomes favouring the sponsor than studies that have other sponsors.^{154,155} As the evidence relates to published studies, we do not know whether or not the findings are applicable to CSRs.

Potential biases in the review process

The main limitation of our study is our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents, such as randomisation lists. Randomisation lists appeared to be of two types. The first was a pre-randomisation list of random codes with which participants' IDs cannot be matched with the participant IDs used within other sections of the CSR. The second was a post hoc randomisation list to which individual participants can be matched but the original generated codes are not shown. In both cases the truly random generation of the sequence could not be

properly assessed because either the original codes are not provided or the original codes cannot be matched to patients.

We have created methods and procedures to address the risk of reporting bias that we identified in published trials, but remain uncertain about the success of these new methods.

Agreements and disagreements with other studies or reviews

Several reviews of NIs are now available,^{156–160} including several separate versions of our previous reviews.^{30–32,35} All are mainly based on published information and reach similar conclusions to our 2006 review, which sparked the reader's comment and subsequent investigation and change of methods.

Following publication of our review update in December 2009, Roche asked the Harvard-based academics Hernan and Lipsitch¹⁶¹ to repeat the Kaiser analysis⁴ to confirm or reject Kaiser's conclusions. They were not provided with any funding to carry out this analysis and Roche ultimately provided them with patient-level data sets and module 1 for the 10 Kaiser trials and one more treatment trial.⁶⁹ An important methodological difference between Hernan and Lipsitch's analysis¹⁶¹ and that of Kaiser⁴ was Hernan and Lipsitch's decision to privilege a true ITT analysis over the subpopulation analysis featured in the Kaiser analysis. Our Cochrane review also analyses the ITT population.

The Kaiser analysis⁴ concluded that oseltamivir provided two statistically significant reductions: in lower respiratory tract complications and in hospitalisations.

Hernan and Lipsitch¹⁶¹ evaluated lower respiratory tract complications and found a statistically significant, but smaller, reduction in the risk of these complications.

Hernan and Lipsitch¹⁶¹ omitted evaluating the Kaiser paper's conclusion that oseltamivir reduced the risk of hospitalisation. They wrote, 'it was not possible to assess the potential benefit for high-risk participants who are hospitalised, because the sample size of most studies was too small to consider hospitalisation as an outcome'.

Hernan and Lipsitch¹⁶¹ do not elaborate on or highlight their apparent methodological disagreement with the Kaiser 2003 analysis⁴ and it is not reflected in the news article published on the Harvard website entitled 'Oseltamivir effect on complications confirmed by reanalysis' (<http://ccdd.hsph.harvard.edu/NewsEvents/Oseltamivir-reanalysis>). In fact, Hernan and Lipsitch¹⁶¹ did not confirm one of the key conclusions of the Kaiser paper.⁴

Unfortunately, the Hernan–Lipsitch analysis¹⁶¹ has been cited by influential bodies, such as the European Centre for Disease Prevention and Control, as 'confirmation of the original Kaiser meta-analysis' (http://ecdc.europa.eu/en/activities/sciadvce/_layouts/forms/Review_DispForm.aspx?ID=561&List=a3216f4c%2Df040%2D4f51%2D9f77%2Da96046dbfd72) despite the fact that Hernan and Lipsitch¹⁶¹ did not confirm one of the key conclusions of the Kaiser paper.⁴

For complications, although Hernan and Lipsitch¹⁶¹ clearly produced similar results to Kaiser,⁴ we do not think that this means that the result is more credible. In view of our findings, we suggest that these results should be interpreted with caution. We have published our preliminary comments.¹⁶² The approach Hernan and Lipsitch¹⁶¹ took in analysing data was insufficient to provide a credible, independent check on validity, and reinforces the importance of detailed, critical assessment of entire trial programmes, with access to full-length study reports. Our analysis questions the coherence between the evidence and the proposed mode of action of oseltamivir.

The Ebell *et al.*¹⁶³ review concluded that there was 'no evidence that oseltamivir reduces the likelihood of hospitalisation, pneumonia or the combined outcome of pneumonia, otitis media and sinusitis in the ITT population'. This conclusion was based on module 1 of the 10 Kaiser trials plus WV16277.⁶⁹ These are the same 11 trials included by Hernan and Lipsitch.¹⁶¹

Conclusions

Main conclusions

These data show that oseltamivir and zanamivir cause small reductions in the time to alleviation of influenza symptoms in adults, but not in asthmatic children. The use of oseltamivir increases the risk of nausea, vomiting and psychiatric events in adults and vomiting in children and may reduce risk of diarrhoea and cardiac events in adults. Observational studies fail to show that oseltamivir has a protective effect on mortality among patients with 2009A/H1N1 influenza. Prophylaxis with either oseltamivir or zanamivir may reduce symptomatic influenza in individuals and in households but there was no reduction in all other influenza outcomes, including overall ILI reported as an adverse event on-treatment. In previous Cochrane reviews it is likely that evidence from published data was insufficient to fully assess risk of bias within the trials. Our results do not discount a potential benefit of using zanamivir and oseltamivir in individuals under particular situations, for example in immunocompromised or in compassionate cases, for which few other therapeutic options may exist. However, NIs themselves may be immunosuppressants.

The balance between benefits and harms should be considered when making decisions about use of NIs for either prophylaxis or treatment of influenza.

Implications for practice

These results show that both oseltamivir and zanamivir reduce the time to symptomatic improvement in adults (but not asthmatic children) with ILI. The size of this effect is small – approximately half a day. We have no data comparing oseltamivir or zanamivir with paracetamol and other antipyretics. We did not find convincing evidence that either oseltamivir or zanamivir reduces the risk of complications of influenza, particularly pneumonia, or reduce risk of hospitalisation or death. Even in individuals at higher risk of complications, such as children with asthma or the elderly, there was no evidence of a beneficial effect for reducing risks of complications.

The findings demonstrate a minimal effect on prevention of influenza by oseltamivir or zanamivir among individuals or families. This suggests little support for their use as prophylactic agents, for example during influenza epidemics.¹⁶⁴

Implications for research

The considerable body of evidence from RCTs included in this review indicates either no effect or a relatively small absolute effect size against the complications of influenza. Such an effect, even if statistically significant, would be too small to warrant treatment with NIs in a primary care setting, especially as effective diagnosis and treatments for rare complications (such as pneumonia) are available. Lack of evidence of an effect on hospitalisations probably indicates lack of severity in the first place. Assuming an influenza incidence rate of 2% (similar to that in the control arms of oseltamivir treatment trials) to detect a 25% clinically significant reduction in pneumonia, 21,500 participants would have to be enrolled in a clinical trial.

Our findings have implications for research on the mechanism of action of NIs, with special regard to any direct central action of oseltamivir and the inhibitory effect of the host endogenous neuraminidase of various organs and systems. We could not reach a consensus on whether or not further trials are warranted and whether or not current trials should be discontinued.

Published trials are unlikely to provide the level of detail to allow the results of a drug trial to be properly evaluated and risk presenting a partial and potentially biased report of trial conduct and findings. This has implications not only for the reporting of trials but also the weight that can be applied to published studies alone.

Our calculation is likely to underestimate population size, as the 2% incidence rate was derived from trials that used enhanced ad hoc surveillance systems. Any trial design would have to ensure that the presence of complications is ascertained using objective diagnostic criteria (e.g. with confirmation using imaging or laboratory testing for pneumonia). Such trials would also have to consider the ethical implications of conducting studies for which the estimate of benefit (based on 11 RCTs) in otherwise healthy people is likely to be small, and would have to be balanced against the apparent risks of adverse effects from NIs. We think research should be aimed at more effective preventative measures and early identification of complications.

The methods used to conduct our evidence synthesis need to be repeated across further interventions and by other researchers, and may need to be refined further. Given the considerable resources involved in using these methods, a system is needed to prioritise reviews of important drugs so that such methods are reserved for drugs that meet certain conditions. Priority could perhaps be given to first drugs of a new family, drugs considered to be innovative or those that are likely to have a big market impact. Such reviews should be publicly funded and be independent of both regulators and manufacturers. Researchers who conduct these 'high-scrutiny' reviews need to be free of recent ties to either government or the pharmaceutical industry. Systematic review groups such as The Cochrane Collaboration should consider adopting these methods for other drugs and whether, perhaps, to scrutinise the published reviews of prioritised drugs.

Implications for policy

These findings suggest that the current recommendations for oseltamivir as an essential medicine for the treatment of seriously ill patients or those in higher-risk groups with influenza 2009A/H1N1 need revision.^{33,34} The small benefits in symptomatic improvement and the lack of evidence for an effect on serious complications need to be balanced with the adverse effects found with these drugs in meta-analyses, especially diabetic/hyperglycaemic, renal and neuropsychiatric effects in all of those people for whom the WHO recommends its use.

Policy-makers should be cautious in interpreting and using the findings of systematic reviews including only published studies, particularly those that comprise only a portion of an entire drug trial programme or which contain only a portion of the results of trials. The current findings suggest that numerous national and international bodies may have been based on inadequate or poor-quality information.¹⁶⁵ This could be obviated by ensuring that documentary evidence relating to a trial on humans (including CSRs, regulatory documents, evidence syntheses) should be archived electronically with no statute of limitations.

Several steps are required to provide patients, clinicians and policy-makers with the most transparent assessment of the relative benefits and risks of new drugs.

Based on the length of time it has taken to provide a definitive answer on the efficacy of the NIs, the challenges in obtaining the full information and the methods that we needed to develop to conduct the evidence synthesis, we believe the main implication of our review is the need for reform of multiple components of the research and development, regulatory and assessment pathway of new drugs.

Pharmaceutical sponsors of drug trials should follow a data access and sharing procedure which is similar to that of the EMA, and sponsors should make all full CSRs available to be downloaded from their websites and shared freely once a regulatory decision has been made. Redactions should be kept to the minimum. Part of this process needs to include a full list of the entire drug development programme to avoid assessment of an incomplete set of trials. Researchers and industry employees who are listed in trial documents should be considered to have legal responsibility for the conduct and reporting of a trial.

Regulators should post an inventory of their documentary holdings on their websites with a brief description of the main content and size of each file. They should make all information available shortly after making a registration decision on a drug and within a reasonable time period. The information should be in electronic format and anonymised (i.e. participants' details should be removed to prevent each person being identified but no further).

Trial registries have improved the reporting of new trials. However, on their own they will not be adequate to resolve the problems we encountered. The completeness of trial registries needs to be tested with a random sampling procedure. Clear instructions for the reporting and updating of their content should be promulgated and penalties imposed on breaches of these procedures. Trial registration should include the original and final versions of a trial protocol, with a full declaration of dated amendments. Procedures for trial unblinding and dates of unblinding should be routinely reported. Registration should be made compulsory for all studies in which human beings are randomly assigned to experimental arms. Ethical and consent procedures for all trials should include obligations of the trial sponsor to ensure that results are made public. Failure to report the existence of a trial on humans and to make results available should be considered as an ethical breach of conduct and be subject to appropriate penalties.

Authors' note: In reviewing over 2 GB of data there is the possibility of mistakes. The authors would be grateful if readers could identify these. We promise that, if we concur, the record will be amended accordingly.

Chapter 3 Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza: a systematic review and individual patient data meta-analysis of observational studies

Abstract

Objectives

To determine the effect of oseltamivir on mortality in 2009A/H1N1 influenza patients.

Design

Systematic review of observational studies.

Data sources

Summary and individual patient data (IPD) from published observational studies.

Eligibility criteria for selecting studies

Any study of 2009A/H1N1 influenza patients reporting mortality outcomes and exposure to oseltamivir with at least 5% of patients untreated with influenza antivirals and five or more deaths overall.

Main outcome measures

Mortality.

Results

A total of 1117 studies were identified and screened, with 154 full-text articles assessed for eligibility. Of these, 30 observational studies of hospitalised patients were eligible and a total of 11,013 patients were available for qualitative synthesis. Overall there were 1301 deaths (12%) with the percentage of deaths receiving oseltamivir similar to that of survivors (83% vs. 82%). We found evidence of time-dependent bias in the summary data and the IPD. The IPD came from four studies including 3071 patients and 242 (8%) deaths. After taking account of time-dependent bias, potential confounding variables, and the competing risk of hospital discharge, analysis of the IPD showed insufficient evidence that oseltamivir reduced the risk of mortality [hazard ratio (HR) 1.03, 95% CI 0.64 to 1.65].

Conclusions

We found insufficient evidence from 30 observational studies to support oseltamivir having a protective effect on 2009A/H1N1 influenza patients for mortality. However, the included studies were observational and IPD analysis was based on only four studies without adjustment for baseline severity of illness or other drug use hence the findings should be interpreted with caution. Observational studies with time-dependent treatment exposure appear to be at a high risk of time-dependent bias unless an appropriate analysis is conducted.

Introduction

Influenza is a seasonal, mostly mild and self-limiting infection of the upper airways. Occasionally, patients with influenza develop complications, including pneumonia, encephalopathy and multiorgan failure, often requiring hospitalisation and, in a small number of cases, patients die. Influenza is mainly caused by influenza A and B viruses and the predominant subtype of viruses changes from season to season. A novel strain of influenza 2009A/H1N1 was the predominant cause of influenza infections worldwide resulting in the WHO declaring a pandemic in April 2009.

Oral oseltamivir is an antiviral and a NI. It has been used primarily in Japan and the USA prior to 2009. However, its use increased dramatically in the A/H1N1 pandemic when oseltamivir became a widespread public health intervention.¹⁶⁶

Mortality is a generally rare, but important, outcome of influenza and RCTs have not been powered to address this outcome. To our knowledge, there have been five deaths in comparative Phase II/III RCTs of oseltamivir,^{167,168} however, none of the deaths was in a patient with confirmed influenza. Reviews of observational studies of influenza 2009A/H1N1 have shown protective effects of NIs on mortality^{169–173} and oseltamivir is now listed as an essential medicine,¹⁷⁴ although there is insufficient evidence based on randomised studies to show that oseltamivir reduces complications of influenza¹⁰⁶ and case series have suggested increased mortality.^{15,141}

The objective of this systematic review was to determine the effect of oseltamivir treatment on mortality in patients with 2009A/H1N1 influenza. We focused on 2009A/H1N1 influenza specifically because WHO and others have suggested that studies of antivirals for seasonal influenza may not be relevant to the current novel form of circulating influenza,^{46,47} and current antiviral treatment policies have been largely influenced by the results of observational studies of 2009A/H1N1 influenza.

Methods

Ethics approval was not required for this research because it is a systematic review of published studies. Any study comparing oseltamivir with no treatment in patients with confirmed 2009A/H1N1 influenza and reporting mortality outcomes was eligible for inclusion. The definitions for mortality and treatment exposure were as used in the individual studies. We did not include studies where < 5% of patients or < 10 patients were untreated and studies in which fewer than five patients in total died. If there were multiple publications of the same or overlapping cohorts of patients we included the largest cohort in our review. Studies reported in languages other than English were potentially eligible for inclusion but only if data were clearly reported by mortality and treatment status. Studies that were reported in abstracts but not published in full were not eligible for inclusion. We searched MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Web of Science and Latin American and Caribbean Health Sciences Literature databases (see *Appendix 12* for details of our search strategy). We also hand-searched bibliographies from two relevant documents published by WHO^{169,175} and two previous reviews.^{171,172}

Three reviewers separately assessed the studies identified during the search and applied inclusion criteria. Any disagreements were resolved by discussion. Data from included studies were extracted and checked by a second reviewer. Variables included in the extraction were citation; study design; study setting (country, city, institution); study population (sex, age groups, types of patients, severity of disease); time period of study; how and if influenza was confirmed; number of patients (by survival status and antiviral treatment received); and timing of hospital admission and treatment from onset of symptoms.

To address the limitations of using summary information from observational studies for meta-analysis, we requested IPD from the corresponding authors of all of the included studies and kept a record of all of the correspondence that ensued (see *Appendix 13* for a template of the letters that we sent to the corresponding authors).

Our primary analysis was to compare use or non-use of oseltamivir as a binary exposure between patients with fatal and non-fatal outcome. We planned to use Cochran's Q chi-squared statistic to test for statistical heterogeneity and the I^2 statistic to estimate heterogeneity and perform a random-effects meta-analysis of the primary outcome using the method of DerSimonian and Laird.¹⁰⁷ For studies with no events in one of the treatment groups we added a continuity correction of one event to all four cells of the study to enable estimation of ORs. Small study effects were intended to be formally assessed using the method of Harbord *et al.*¹⁷⁶ and investigated using a funnel plot. In fact we used the method of Rucker *et al.*¹⁷⁷ to test for small studies effect as a result of their method of moments test being the only one we could find that is appropriate when heterogeneity is substantial ($\tau^2 > 0.1$). The Meta-analysis of Observational Studies in Epidemiology guidelines were followed in the reporting of this systematic review.¹⁷⁸ A protocol outlining our proposed study is available from: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002245.

In the subgroup of studies for which we obtained IPD we planned to investigate the time-dependent effect of oseltamivir on mortality (by fitting treatment as a time-dependent exposure in a Cox regression model), adjust for potential confounding variables and identify predictors of treatment using logistic regression. A detailed example of the methodology we used for fitting a time-dependent variable in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) is provided in the following web link: http://support.sas.com/documentation/cdl/en/statug/63347/HTML/default/viewer.htm#statug_phreg_sect049.htm. Analysis 1 is appropriate for our study because we had one time-dependent exposure variable and a number of baseline covariates. Potential confounding variables that were investigated included patient comorbidities (respiratory, cancer, obesity, heart disease, infection, immunosuppression, diabetes, neurological), age and time from onset of symptoms to hospital presentation. After taking account of time-dependent bias (using proper hazard-based analyses for which oseltamivir is included as a time-dependent exposure) and missing data (using multiple imputation and adjusting for potential confounding variables), we planned to report the overall estimate of treatment effect of oseltamivir on mortality, as well as the treatment effect by the timing of treatment categorised into early (≤ 2 days from onset of symptoms) or late (> 2 days from onset of symptoms). Survival analyses were stratified by study, and logistic models were adjusted for study. Multivariable analysis was conducted when all potential confounders were included in the models. Multiple imputation was implemented in a sensitivity analysis to assess the potential influence of missing data using *proc mi* and *proc mianalyze* commands in SAS. We specified multivariate imputation by a fully conditional specification method using regression models that we developed for predicting the missing data and created 20 imputed data sets. Covariates included in the regression models were mortality status, age, study, treatment group, time from onset to presentation and comorbidities (as detailed above).

On the basis of a recommendation by Wolkewitz and Schumacher,¹⁷⁹ we conducted competing risks survival analysis on the IPD, for which the competing risks were death and hospital discharge. Wolkewitz and Schumacher¹⁷⁹ suggest that a fundamental assumption in survival analysis is that the death hazard remains the same after censoring. This may be violated because discharged patients are usually in a better health condition than patients who remain in hospital. Hence, discharge from hospital should be directly modelled and treated as a competing event for dying in hospital. We performed competing risks analysis using the method of Fine and Gray¹⁸⁰ on the three cohorts that provided data on hospital discharge, with adjustment for all potential confounders but no imputation for missing data. Oseltamivir treatment was fitted as a time-dependent exposure because time-dependent bias may also occur for hospital discharge because, for example, patients who recover quickly may not get the opportunity for antiviral treatment.

Results

On the basis of searches conducted on 15–18 February 2013, we identified 1107 potential studies for inclusion. We identified a further 10 studies through hand-searching. After assessing the abstracts of these studies, we agreed that 154 full manuscripts were required for further assessment. Of these 154 full manuscripts, 124 were excluded for the reasons given in *Figure 16* and references are provided in *Appendix 14*. We initially excluded 18 studies because they did not present a breakdown of numbers of patients dying as a

result of oseltamivir exposure. We wrote to the corresponding authors of these studies requesting this additional summary data and received replies from 12, of which six provided data that we were able to use. In total, 30 studies^{181–210} are included in the qualitative synthesis (Table 16 and see Figure 16).

Quality of the included studies

We included observational studies that reported on series of cases with laboratory-confirmed 2009A/H1N1 influenza. There were no randomised or prospective cohort studies or case-control studies comparing death or severe cases with matched uncomplicated patients despite the call for this type of study.^{211,212} Table 16 shows information on the design characteristics of the included studies and Table 17 provides details on outcomes and analysis methods used. The proportion of patients treated in the studies ranged from 35% to 94%, with a median of 82%.

Although all 30 studies classified patients by treatment exposure, only two defined it: one as 'at least one dose of oseltamivir'¹⁸¹ and the other as 'at least one day of treatment'¹⁸² [although it was unclear how they classified patients who received one dose only; there were 26 such patients excluded from the study [Iratxe Puebla, PLOS ONE journal editor, 7 August 2012, personal e-mail communication]]. It is unknown how many other studies failed to report excluded patients but we note that a number of studies had missing information on mortality status and/or treatment status (for 200 patients in one study,¹⁸³ for which missing data were more common in patients with less-severe disease), whereas other studies reported complete information. None of the included studies reported over-the-counter medication use prior to

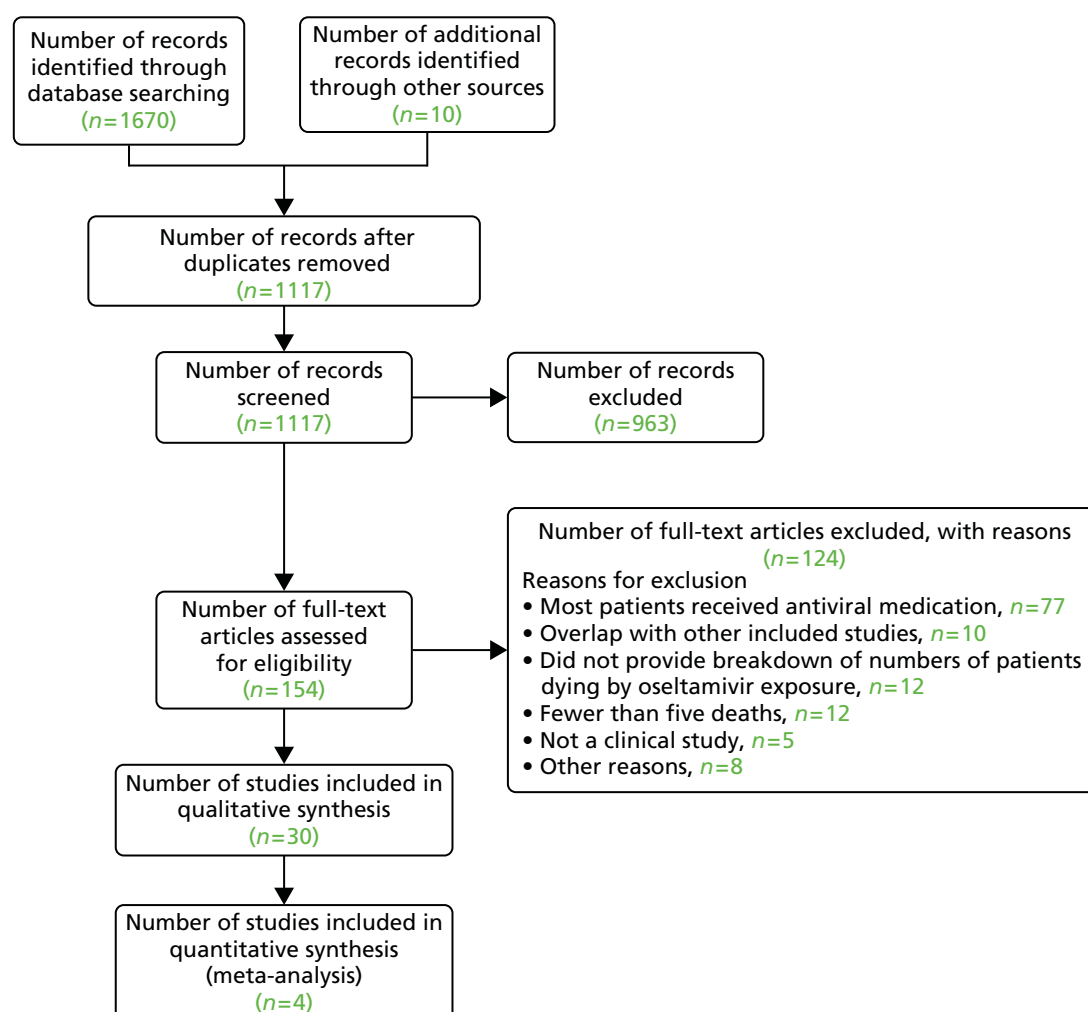


FIGURE 16 Flow diagram showing process for inclusion and analysis of observational studies examining the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza.

TABLE 16 Characteristics of the 30 included studies

Study	Setting and population	Time period	Definition for death	Description of treatment exposure	Drug use before admission
Siston <i>et al.</i> ¹⁸³	USA, pregnant women	April to December 2009	Maternal influenza deaths	Antiviral (492/496 received oseltamivir)	Not reported
Louie <i>et al.</i> ¹⁸¹	California, all ages, critically ill	3 April 2009 to 10 August 2010	Died from pandemic H1N1 infection	One dose of antiviral (1671/1675 received oseltamivir) ^a	Not reported
Jain <i>et al.</i> ¹⁸⁹	USA, all ages, hospitalised	April to June 2009	Not reported	Antiviral (188/200 received oseltamivir)	Antiviral, antibiotic
Farias <i>et al.</i> ¹⁹⁰	Argentina, children, critical	15 June to 31 July 2009	Mortality at 28 days	Oseltamivir	Not reported
Yang <i>et al.</i> ¹⁹¹	Beijing, all ages, hospitalised	Up to 31 December 2009	Cause of death 2009 H1N1 influenza	NI	Not reported
Altmann <i>et al.</i> ¹⁸⁵	Germany, children, critically ill	August 2009 to 30 April 2010	Not reported	Oseltamivir	Not reported
Enstone <i>et al.</i> ¹⁹²	UK, all ages, hospitalised	11 May 2009 to 31 January 2010	Deaths attributed to pandemic (H1N1) 2009	Received antiviral as inpatients	Patients infected in hospital
Dominguez-Cherit <i>et al.</i> ¹⁸⁴	Mexico, all ages, critically ill	24 March to 1 June 2009	ICU and hospital mortality at 14, 28, 60 days	NI (44/45 received oseltamivir)	Not reported
Kumar <i>et al.</i> ¹⁸⁷	Canada, adults, critically ill	16 April to 12 August 2009	28- and 90-day mortality	Oseltamivir	Not reported
Nguyen-Van-Tam <i>et al.</i> ¹⁸⁶	UK, all ages, hospitalised	27 April to 30 September 2009 ^b	In-hospital death	Oseltamivir	Antiviral
Chitnis <i>et al.</i> ¹⁹³	Wisconsin, USA, all ages, hospitalised	23 April 23 to 15 August 2009	Not reported	Antiviral (99% got oseltamivir)	Not reported
ANZIC ¹⁹⁴	Australasia, pregnant women, intensive care	1 June to 31 August 2009	Maternal death	Oseltamivir	Not reported
Yung <i>et al.</i> ¹⁹⁵	Australasia	From 1 June to 31 August 2009	In-hospital death	Oseltamivir	Not reported
Javadi <i>et al.</i> ¹⁹⁶	Iran, all ages, hospitalised	September 2009 to February 2010	Not reported	Oseltamivir	Not reported
Miranda-Choque <i>et al.</i> ¹⁹⁷	Peru, children, hospitalised	June to September 2009	Death related to pandemic influenza	Oseltamivir	Antibiotics
Poepl <i>et al.</i> ¹⁹⁸	Austria, all ages, hospitalised	20 September 2009 to 2 February 2010	In-hospital death	Oseltamivir	Not reported
Riquelme <i>et al.</i> ¹⁹⁹	International, all ages, hospitalised	April to October 2009	In-hospital all-cause mortality	Oseltamivir	Not reported
Yokota <i>et al.</i> ²⁰⁰	Brazil, all ages, hospitalised	July 2009	Death caused by pandemic (H1N1) 2009	Oseltamivir	Oseltamivir
Thompson <i>et al.</i> ¹⁸⁸	USA, all ages, hospitalised	14 September 2009 to 13 January 2010	Influenza-related in-hospital death	Neuraminidase antiviral	Not reported

continued

TABLE 16 Characteristics of the 30 included studies (continued)

Study	Setting and population	Time period	Definition for death	Description of treatment exposure	Drug use before admission
Bagdure <i>et al.</i> ²⁰¹	Colorado, USA, children, hospitalised	1 May to 30 November 2009	Death in hospital or emergency room	Oseltamivir	Not reported
Blumental <i>et al.</i> ²⁰²	Belgium, children > 2 years, hospitalised ^c	1 July 2009 to 31 January 2010	Not reported but all were due to influenza	Oseltamivir	Not reported
Chemaly <i>et al.</i> ²⁰³	International, hospitalised cancer patients	During the 2009–10 H1N1 pandemic	Death within 60 days of onset of symptoms	Oseltamivir	Not reported
Çiftçi <i>et al.</i> ²⁰⁴	Turkey, children, hospitalised	17 July 2009 to 10 February 2010	Not reported but causes described	Oseltamivir	Not reported
del Rosal <i>et al.</i> ²⁰⁵	Spain, children, hospitalised	1 May to 30 November 2009	Not reported but causes described	Oseltamivir	Not reported
Kusznierz <i>et al.</i> ²⁰⁶	Argentina, all ages, hospitalised	May to December 2009	Not reported	Oseltamivir	Not reported
Mickienė <i>et al.</i> ²⁰⁷	Lithuania, adults, hospitalised	1 November 2009 to 15 March 2010	Not reported	Antiviral (all received oseltamivir)	Not reported
Moretti <i>et al.</i> ²⁰⁸	Brazil, all ages, hospitalised	28 April to 31 December 2009	Not reported	Oseltamivir	Not reported
Brink <i>et al.</i> ²⁰⁹	Sweden, all ages, critically ill	August 2009 to February 2010	Mortality at 28 and 90 days after admission	Oseltamivir	Oseltamivir, antibiotics
Rahamat-Langendoen <i>et al.</i> ²¹⁰	Netherlands, all ages, hospitalised	June 2009 to July 2010	Not reported	Oseltamivir	Not reported
Yang <i>et al.</i> ¹⁸²	China, children, hospitalised with pneumonia ^d	1 September to 31 December 2009	In-hospital and 60-day mortality	1-day oseltamivir ^a	Not reported

ICU, intensive care unit.

a Data on a larger cohort of patients were supplied by the corresponding author.

b A second wave of patients was also included in the data supplied by the corresponding author.

c Cohort of < 2 years was not included as there were no deaths.

d Adult cohort not included as > 95% received oseltamivir.

TABLE 17 Details on timing of admission and treatment, numbers and percentages of patients with oseltamivir exposure by survival status, number of patients not included in mortality breakdown and analysis methods for the 30 included studies

Study	Time from symptom onset to admission ^a	Time from symptom onset to treatment ^a	Time from admission to treatment ^a	Oseltamivir exposure for deaths, n/N (%)	Oseltamivir exposure for survivors, n/N (%)	Not included because of missing data	Statistical analysis method used
Siston <i>et al.</i> ¹⁸³	Not reported	2 (–2 to 21) ^b	Not reported	25/30 (83)	471/545 (86)	200 patients	Mantel–Haenszel test, Fisher's exact test
Louie <i>et al.</i> ¹⁸¹	3 (0–42)	4 (0–52)	Not reported	416/492 (85)	1260/1367 (92)	91 patients	Chi-squared test, Fisher's exact test, Cochran–Armitage test
Jain <i>et al.</i> ¹⁸⁹	3 (0–18)	3 (0–29)	46% after admission	17/19 (89)	183/249 (73)	4 patients	Multivariate logistic regression
Farias <i>et al.</i> ¹⁹⁰	Not reported	Not reported	86% within 24 hours	52/57 (91)	83/90 (92)	0 patients	Multivariate logistic regression
Yang <i>et al.</i> ¹⁹¹	30% after 48 hours	71% not within 48 hours	Not reported	54/69 (78)	355/436 (81)	112 patients	Multivariate logistic regression
Altmann <i>et al.</i> ¹⁸⁵	2 (IQR 1–5)	4 (IQR 1–7)	Not reported	7/10 (70)	44/74 (59)	9 patients	Logistic regression
Enstone <i>et al.</i> ¹⁹²	Not applicable	Range 0–8	Not applicable	5/6 (83)	15/20 (75)	4 patients	No statistical analysis performed
Dominguez-Cherit <i>et al.</i> ¹⁸⁴	6 (IQR 4–8)	Not reported	Not reported	14/18 (78)	31/34 (91)	6 patients	Multiple logistic regression, Kaplan–Meier
Kumar <i>et al.</i> ¹⁸⁷	4 (IQR 2–7)	Not reported	Not reported	105/117 (90)	435/461 (94)	23 patients	No analysis by treatment performed
Nguyen-Van-Tam <i>et al.</i> ¹⁸⁶	2 (0–33)	Not reported	Not reported	60/80 (75)	1023/1440 (71)	0 patients	Multivariable logistic regression
Chitnis <i>et al.</i> ¹⁹³	50% < 48 hours	38% within 48 hours	77% within 24 hours	9/11 (82)	206/239 (86)	2 patients	Chi-squared test, Fisher's exact test, Mantel–Haenszel test

continued

TABLE 17 Details on timing of admission and treatment, numbers and percentages of patients with oseltamivir exposure by survival status, number of patients not included in mortality breakdown and analysis methods for the 30 included studies (*continued*)

Study	Time from symptom onset to admission ^a	Time from symptom onset to treatment ^a	Time from admission to treatment ^a	Oseltamivir exposure for deaths, n/N (%)	Oseltamivir exposure for survivors, n/N (%)	Not included because of missing data	Statistical analysis method used
ANZIC ¹⁹⁴	6 (0–35)	6 (0–37)	Not reported	7/7 (100)	45/57 (79)	0 patients	Descriptive analysis
Yung <i>et al.</i> ¹⁹⁵	5 (IQR 2–8)	Not reported	Not reported	5/6 (83)	58/72 (81)	5 patients	Multivariable logistic regression
Javadi <i>et al.</i> ¹⁹⁶	Mean (range) 5 (1–15)	Not reported	Not reported	34/36 (94)	166/180 (92)	0 patients	Multivariable logistic regression
Miranda-Choque <i>et al.</i> ¹⁹⁷	5 (1–10)	Time of treatment unknown	Time of treatment unknown	11/12 (92)	50/62 (81)	0 patients	Multivariable logistic regression
Poepl <i>et al.</i> ¹⁹⁸	Not reported	Not available	Not reported	9/14 (64)	232/327 (71)	2 patients	Multivariable logistic regression
Riquelme <i>et al.</i> ¹⁹⁹	Not reported	Not reported	Not reported	40/41 (98)	193/206 (93)	0 patients	Chi-squared test, Fisher's exact test, bivariate analysis
Yokota <i>et al.</i> ²⁰⁰	5 (0–15)	Deaths 6 (1–16); survivors 5 (0–19)	Not reported	25/52 (48)	64/105 (61)	0 patients	Multivariate unconditional logistic regression
Thompson <i>et al.</i> ¹⁸⁸	Mean 2.1 days (95% CI 2.0 to 2.3 days)	Mean 3.2 days (95% CI 3.0 to 3.5 days)	Mean 1.3 days (95% CI 1.2 to 1.5 days)	23/32 (72)	646/869 (74)	25 patients	Multivariable Poisson regression
Bagdure <i>et al.</i> ²⁰¹	3 (IQR 1–5)	2 (IQR 1–4)	0 (IQR 0–1)	7/8 (88)	262/299 (88)	0 patients	Multiple logistic regression
Blumental <i>et al.</i> ²⁰²	2 (IQR 1–4)	Not reported	79% started on admission	4/5 (80)	36/110 (33)	0 patients	Chi-squared test, Fisher's exact test
Chemaly <i>et al.</i> ²⁰³	2 (0–21)	2 (0–24)	Not reported	11/11 (100)	89/104 (86)	0 patients	Survival analysis
Çiftçi <i>et al.</i> ²⁰⁴	Not reported	Median 24 hours (range 3–240 hours)	Not reported	33/35 (91)	718/786 (91)	0 patients	Chi-squared test, Fisher's exact test
del Rosal <i>et al.</i> ²⁰⁵	3 (IQR 1–5)	Not reported	Not reported	4/5 (80)	385/512 (75)	0 patients	Multiple logistic regression

Study	Time from symptom onset to admission ^a	Time from symptom onset to treatment ^a	Time from admission to treatment ^a	Oseltamivir exposure for deaths, n/N (%)	Oseltamivir exposure for survivors, n/N (%)	Not included because of missing data	Statistical analysis method used
Kusznierz <i>et al.</i> ²⁰⁶	Not reported	Mean (range) 3 (0–30)	Not reported	70/81 (86)	157/161 (97)	0 patients	Mantel–Haenszel test, chi-squared test, bivariate analysis
Mickiené <i>et al.</i> ²⁰⁷	2 (0–7)	3 (0–10)	Not reported	6/6 (100)	63/115 (55)	4 patients	Multivariate logistic regression
Moretti <i>et al.</i> ²⁰⁸	Mean 2.3 days	Mean 4 days	Not reported	7/10 (70)	59/129 (46)	0 patients	Chi-squared test, Fisher's exact test
Brink <i>et al.</i> ²⁰⁹	6 (IQR 3–7)	Not reported	Not reported	11/14 (79)	100/108 (93)	14 patients	Relative risk for death, Kaplan–Meier curves
Rahamat-Langendoen <i>et al.</i> ²¹⁰	2 (IQR 1–4)	Not reported	Not reported	7/7 (100)	58/78 (74)	0 patients	Multinomial logistic regression
Yang <i>et al.</i> ¹⁸²	Not reported	13% within 48 hours, 39% within 5 days	Not reported	7/10 (70)	485/531 (91)	0 patients	Survival analysis

IQR, interquartile range.

a Median (range) in days unless otherwise stated.

b Negative number implies prophylactic treatment.

hospital presentation. This may be important as, for example, NSAIDs have been shown to increase mortality in influenza-infected animals.²¹³

Although a number of the included studies conducted analyses adjusting for potential confounding variables, such as patient comorbidities, they used logistic regression or standard survival analysis, which may not be appropriate for observational studies in which treatment exposure is time dependent. This type of analysis misallocates the time from initiation of the study (e.g. hospital admission) to start of antiviral treatment and leads to time-dependent bias. Beyersmann *et al.*²¹⁴ provide mathematical proof that analyses which ignore the time-dependent nature of an exposure variable lead to biased estimates of treatment effect in favour of treatment. Time-dependent bias is also referred to as immortal time bias,²¹⁵ survivor treatment selection bias²¹⁶ and survival bias.²¹⁷ It causes selection bias because patients who die early do not get an opportunity to receive treatment. In addition, patients who are extremely sick may not be given the opportunity to receive treatment because other more critical procedures take priority. Only two of the included studies^{182,184} attempted to take account of time-dependent bias but they appeared to have used flawed approaches. One study excluded all deaths within 3 days of onset of symptoms and the other obtained results that appear incorrect because their analysis – taking into account time-dependent bias – increased the treatment effect in favour of oseltamivir. Only six studies reported data on time from hospital admission to treatment initiation (see *Table 17*). Beyersmann *et al.*²¹⁴ suggest that time-dependent bias can be avoided by proper hazard-based analyses. See *Appendix 15* for a detailed description and example of time-dependent bias.

Analysis of summary data from included studies

Table 17 shows a summary of the numbers and percentages of patients with oseltamivir exposure by survival status for each of the 30 included studies. In total there are 11,013 patients included and 1301 deaths (12%). Overall, the percentage receiving oseltamivir among deceased patients ($1085/1301 = 83\%$) was similar to the percentage receiving oseltamivir among survivors ($7918/9712 = 82\%$). Meta-analysis of the included studies showed moderate heterogeneity [$I^2 = 44\%$, $\chi^2 = 51.93$, degrees of freedom (df) = 29, $p = 0.006$, $\tau^2 = 0.217$] and no evidence of small study effects ($p = 0.25$). *Figure 17* shows a funnel plot of the 30 included studies.

To investigate heterogeneity we conducted a random-effects metaregression using the *metareg* command in Stata/IC. Factors investigated included age group (adults vs. children), severity of illness (critically ill vs. hospitalised), log-odds of death (another measure of severity of illness) and log-odds of treatment. This last factor was included to investigate the potential effect of time-dependent bias on treatment effects. If time-dependent bias is apparent then we would expect it to have a greater influence in cohorts that had higher odds of treatment. This is because if few patients were untreated then patients dying before initiation of treatment would tend to have a large influence on the odds of patients dying in the untreated group. Results showed no effect of age group ($p = 0.40$) or severity of illness ($p = 0.38$), but evidence of an effect of log-odds of death ($p = 0.024$) when, as odds of death increases, the treatment effect in favour of oseltamivir increases, and log-odds of treatment ($p = 0.003$), when, as odds of treatment increases, the treatment effect in favour of oseltamivir increases. These effects appear to be independent as p -values in multivariable analysis are 0.031 and 0.006, respectively.

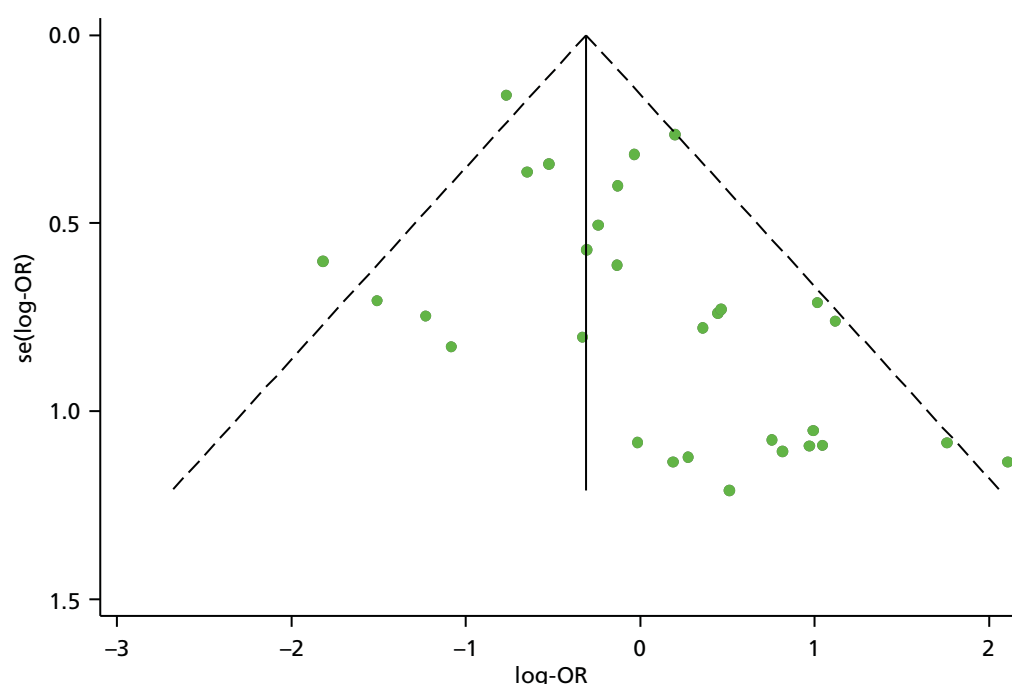


FIGURE 17 Funnel plot of the 30 included studies. Please note that the pseudo 95% confidence limits are shown by the dotted lines. The funnel shape, bounded by the confidence limits, represents the expected distribution of studies where, assuming no heterogeneity, 95% of the treatment effect estimates should lie.

To illustrate these effects we conducted subgroup analysis by odds of treatment: ' < 5 ' compared with ' ≥ 5 ' and percentage of death: ' $< 10\%$ ' compared with ' $\geq 10\%$ '. An odds of treatment of ' ≥ 5 ' equates to a percentage of $\geq 83.3\%$. Results show treatment effect is in favour of oseltamivir and more heterogeneous in cohorts when odds of treatment were ' ≥ 5 '. Conversely, in cohorts for which odds were ' < 5 ', heterogeneity is smaller and overall effect is in favour of no treatment (*Figure 18*). Similarly, treatment effect is in favour of oseltamivir and more heterogeneous in cohorts in which percentage of death was $\geq 10\%$; conversely, in cohorts in which the percentage is $< 10\%$, heterogeneity is smaller and overall effect is in favour of no treatment (*Figure 19*).

Meta-analysis of individual patient data

We were able to obtain IPD from four included studies.^{185–188} One was a German study of 93 critically ill children;¹⁸⁵ another was a UK study of 1520 hospitalised patients of all ages;¹⁸⁶ another was a Canadian study¹⁸⁷ of 605 critically ill adults; and the last study¹⁸⁸ was a US study of 926 hospitalised patients of all ages. After removing data from patients who received zanamivir and patients with missing death status ($n = 73$, 2%), we had data for 3071 patients, of whom 242 (8%) died, 1803 (59%) were discharged, 140 (4%) remained in hospital and 886 (29%) had missing date of discharge. Details of responses and non-responses from corresponding authors of included studies to our request for IPD are shown in *Table 18*.

In *Table 19* we present results of analysis of our primary outcome using five different methods. The first is logistic regression; the second is standard Cox regression; the third is Cox regression including treatment as a time-dependent exposure (td-Cox); the fourth is td-Cox with inclusion of potential confounders as covariates; and the fifth is td-Cox with inclusion of covariates as well as imputing missing time from hospital admission to death/discharge (for which 33% of values are missing, mainly due to the US study not providing date of discharge for survivors), time from hospital admission to oseltamivir exposure (for which 10% of values of the patients treated with oseltamivir are missing) and time from onset of symptoms to hospital admission (16% missing). The percentages of missing data were smaller for the deaths than the survivors (0.4% vs. 36% for time to death/discharge for example), suggesting that data collection was more thorough for patients who died.

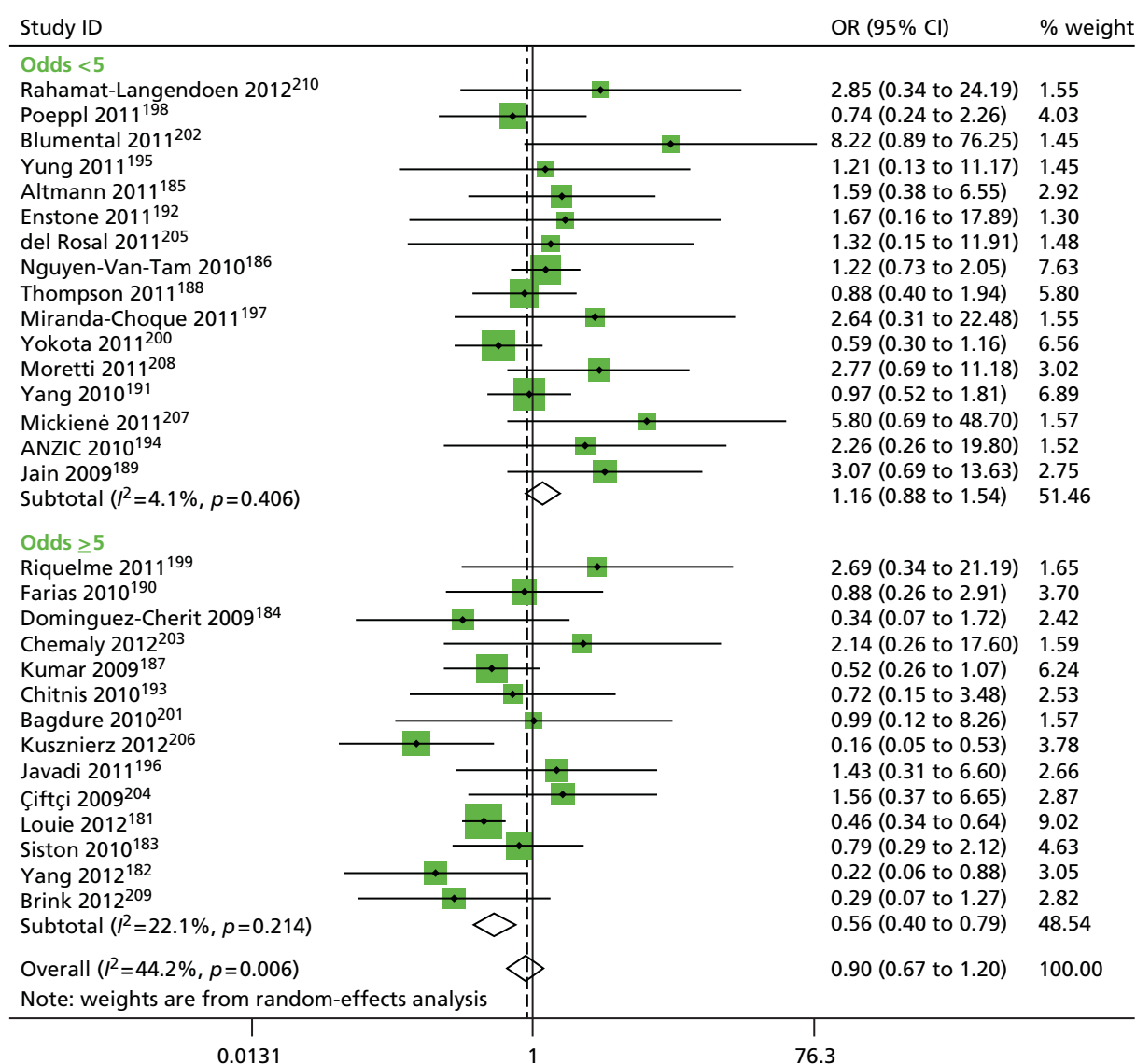


FIGURE 18 Meta-analysis of included studies by odds of treatment with oseltamivir.

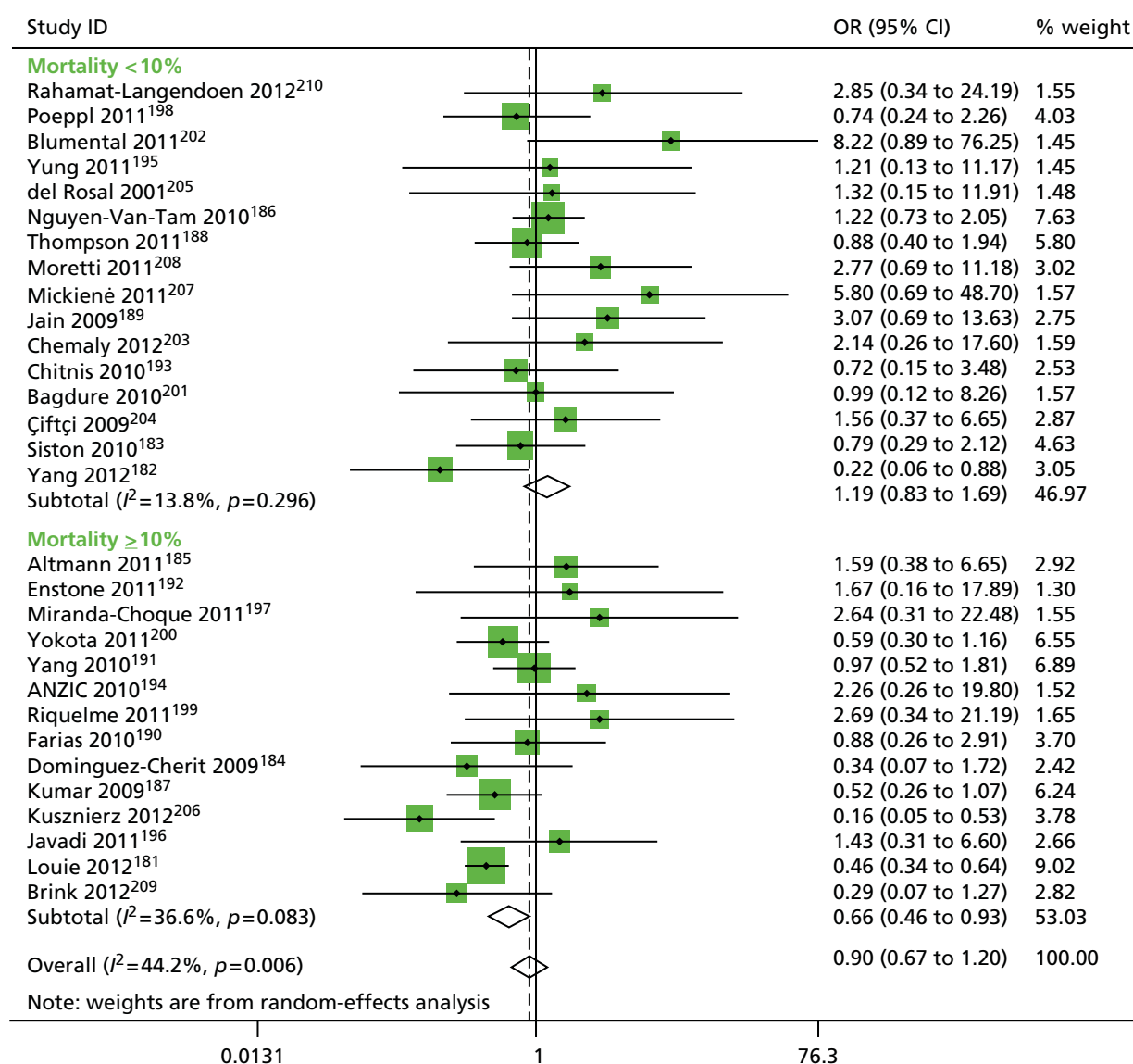


FIGURE 19 Meta-analysis of included studies by proportion of death.

TABLE 18 Responses and non-responses from corresponding authors of included studies to our request for IPD

Outcome from our request	Number of studies
Obtained IPD	4
No response to request	20
Response to our request but did not provide IPD ^a	6

a Reasons given for not providing IPD were as follows:

- 'We have no variables you need. We are epidemiologists, we didn't collect clinical data.'
- 'Unfortunately, the dataset is currently being used for a similar project.'
- 'Unfortunately we just didn't collect the data to be able to make a contribution.'
- 'We will not be able to contribute this time due to current overload of work.'
- 'The information we collected is less detailed than what you ask for.'
- 'Unfortunately it will be difficult to provide you the data as this was a multi-institutional study with centres from outside the US'.

TABLE 19 Results of analysis of primary outcome of death by oseltamivir exposure

Method	Estimate ^a	95% CI	p-value
1. Logistic regression	0.93	0.65 to 1.33	0.71
2. Standard Cox regression ^b	0.75	0.51 to 1.10	0.14
3. Cox regression with time-dependent treatment exposure (td-Cox) ^b	1.11	0.75 to 1.65	0.59
4. td-Cox adjusting for covariates ^b	1.10	0.74 to 1.63	0.64
5. td-Cox with imputation and adjusting for covariates	1.11	0.77 to 1.62	0.57

a OR for logistic regression; HR for all other analyses.
b Based on the three studies for which date of discharge for survivors was available.

Results show that when the time-dependent nature of treatment is taken into account appropriately the treatment effects change direction, although none of the results is statistically significant. Adjusting for potential confounders and imputing missing data made little difference to the results. *Table 20* shows results of the first three analysis methods by study, and a detailed analysis of the Canadian study,¹⁸⁷ shown in *Appendix 15*, further illustrates why the time-dependent nature of treatment needs to be taken account of appropriately. This study was used for illustration because it had the most deaths and 93% of patients were treated, hence we would expect time-dependent bias to be large. However, bias is also apparent in the other studies if treatment is incorrectly assumed to be time independent (see *Table 20*). *Table 21* shows distributions of potential confounding variables by treatment received stratified by study with *p*-values based on the chi-squared test. Detailed examination suggests a possible explanation for the reason oseltamivir is associated with greater risk of mortality in the Altmann *et al.*¹⁸⁵ and Nguyen-Van-Tam *et al.*¹⁸⁶ studies. In these two studies,^{185,186} comorbidities are generally more prevalent in the group that received treatment.

In *Table 22* we show the variables that were associated with oseltamivir treatment. Respiratory and neurological comorbidities, as well as cancer, were all associated with increased odds of treatment, whereas the ages of < 20 years and > 64 years, as well as missing time from symptom onset to hospital presentation, were associated with lower odds of treatment. Early presentation was not associated with increased odds of treatment. In multivariable competing risks analysis, respiratory comorbidity was protective for mortality irrespective of exposure to treatment (HR 0.60, 95% CI 0.43 to 0.84) and each 10 years increase in age was associated with increased risk of death by 22% (95% CI 10% to 35%). Respiratory comorbidity was also associated with 15% (95% CI 3% to 28%) increased likelihood of discharge suggesting despite the comorbidity these patients had a good prognosis. Furthermore, a two-sample *t*-test showed respiratory comorbidity was associated with slightly lower Acute Physiology and Chronic Health Evaluation (APACHE) II scores in the Kumar *et al.*¹⁸⁷ study [mean (SD) 20 (10)¹⁰ vs. 22 (10);¹⁰ *p* = 0.014].

The results of mortality analyses by timing of treatment (*Table 23*) further illustrate the importance of appropriate analysis of a time-dependent treatment exposure. Logistic regression shows a statistically significant reduced odds of death associated with early treatment compared with no treatment, and estimates from standard Cox regression suggest treatment reduces risk of death compared with no treatment, although the result is not statistically significant. However, when time-dependent exposure to treatment is included appropriately in the Cox model, the results show no evidence treatment is beneficial. There is a suggestion that patients receiving late treatment do worse than those who received early treatment; however, this can be at least partially explained by the patients receiving late treatment having worse prognosis due to being older and having increased likelihood of a number of comorbidities, including infection, cardiovascular, diabetes and obesity (*Table 24*).

TABLE 20 Results of IPD analysis by study

Study	Number of patients	Age in years ^a	Days admission to treatment ^a	Percentage treated	Percentage died	OR from logistic regression	HR ^b from Cox regression	HR ^c from td-Cox regression
Altmann <i>et al.</i> ¹⁸⁵	88	5 (0–14)	0.85 (0–6)	60	16	1.23	1.36	1.67
Nguyen-Van-Tam <i>et al.</i> ¹⁸⁶	1480	29 (0–95)	1.7 (0–79)	73	5	1.13	0.84	1.22
Kumar <i>et al.</i> ¹⁸⁷	583	47 (19–92)	0.62 (0–45)	93	20	0.54	0.52	0.87
^a Thompson <i>et al.</i> ¹⁸⁸	936	30 (0–02)	1 (0–34)	74	4	0.99	^d	^d
^a Mean (range). ^b Time-independent treatment exposure. ^c Time-dependent treatment exposure. ^d Discharge date not available for survivors.								

TABLE 21 Comorbidities and presentation timing by treatment and study

Variable	No-treatment group, <i>n</i> (%)	Oseltamivir group, <i>n</i> (%)	<i>p</i> -value
Altmann et al.¹⁸⁵			
Age group (years)			
< 20	35 (100)	53 (100)	–
20–64	0 (0)	0 (0)	
65+	0 (0)	0 (0)	
Presentation timing			
< 2 days	17 (48)	21 (40)	0.65
> 2 days	15 (43)	28 (53)	
Missing	3 (9)	4 (7)	
Infection	25 (71)	49 (92)	0.019
Cardiovascular	5 (14)	6 (11)	0.93
Neurological	17 (49)	37 (70)	0.075
Cancer	1 (3)	4 (8)	0.65
Immunosuppression	3 (9)	8 (15)	0.56
Respiratory	13 (37)	32 (60)	0.055
Obesity	0 (0)	0 (0)	–
Diabetes	0 (0)	0 (0)	–
Nguyen-Van-Tam et al.¹⁸⁶			
Age group (years)			
< 20	216 (54)	355 (33)	< 0.0001
20–64	163 (41)	656 (61)	
65+	18 (5)	72 (7)	
Presentation timing			
< 2 days	140 (35)	467 (43)	< 0.0001
> 2 days	97 (25)	346 (32)	
Missing	160 (40)	270 (25)	
Infection	–	–	–
Cardiovascular	31 (8)	159 (15)	0.0006
Neurological	39 (10)	170 (16)	0.005
Cancer	8 (2)	43 (4)	0.096
Immunosuppression	10 (3)	34 (3)	0.65
Respiratory	115 (29)	496 (46)	< 0.0001
Obesity	9 (2)	40 (4)	0.23
Diabetes	24 (6)	77 (7)	0.55

TABLE 21 Comorbidities and presentation timing by treatment and study (*continued*)

Variable	No-treatment group, <i>n</i> (%)	Oseltamivir group, <i>n</i> (%)	<i>p</i> -value
Kumar et al.¹⁸⁷			
Age group (years)			
< 20	0 (0)	8 (2)	0.23
20–64	32 (82)	480 (88)	
65+	7 (18)	56 (10)	
Presentation timing			
< 2 days	11 (28)	135 (25)	0.26
> 2 days	26 (67)	402 (74)	
Missing	2 (5)	7 (1)	
Infection	22 (56)	332 (61)	0.69
Cardiovascular	16 (41)	215 (40)	0.99
Neurological	1 (3)	30 (6)	0.67
Cancer	0 (0)	36 (7)	0.19
Immunosuppression	2 (5)	33 (6)	1.0
Respiratory	18 (46)	298 (55)	0.38
Obesity	8 (21)	135 (25)	0.68
Diabetes	9 (23)	138 (25)	0.90
Thompson et al.¹⁸⁸			
Age group (years)			
< 20	96 (40)	292 (43)	0.001
20–64	104 (43)	327 (48)	
65+	42 (17)	59 (9)	
Presentation timing			
< 2 days	137 (57)	362 (53)	0.048
> 2 days	90 (37)	295 (44)	
Missing	15 (6)	21 (3)	
Infection	–	–	–
Cardiovascular	46 (19)	94 (14)	0.071
Neurological	23 (10)	79 (12)	0.43
Cancer	3 (1)	22 (3)	0.16
Immunosuppression	10 (4)	73 (11)	0.003
Respiratory	89 (37)	275 (41)	0.34
Obesity	42 (17)	149 (22)	0.15
Diabetes	50 (21)	101 (15)	0.048

TABLE 22 Variables associated with oseltamivir treatment

Variable	OR for treatment	95% CI	p-value
Age (years)			
< 20 ^a	0.61	0.50 to 0.74	< 0.0001
> 64	0.52	0.38 to 0.72	
Time from onset of symptoms to hospital presentation ^b	0.89 (early vs. late)	0.72 to 1.09	< 0.0001
	0.44 (missing vs. late)	0.34 to 0.57	
Neurological comorbidity	1.57	1.18 to 2.09	0.002
Cancer	2.93	1.55 to 5.54	0.001
Respiratory comorbidity	1.56	1.30 to 1.88	< 0.0001
a Reference group: age 20–64 years.			
b Early ≤ 2 days; late > 2 days; missing = timing of treatment missing.			

TABLE 23 Results of analysis of primary outcome of death by timing of oseltamivir exposure

Method	Estimate ^{a,b}	95% CI	p-value
1. Logistic regression	0.54 (early vs. none)	0.33 to 0.89	0.008
	1.12 (late vs. none)	0.76 to 1.66	
	1.11 (missing vs. none)	0.73 to 1.71	
2. Standard Cox regression ^c	0.68 (early vs. none)	0.40 to 1.16	0.12
	0.85 (late vs. none)	0.56 to 1.29	
	0.69 (missing vs. none)	0.44 to 1.06	
3. Cox regression with time-dependent treatment exposure (td-Cox) ^c	0.89 (early vs. none)	0.52 to 1.52	0.69
	1.15 (late vs. none)	0.74 to 1.77	
	1.25 (missing vs. none)	0.72 to 2.16	
4. td-Cox adjusting for covariates ^c	0.92 (early vs. none)	0.54 to 1.57	0.76
	1.16 (late vs. none)	0.75 to 1.79	
	1.14 (missing vs. none)	0.65 to 1.99	
5. td-Cox with imputation and adjusting for covariates	1.10 (early vs. none)	0.60 to 1.47	0.64
	1.28 (late vs. none)	0.86 to 1.90	
a OR for logistic regression; HR for all other analyses.			
b Early ≤ 2 days; late > 2 days; missing = timing of treatment missing; none = no treatment given.			
c Based on the three studies for which date of discharge for survivors was available.			

TABLE 24 Comorbidities by treatment timing

Variable	Early treatment group, <i>n</i> (%)	Late treatment group, <i>n</i> (%)	<i>p</i> -value
Age group (years)			
< 20	313 (42)	237 (23)	< 0.0001
20–64	375 (51)	686 (68)	
65+	55 (7)	90 (9)	
Infection ^a	80 (19)	201 (30)	0.0001
Cardiovascular	106 (14)	235 (23)	< 0.0001
Neurological	101 (14)	133 (13)	0.83
Cancer	24 (3)	42 (4)	0.38
Immunosuppression	51 (7)	63 (6)	0.66
Respiratory	344 (46)	486 (48)	0.52
Obesity	87 (12)	179 (18)	0.0007
Diabetes	78 (11)	159 (16)	0.002

^a Data not provided by Nguyen-Van-Tam *et al.*¹⁸⁶

Competing risks survival analysis on the three cohorts that provided date of hospital discharge showed insufficient evidence that oseltamivir is associated with mortality (HR 1.03, 95% CI 0.64 to 1.65) but the results showed an association with increased likelihood of hospital discharge for survivors (HR 1.44, 95% CI 1.26 to 1.64).

Discussion

We have systematically reviewed the literature on the relationship between mortality from influenza 2009A/H1N1 and oseltamivir exposure. We included 30 studies in our review and obtained IPD for four of those studies. Analysis of both the summary data of the 30 studies, as well as the IPD, showed evidence of time-dependent bias, with bias increasing with increasing odds of treatment. Analysis of the IPD using Cox regression, with treatment exposure included as a time-dependent variable, adjusting for covariates and imputing missing data, has shown insufficient evidence that oseltamivir is associated with a reduction in mortality. Furthermore, early treatment with oseltamivir did not appear to have a beneficial effect on survival compared with no treatment. Competing risks survival analysis also showed insufficient evidence of association of treatment with mortality but the results showed an association with increased likelihood of hospital discharge for survivors.

Analysis of the IPD using logistic regression included 3071 patients and showed an OR of 0.93, whereas standard Cox regression on the 2056 patients with survival times gave a HR of 0.75, reflecting that untreated subjects who died did so earlier than those treated. When the time-dependent nature of oseltamivir exposure was incorporated into the Cox model, results showed a HR of 1.11, a marked difference from 0.75, illustrating the large time-dependent bias associated with standard Cox regression. After adjusting for covariates, the HR was virtually unchanged (1.10) and multiple imputation of the missing data had a negligible effect (HR 1.11). A competing risks survival analysis showed a consistent result, with a HR of 1.03 for mortality. We suggest that the competing risks analysis result may be the most appropriate because it takes into account the competing risk of discharge for treated patients, although a limitation is that it is based on only three studies because the fourth (US) study did not have data available for date of discharge.

The metaregression result that showed increasing mortality rate is associated with an increasingly favourable outcome for treatment is difficult to interpret because of the presence of time-dependent bias that cannot be quantified with access to only summary data. The metaregression result suggests that increasingly severe patients may lead to a better efficacy/toxicity trade-off of treatment. However, without the IPD it is unknown where, if anywhere, oseltamivir becomes a beneficial treatment. An alternative explanation is that cohorts with higher mortality rates were associated with greater time-dependent bias, as a greater proportion of patients died before they had the opportunity to receive antiviral treatment.

Confounding by indication is a possibility in observational studies and it is possible that sicker patients were more likely to get treatment. We were not able to adjust for severity of illness at baseline, as this information was not generally available for the included studies. However, APACHE II score was available for Kumar *et al.*¹⁸⁷ and comparison of treated with untreated patients showed no evidence of a difference in severity of illness (see *Appendix 15*). Prevalence of some comorbidities appeared higher for treated patients than untreated patients for two of the studies for which we had IPD, and this is reflected in the higher odds of mortality for treated patients in those studies. We adjusted for variables associated with treatment in the IPD analysis and this made little difference to the results. In addition, the competing risks survival analysis showed that treated patients who survived were discharged sooner than untreated patients. It is plausible that late treatment could indicate a sicker patient, as normally it takes time for patients to become severely ill. Patients who were treated late were older, and had greater prevalence of some comorbidities than patients who were treated early. This could at least partially explain why these patients had an increased risk of mortality.

Our results are different from those of three other recent reviews. Hsu *et al.*¹⁷² included studies of seasonal influenza and 2009A/H1N1 influenza and based their primary analysis of mortality on three small studies of 681 patients, none of whom had 2009A/H1N1. They did not consider the time-dependent nature of treatment exposure and reported an OR of 0.23 (95% CI 0.13 to 0.43) based on summary data only. Muthuri *et al.*¹⁷¹ focused on 2009A/H1N1 influenza, included 20 studies, did not consider time-dependent treatment exposure and reported an OR of 0.72 (95% CI 0.51 to 1.01) based on summary data only. Muthuri *et al.*¹⁷⁰ conducted an analysis of almost 30,000 patients from 78 studies using IPD; of the 78 studies included, only 22 would have been eligible for our study. For example, all included patients in 27 studies received NIs and 16 studies had no mortality. It is unclear how these studies were included in a mortality comparison between NIs and no treatment because, in meta-analyses, studies with no events and studies without a control group are dropped from the analysis. Muthuri *et al.*'s crude analysis results¹⁷⁰ are consistent with ours but the results from their analysis taking into account the time-dependent treatment exposure are different and appear to be incorrect, as they result in an increased protective effect of treatment. As Beyersmann *et al.*²¹⁴ show, mathematically time-dependent bias is always in the same direction (i.e. in the direction of showing a larger protective effect of treatment than is actually the case). Furthermore, the authors' reply to criticisms of their analysis²¹⁸ shows a crude HR of 0.36 (95% CI 0.32 to 0.41) for antiviral use modelled as a time-constant exposure without taking into account clustering or immortal time bias. However, this result is logically inconsistent with the descriptive data, which show that crude mortality in the antiviral group is larger than that of the no-treatment group (9.7% vs. 9.2%).

The results of this systematic review of observational studies are consistent with a recent Cochrane review⁹ of NIs for influenza based on a full set of manufacturer compiled CSRs of RCTs and regulatory information. The Cochrane review⁹ showed no evidence that NIs reduce the risk of hospitalisation or risk of complications classified as serious or leading to study withdrawal, a result consistent with oseltamivir not having a protective effect on mortality. The likelihood of treated survivors being discharged earlier is inconsistent with these findings, but is consistent with symptomatic relief that is not specific to influenza infection. The reasons for this inconsistency is unclear.

The problem of time-dependent bias is not confined to survival outcomes. For example, Beyersmann *et al.*²¹⁴ show time-dependent bias for the effect of hospital-acquired pneumonia on hospital length of stay. Yorifuji *et al.*¹⁴⁷ show the importance of taking account of time-dependent exposure of oseltamivir appropriately in a prospective observational study of Japanese children for which the outcomes related to abnormal behaviours. In the case of observational studies of 2009A/H1N1 influenza, outcomes by oseltamivir exposure – including pneumonia, hospitalisation and intensive care unit admission – have been compared and reported^{171,172} without regard to the time-dependent nature of treatment exposure. Beyersmann *et al.*²¹⁴ state that ‘because time-dependent bias inevitably leads to erroneous findings, it is a major concern that it is common in the clinical literature’. Van Walraven *et al.*²¹⁹ surveyed the medical literature and found that ‘in medical journals, time-dependent bias is concerning common and frequently affects key factors and the study’s conclusion’. It is critical that analyses of all outcomes reported from observational studies with time-dependent exposures take account of time-dependent bias appropriately.

Strengths

We systematically searched five widely used databases over a 4-year period, as well as hand-searched relevant WHO documents and previous reviews. There were no restrictions on the type of research articles or studies considered for inclusion in the review. Studies from the Americas, UK and Europe, Australasia, Asia and the Middle East were included. We were able to obtain IPD for four studies that included > 3000 patients and more than 240 deaths. Using the IPD we were able to take account of the time-dependent nature of treatment exposure appropriately, impute missing time to event data and adjust for important covariates in the analysis. We were also able to take account of the competing risk of hospital discharge in estimating the effect of oseltamivir on mortality.

Limitations

Limitations of this review include the observational nature and quality of the included studies. All included studies were of hospitalised patients, and severity of illness of patients at baseline was not always reported. Limited information was provided on drug use prior to admission and no study reported NSAID use. Only two studies reported a definition for treatment and the comparison groups were assumed to be the subsets of patients who were not exposed to antivirals. The percentage of unexposed patients was often small (median 18%). Reasons for non-treatment with antivirals were not provided and none of the studies described a policy or criteria used for selecting patients for treatment. Our IPD analysis showed that patients with certain comorbidities were more likely to be treated, whereas children, the elderly and patients with unknown duration of symptoms were less likely to be treated.

We were able to obtain IPD for only four of the included studies, thus limiting the amount of statistical power that we had for our IPD analysis and potentially resulting in a biased subset of the 30 included studies. However, some of the responses to our request for IPD suggest critical data to assess the impact of oseltamivir on mortality were not collected. Furthermore, the IPD we obtained appears to be a representative sample of the 30 included studies as the ORs for mortality were similar for the IPD (0.93 – see *Table 19*) and the summary data (0.90 – see *Figure 19*). These estimates are also consistent with the crude OR of 0.92 reported by Muthuri *et al.*¹⁷⁰ Furthermore, the studies were from four different countries with varying mortality rates (4–20%), varying odds of treatment (60–93%) and included patients with ages from 0 to 102 years.

There were missing data for time to death/discharge and time to treatment (33% and 10% missing, respectively) in the four studies for which we had IPD. The majority of missing data for time to death/discharge was due to one study that did not report date of discharge for survivors. Analysis excluding this study showed similar results to those based on all four studies, hence we do not believe the missing time to discharge data has introduced a significant bias.

Conclusion

Our systematic review has found insufficient evidence that oseltamivir is associated with a reduced risk of mortality. However, this result is based primarily on an IPD analysis of just 4 of 30 eligible observational studies without adjustment for baseline severity of illness or other drug use. Analysis of all 30 included observational studies using summary data showed evidence of time-dependent bias that had an increasing effect with increasing odds of treatment. Observational studies with time-dependent treatment exposure are at high risk of time-dependent bias unless an appropriate analysis is conducted.

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Contributions of authors

Carl J Heneghan (Professor, Evidence-Based Medicine) amended the review protocol, applied the inclusion criteria to the zanamivir CSRs and contributed to the draft.

Igho Onakpoya (Research Fellow, Evidence-Based Practice and Pharmacovigilance) applied the inclusion criteria to the zanamivir CSRs, extracted data from the CSRs and contributed to the draft.

Mark A Jones (Senior Research Fellow, Biostatistics) amended the review protocol, arbitrated the process for inclusion of studies where necessary, performed statistical analyses and contributed to the draft.

Peter Doshi (Assistant Professor, Pharmaceutical Health Services Research) amended the review protocol, applied the inclusion criteria to the oseltamivir CSRs and contributed to the draft.

Chris B Del Mar (Professor, Public Health) amended the review protocol, screened the electronic search updates and contributed to the draft.

Rokuro Hama (Chairperson, Japan Institute of Pharmacovigilance) amended the review protocol and contributed to the draft.

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Elizabeth A Spencer (Epidemiologist) extracted data from the CSRs and contributed to the draft.

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David Nunan (Research Fellow, Evidence-Based Practice and Physical Activity) extracted data from the CSRs and contributed to the draft.

Jeremy Howick (Research Fellow, Centre for Evidence-Based Medicine) extracted data from the CSRs and contributed to the draft.

Tom Jefferson (Reviewer, Cochrane) amended the review protocol, applied the inclusion criteria to the oseltamivir CSRs and prepared the final text.

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Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. *PLOS Med* 2012;**9**:e1001201.

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Data sharing statement

The full set of CSRs for the NI Tamiflu (Oseltamivir) and Reenza (Zanamivir) produced by Roche were made available to the Cochrane collaboration for the production of their meta-analysis of neuraminidase inhibitors for preventing and treating influenza in adults and children are available at <http://datadryad.org/resource/doi:10.5061/dryad.77471>. (Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, *et al.* Data from: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Dryad Digital Repository*, 2014. <http://dx.doi.org/10.5061/dryad.77471>).

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Appendix 1 The story of A159

The 2009 review: from A047 to A159

In the midst of the A/H1N1 influenza outbreak in June 2009, the Australian and UK governments commissioned an update of our long-standing Cochrane review on NIs for influenza in (otherwise) healthy adults (known as A047). Prior to the emergence of influenza A/H1N1 in 2009, governments worldwide stockpiled nearly CHF (Swiss francs) 7.6B worth of oseltamivir.¹⁶⁶ The WHO considered antivirals for influenza important (WHO has recently added oseltamivir to the list of essential medicines^{169,174,175}). Oseltamivir and zanamivir have been prescribed for the treatment of influenza worldwide since the outbreak of 2009 A/H1N1 influenza. The review (on healthy adults) had first been published in 1999 (as A047) and was updated in 2006 and 2008. At the same time a similar review on children³² (or A046) had also been published.

As the review had been updated the previous year, we initially anticipated that the commissioned 2009 update would not require substantial effort and would probably reflect only updated pharmacovigilance data and not the incorporation of new trial evidence.⁶

In the end, the 2009 update was inconclusive regarding whether or not oseltamivir reduced the risk of complications of influenza,¹⁴ as we were unable to verify the data underlying manufacturer and government claims to this effect. The claims were based on clinical trial evidence included in a published pooled analysis of 10 manufacturer-funded clinical trials of oseltamivir for the treatment of influenza in people aged ≥ 13 years.⁴ Eight of the 10 trials in the Kaiser *et al.*⁴ pooled analysis have never been published,³¹ and their complete data sets were not available from either the authors or the manufacturers. Some of the published trials had been ghost written.⁴³ The largest of the 10 Kaiser trials (M76001³⁶), involving over 1400 people, had been briefly reported in conference abstract format but the person whose name appeared on the abstract could not recall ever presenting its results or being involved with the study.⁴³ Our early requests for data from the 10 Kaiser studies were met with an offer from Roche to sign a confidentiality agreement with an embedded secrecy clause preventing us from mentioning the existence of the agreement. The unsigned agreement can be seen at www.bmj.com/highwire/filestream/440792/field_highwire_adjunct_files/0.

At the time of publication of the 2009 update and its linked investigation by the BMJ, we were unaware of the size and depth of the oseltamivir evidence development programme. We thought it comprised around 36 trials and we expected that only a proportion of these would fit our inclusion criteria. We also did not realise the size and the level of detail that the CSRs contained.

On 31 December 2009, Roche released the core reports (or module 1s) of the 10 Kaiser trials with no legal agreement signed (only a web-based agreement that we would not share the documents with other commercial companies). After requesting Roche to provide us with the full study reports, Roche said that the module 1s were all that were needed for us to complete our job.⁶ The missing modules (or parts), numbered 3–4 according to the trial in question, contained protocols, amendments, individual listings and demographic information. It seemed to us that these documents would have contained some important additional material for understanding the trials, their design and interpretation but we were not sure.

In 2010 we started exploring the relationship between the available module 1s for the only two Kaiser trials that had been published (Doshi⁸ or Nicholson *et al.*,²²⁰ and WV15671⁵⁸ or Treanor *et al.*²²¹).

At about this time we started getting concerned that the oseltamivir trial programme was considerably larger than we first thought. Our interest was awakened by the casual discovery of a confidential 2009 Roche Tamiflu Investigator's Brochure, which was freely accessible on the web. This reported a clinical trial programme of over 60 studies. Searching for an unpublished and hitherto unseen data set requires

constructing a reasonably accurate list of all studies of the drug in question. The Roche Investigator's Brochure did not mention some studies that we were aware of and reinforced an idea that we had become clear was essential: the need to develop our own list of trials, because a single, authoritative, up-to-date and complete list of all clinical trials conducted on humans using both drugs did not seem to exist.

When thinking about our next update we decided not to use publications because the majority of treatment trial evidence for Tamiflu remained unpublished; we had found some discrepancies between CSRs and published equivalents; and, mostly, CSRs were so much more detailed and comprehensive than short journal articles, enabling a more thorough critical analysis of the trials. We also decided to expand the scope of A047 by including evidence relating to people of all ages except for immune-suppressed individuals. This, de facto, amounted to the creation of one new review (A159) with a new protocol subsuming A047 and A046. The protocol for A159 was publicly posted in December 2010.

A new source of evidence for A159

Today, the obvious source of information on CSRs would be trial registries and company websites, but most trials of both NIs were carried out before inception or wide acceptance of centralised registries and company websites. In 2009–11, company websites did not, and still do not, have extensive lists of trials with downloadable CSRs. Most people had never heard of CSRs before media coverage of our efforts.

We decided to construct our list by using multiple cross-referencing methods. We constructed a list beginning with clinical trials identified from previous review updates. To this end, we added additional trials in humans from multiple sources, including manufacturer submissions to regulators, drug product information sheets, previous published reviews, Health Technology Assessment (HTA) documents and public and manufacturers' registers,^{5,156,157,159,160} such as www.ClinicalTrials.gov and www.roche-trials.com. Regulatory documents also aided the identification of unknown trials. Finally, we also conducted traditional database and grey literature searches (see *Appendix 3*) to identify previously unknown trials.

One of the first things we learned was that to ensure that the list did not include duplicate entries, we had to assign to each trial a unique trial ID. 'Author' is not a good choice of unique trial ID, as different authors can be present across different versions of the same trial (i.e. the authors of CSRs can be different from publications arising from the same clinical trial). Nor are any other details connected to publications a good option for unique trial ID because not all studies are published. Some trials will have company-specific codes and some will have public clinical trial registry numbers, or both, or neither. To simplify recognition and terminology we used the manufacturer protocol ID as our unique trial ID.

Our list was going to be useful only if it had sufficient details to enable us to decide whether or not it met our inclusion criteria. For each unique trial ID, we gathered the following details:

1. unique trial ID
2. other IDs
3. phase of study
4. sponsor
5. short description
6. official trial title
7. first authors (name and e-mail)
8. type of trial
9. comparator
10. outcomes assessed
11. date of trial
12. study period (days)
13. population

14. number of participants planned
15. number of participants enrolled
16. number of participants completing
17. trial status (e.g. completed, ongoing or early termination)
18. publication status (a citation or understanding of why it was not published)
19. how identified (to record how the trial was discovered)
20. notes.

Once we had as complete a list of trials as possible, we contacted manufacturers and sent them our draft list, asking them to check the accuracy and completeness of our list. Roche, GSK and BioCryst all did so and, in doing so, we learned of hitherto unknown trials.

Occasionally, the existence of further unknown trials was detected weeks and months after we thought we had a 'complete' list. This may be inevitable, given that trial identification often takes place in unpredictable ways, for example while reading through detailed regulatory reports.

We engaged in prolonged correspondence with Roche and GSK, and requested a series of regulatory documents under freedom of information policies from both the FDA and EMA. No substantial comments were made by Roche on the protocol of 159, which has been publicly available in one form or another since December 2010.

Specifically, we applied to EMA under their new release policy for 26 CSRs in their holdings relating to oseltamivir and GSK's zanamivir. The result was the delivery (starting in late March 2011) of 16 CSRs, all containing modules 1 and 2 plus one complete report for oseltamivir (trial WP16263¹⁰⁴). (See table 1 in Doshi *et al.*⁶) None was available for zanamivir, as the EMA had not played a part in its market authorisation. These formed the basis for the 2012 version of A159.

At the date of completion of data searches for A159 (12 April 2011), Roche had provided us with only partial CSRs despite five requests for full CSRs. The material obtained from Roche included the first section (or so-called 'module 1' or 'core report') of a full CSR, each of which contain four to five modules (see *Appendix 9*) for the 10 oseltamivir treatment trials included in the Kaiser *et al.*⁴ meta-analysis. Not contained in the provided module 1s are trial protocols with the list of amendments and original reporting analysis plans (RAPs). These module 1s comprise 3195 pages. Roche had not made available any further material and indicated that it did not intend to answer our requests for clarification on aspects of trials and for availability of the missing parts of complete CSRs. In addition we had a 53-page report in English of the treatment trial ML16369,⁷⁶ sponsored by Shanghai Roche Pharmaceutical Ltd. Regardless of success with our requests to obtain full CSRs, we decided to update our review with available material and subsequently update it as and when additional data became available.

Our searches of publication databases did not add any significant information.

Following a change of policy at the EMA, prompted by similar efforts of the Nordic Cochrane Centre,²²² we received an additional eight CSRs (10,737 pages) in response to a FOI request. An additional 14,700 pages of further CSRs and 33 pages of regulators' comments arrived after our search deadline. All of the materials received from the EMA are related to oseltamivir. The EMA has no access to information for zanamivir, as it is a nationally authorised product in Europe (correspondence with Xavier Luria, 23 March 2011, and David Mackay, 20 July 2011). At present, we hold all of the module 1s and module 2s of oseltamivir trials we have requested. From GSK we have received the promise of IPD. Many of the CSRs used in this review were obtained via FOI requests.

We still await a FDA decision regarding similar requests sent to FDA in January 2011.

We were able to download 2673 pages of SBA documents from the FDA website, 31 from EMA and 508 pages of Japanese SBA. We indexed the content and then constructed an extended table of contents, giving a summary of each file, thereby facilitating navigation of these complex documents. Once the table of contents had been constructed, we postulated that, given the huge work involved in reviewing lots of regulatory files, including CSRs, we needed new instruments to indicate which parts were more important than others, thus focusing our efforts. We experimented with a variety of methods reported in the earlier version of the review. We have now devised and used what, for us, is a satisfactory instrument for critically assessing CSRs in their entirety. We intend to publish this separately.

The EMA releases, coupled with documents from the FDA SBA for both drugs, formed the basis for the version of A159 that we eventually published in January 2012. The review reported our efforts to get to the bottom of the issue of the effects of NIs by appraising evidence from unpublished CSRs (see *Appendix 1*) and regulatory documents containing comments and reviews. We called the body of clinical studies and regulatory comments 'regulatory information', as all of these documents are either created for, or by, regulators. To our knowledge, this was the first Cochrane review ever conducted on the basis of regulatory documents only.

Owing to funding timelines and the sizeable amount of regulatory information already available to us, we decided to review material available as at 12 April 2011. This meant reviewing FDA SBA material and core reports (module 1s) in our possession from EMA data releases received by this time.

Study selection and extraction in 2011

In 2011 our methods were a mixture of established and novel, reflecting the size of the task, our lack of experience in dealing with large amounts of very detailed regulatory information and the lack of a complete set of CSRs. For example, scanning of titles and abstracts was doubled, but selection of studies for inclusion from the list constructed during our search was quadrupled, with disagreements resolved by discussion.

For many studies we had only titles and, in some cases, a very brief description of content, thus we assigned three categories to our trials:

1. definitely included
2. definitely excluded
3. trials for which we needed further information.

We excluded studies that were definitely not meeting the inclusion criteria on the basis of the available information (e.g. the title described the trial as a pharmacokinetic study). Where appropriate we requested further information from the trials' sponsor: usually copies of the CSRs (minus participant identification) for each trial that was definitely included or for which we needed further information. We did not contact first/corresponding authors of published versions of the trials on the basis of our experience with the 2009 review.

Data extraction and management reflected the lack of established methods for reviewing regulatory material. We subdivided the extraction, appraisal and analysis of the data into a two-stage exercise, including studies in the analysis phase only if we judged their reports to be reliable and complete. To help structure the information we used CONSORT statement-based extraction forms aimed at assembling a concise version of the CSRs, which included all of the important methods, as well as defined and extracted all relevant outcomes. We colour-coded the original text to flag up uncertainty or lack of clarity or need for more information from other (then inaccessible) parts of the CSR.

During this process we excluded all six peramivir trials, as we were informed by the manufacturers that no CSRs would be available. The 2012 A159 review was based on 15 oseltamivir clinical study core reports and 10 very brief zanamivir study reports. The former came from EMA, whereas the latter had been part of a GSK submission to UK NICE, which the BMJ had passed on to us together with the SBA material. Our 2010 protocol for A159 was not very detailed on how we would handle this mass of information for the simple reason that no one had ever done it before. We quite literally were learning as we were going along, and our understanding of the structure and content of CSRs evolved. We created and tested five post-protocol hypotheses (see *Appendix 8*), which had originated from the findings in the reports. The best example was our finding of an unnaturally high (up to 80%) influenza positivity rate in treatment trials, which, in some cases, had been pooled because of lack of viral circulation. We hypothesised that screening for influenza positivity had been carried out prior to enrolment of people with ILI. This was not borne out by the evidence available to us. We know now that a far simpler explanation is more likely: careful selection of the time period for trial participant enrolment, based on when surveillance data suggested that high influenza activity led to the recruitment of small numbers of participants from each of many centres with a high likelihood of influenza positivity, but at the time we had limited information available.

The 2012 A159 review analyses were based on the ITT population, which we had found to be the only reliable analysis unit, as oseltamivir appeared to have an effect on antibody production in people with influenza, leading to an imbalance in numbers of subjects in the influenza-infected (so-called ITTI) subpopulation. This, in effect, introduced confounding in what otherwise should have been well-designed double-blind trials. The only effect that was clearly identifiable was a modest shortening of ILI symptoms by less than a day. This led us to believe that oseltamivir had an aspecific powerful effect on symptoms, not mediated by any action on influenza viruses but possibly via an anti-inflammatory mechanism. Clearly, the trials had been designed with a commercial focus in mind and some of the claims made by the manufacturer (especially on the effect on interruption of transmission and on pneumonia) were not supported by the evidence in our possession.

2012 to the present day

Soon after the publication of the review, the BMJ agreed to publish our correspondence with Roche, GSK, the EMA, the CDC and WHO, recording our attempts at retrieving the full reports without any conditions attached and to understand the basis for promotion of the drugs (especially oseltamivir) by public health bodies. The correspondence (which is hundreds of pages long) formed the basis for what then became the BMJ Open Data Campaign and a stimulus for the later AllTrials campaign. Public exposure of our efforts and copious media coverage had the direct effect of ensuring the unconditional release of 77 reports of oseltamivir of 82 studies sponsored by Roche, and the equivalent of the 30 studies we had requested from GSK. For the full correspondence, see www.bmj.com/tamiflu and www.bmj.com/relenza.

The reports (amounting to over 140,000 pages) are made available with this review for the first time (at <https://datadryad.org/resource/doi:10.5061/dryad.77471/2>, p. 3), marking a small but significant victory for open science.

Before receiving the full reports, we resumed reviewing the remainder of the material that we had received in 2011. This mainly consisted of module 2s (Roche terminology for pre-study documents). Module 2s contained the information originally denied to us by Roche: study protocols with their amendments, randomisation lists, blank CRFs, certificates of analysis describing appearance and content of active and control capsules and, at times, SAPs. CRFs are containers for the rawest form of recorded data at the individual participant level.

We had no tools for reviewing and synthesising this information so, again, we had to create our own. The instrument is made up of three parts each with a separate function. In the first part there is a template for a brief summary description of the trial. The format fits into the RevMan (RevMan 5.3; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) Characteristics of Included Studies

Table (CIST) and is mainly descriptive. The second part is the appraisal of the trial following the Cochrane risk-of-bias format. The third part reconstructs the trial timeline and provides a checklist and position in the document of the various elements, such as protocol, protocol amendments and study period with dates. The last part aims to check the internal consistency and coherence of each element (such as numbers screened, numbers randomised, interventions, comparators) across all the different documents, starting from the earliest available version of the protocol. The form also contains suggestions on where to look for the information. This is based on our experience gained in this review and in a descriptive review¹¹ of 78 CSRs of 14 different drugs and biologicals.

While designing the tool, we also asked ourselves whether or not access to module 2 information (and later the full study reports) changed our perception of the trial and specifically our risk-of-bias assessment. We found that access to what are supposed to be full study reports should provide clarity and remove the rationale for 'unclear' risk-of-bias judgements, and, ideally, remove the concept of risk leaving just 'bias', at least for certain study design elements, such as attrition bias. Either a design element introduces bias or it does not. In the case of the 15 full oseltamivir CSRs we reviewed when constructing our tool, only one contained a protocol that predated the beginning of participant enrolment, only two had SAPs that clearly predated participants' enrolment and three had clearly dated protocol amendments. No CSR reported a clear date of unblinding.

During the latter part of 2013, we received from the manufacturers tens of thousands of pages of full CSRs for both programmes combined.

The history and conclusions form the backdrop to this version of A159.

Oseltamivir studies received from Hoffman La Roche SA in CSR format:

1. WV16277⁶⁹
2. WV15819/WV15876/WV15978⁶⁷
3. WV15707⁶⁰
4. WV15812/WV15872⁶⁶
5. WV15730⁶²
6. M76001³⁶
7. WV15670⁸
8. WV15671⁵⁸
9. NV16871⁵⁷
10. WV15759/WV15871⁶⁴
11. WV16193
12. WV15825⁶⁸
13. WV15708⁶¹
14. WV15799⁶⁵
15. WV15673/WV15697⁵⁹
16. WV15758⁶³
17. NV20235
18. M76006
19. NV20236
20. NP15717
21. PV15616 (= GS-97-801)
22. PV15615 (= GS-97-802)
23. JV16284
24. WV15731
25. NV22155
26. NP15719
27. WP16254

28. WP16094
29. WP18308
30. WP16225
31. WP16134
32. PP15974
33. NP16472
34. NP15718
35. WP16226
36. NP25139
37. NP25138
38. NP15901
39. WP15525
40. NP25140
41. NP15728
42. NP15810
43. NP15826
44. PP16351
45. WP22849
46. NP22770
47. WP20727
48. PP16361
49. WP15517
50. NP15729
51. BP21288
52. WP21272
53. JP15735
54. WP15647
55. WP15648
56. WP15676
57. WP16263
58. NP15757
59. NV25118
60. NP15743
61. NP15881
62. NP15912
63. WP15979
64. WP16137
65. WP16295
66. NP15827
67. NV25655
68. JV21490
69. JP15734
70. NV22158
71. ML17713
72. ML22789
73. NV25182
74. ML17279 – publication only
75. ML19340 – publication only
76. JV15823⁷⁴ – English translation of Gaiyo summary
77. JV15824⁷⁵ – English translation of Gaiyo summary
78. ML17279 (= WV17052)
79. ML19340 (= COSMOS Study).

Zanamivir studies received from GSK in CSR format:

1. 167-101⁷⁰
2. JNAI-01⁷¹
3. JNAI-04⁷²
4. JNAI-07⁷³
5. NAI30008⁷⁷
6. NAI30009⁷⁸
7. NAI30010⁷⁹
8. NAI30011⁸⁰
9. NAI30012⁸¹
10. NAI30015⁸²
11. NAI30020⁸³
12. NAI30028⁸⁴
13. NAI30031⁸⁵
14. NAI30034⁸⁶
15. NAIA/B2008⁸⁷
16. NAIA/B2009⁸⁸
17. NAIA2005⁸⁹
18. NAIA2006⁹⁰
19. NAIA3002⁹¹
20. NAIA3003⁹²
21. NAIA3004⁹³
22. NAIA3005⁹⁴
23. NAIB2005⁹⁵
24. NAIB2006⁹⁶
25. NAIB2007⁹⁷
26. NAIB3001⁹⁸
27. NAIB3002⁹⁹
28. PE-01¹⁰⁰
29. 167T3-11
30. NAIA2010.

Appendix 2 Compliharms: events alternatively recorded as complications or harms

Roche clinical study report of oseltamivir treatment trial

The following symptoms, signs and common sequelae associated with influenza were excluded from specific adverse event reporting if they occurred during the period of drug treatment provided their appearance was in conjunction with one or more other influenza-related symptoms. The recrudescence of single discrete signs/symptoms associated with influenza syndrome were recorded as adverse events.⁶¹

[Event by body system]

Respiratory cough, pneumonia, bronchitis/tracheitis, sinusitis, dyspnoea/difficulty breathing

Cardiovascular tachycardia

Eyes, ears, nose and throat sore throat, nasal obstruction, earache, otitis, coryza, conjunctivitis

Central nervous system headache, fatigue

Musculoskeletal myalgia

Other fever, rigor, malaise/asthenia, chills

Source: 'Appendix 1. Events Associated with Influenza Syndrome'. Roche Clinical Study Report No. W-144117, Protocol WV15707, module I-43.

A 1999 Food and Drug Administration medical review of oseltamivir

As symptoms and common sequelae of influenza were collected as end point data, these symptoms, signs and common complications were specifically excluded from reporting as adverse events. The following table [above] lists events associated with influenza syndrome which were excluded from adverse event reporting. . . In addition, following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event; however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness). Comment: As the applicant [Hoffman-La Roche] stated in a written response dated 6/11/99, some sites incorrectly reported symptoms occurring prior to the cessation of the primary illness as secondary illness.¹⁰⁹

Emphasis in the original. Oseltamivir Medical Review. US FDA Center for Drug Evaluation and Research, Application No. 021087, 25 October 1999, p. 15. www.accessdata.fda.gov/drugsatfda_docs/nda/99/21087_Tamiflu_medr_P1.pdf.

Appendix 3 Searches of the electronic databases

Although this review focuses on the primary data sources of manufacturers, we ran electronic searches in the following databases to check that there were no published RCTs from non-manufacturer sources:

- CENTRAL (2013, issue 6) limited to year published 2010–13 (20 search results).
- MEDLINE (January 2011 to July week 2, 2013) (56 search results) and MEDLINE (via Ovid) from 1 January 2011 to July week 2, 2013 (56 search results).
- EMBASE (January 2011 to July 2013) (90 search results) and EMBASE.com from 1 January 2011 to July 2013 (90 search results).
- PubMed (not MEDLINE) no date limit (21 records). We searched PubMed to identify publisher submitted records that will never be indexed in MEDLINE and the most recently added records not yet indexed in MEDLINE.

To identify reviews that may possibly have referenced further trials we searched:

- DARE (2013 issue 2 of 4 April; four search results)
- NHS EED (issue 2 of 4 April 2013; two search results) – both resources are part of The Cochrane Library, www.thecochranelibrary.com (accessed 22 July 2013).
- HEED (searched 22 July 2013; three search results).

Previously, we had searched CENTRAL (eight search results); MEDLINE (via Ovid) from 1 May 2009 to 12 April 2011 (31 search results); EMBASE from 1 January 2010 to 12 April 2011 (54 search results); DARE (five search results) and NHS EED (five search results). CENTRAL, DARE and NHS EED are part of The Cochrane Library, www.thecochranelibrary.com (issue 2, 2011, accessed 1 June 2011). All search results were loaded to an electronic library (EndNote X4; Thomson Reuters, CA, USA).

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format.²²³ We adapted the search strategy for EMBASE. We imposed no publication or language restrictions.

MEDLINE (via Ovid)

1. Influenza, Human/
2. exp Influenzavirus A/
3. exp Influenzavirus B/
4. (influenza* or flu).tw.
5. or/1-4
6. Oseltamivir/
7. Zanamivir/
8. neuraminidase inhibitor*.tw.
9. (oseltamivir or zanamivir or tamiflu or relenza or peramivir or gs4071).tw,nm.
10. or/6-9
11. 5 and 10

EMBASE.com

17 #13 AND #16
 16 #14 OR #15 833616
 15 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR
 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1
 blind*):ab,ti
 14 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR
 'crossover procedure'/exp
 13 #4 AND #12
 12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
 11 oseltamivir:ab,ti OR zanamivir:ab,ti OR tamiflu:ab,ti OR relenza:ab,ti OR peramivir:ab,ti OR laninamivir:
 ab,ti OR gs4071:ab,ti
 10 'sialidase inhibitor':ab,ti OR 'sialidase inhibitors':ab,ti
 9 'neuraminidase inhibitor':ab,ti OR 'neuraminidase inhibitors':ab,ti
 8 'sialidase inhibitor'/exp
 7 'peramivir'/de
 6 'zanamivir'/de
 5 'oseltamivir'/de
 4 #1 OR #2 OR #3
 3 influenza*:ab,ti OR flu:ab,ti
 2 'influenza virus a'/exp OR 'influenza virus b'/de
 1 'influenza'/exp

Appendix 4 Searches for regulatory information

We searched the following sources:

1. the FDA
2. the EMA
3. Roche
4. the Japanese regulator [Pharmaceuticals and Medical Devices Agency (PMDA)] SBA.

We conducted a search of the FDA regulatory documentation of the NDAs and supplementary NDAs (sNDAs) of both drugs.²²⁴ The FDA NDA documentation includes medical, statistical, microbiological and other reviews, product labels, reports of site inspections, meetings with manufacturers and records of the decision-making leading to registration and post-marketing requirements. We also searched 'Warning Letters' dispatched by the FDA.²²⁵

To organise receipt of FDA materials, we created a TOC listing all of the regulatory and pharmaceuticals documents that were accessible to us. The TOC's function was that of an index, searchable quick reference guide and research tool to enable us to carry out quantitative (e.g. citation density analysis) and qualitative analyses (e.g. theme summaries) of the content. We also needed a rapid aide-memoire with brief summaries of the evidence contained in each regulatory document listed in the TOC. We called this aide-memoire the table of contents evidence (TOCE). As the TOCE contains copious working personal notes aiming to assist the understanding of the regulatory narrative, we have not reproduced it here but its content is woven into the narrative of this review.

Owing to the length and format of regulatory documents, we realised in building the TOC that there was a need to formalise the search and identification methods of trials referenced in the FDA documentation. We concentrated on where each trial is mentioned in the documentation by its pharmaceutical code. So, for example, if trial WV15670⁸ is mentioned 60 times by that code in a particular file then the TOC will report the page numbers in which it is cited, which could be any number up to 60. The unit of search was the file, as a FDA PDF file can contain many different types of documents scanned into the same file. TOC and TOCE are among the tools we specifically constructed for the review (see *Appendix 1*).

We wanted to validate our new methods, therefore we compared the yield of OCR searching and hand-searching of the PDF files of the FDA regulatory material using the same trial ID as a working example.

We also searched the material sent to us by Roche for our 2009 update.

We searched the website of the Japanese PMDA (www.info.pmda.go.jp/shinyaku/shinyaku_previous_index.html) for data relating to NIs approved in 1999 and 2000 and www.info.pmda.go.jp/approvalSrch/PharmacySrchInit for NIs approved since 2001. We identified 1575 pages of documents relating to the regulatory review by the PMDA and the Japanese Ministry of Health, Labour and Welfare (JMHLW) and the Japanese SBA of oseltamivir capsules for treatment (2000), prophylaxis of oseltamivir dry syrup for children (2002) and oseltamivir capsules for prophylaxis of influenza (2004), and their re-examination results. The Japanese regulatory body introduced a system to disclose their examination results and SBA in 1999 instead of the prior system, 'full disclosure requirement system', which had been introduced in 1967. Although these documents included preclinical, methodological, clinical (pharmacological, toxicity and pharmacokinetics with metabolism) data and clinical (Phase I–III) studies and contain more precise data than the published papers, no complete CSRs were publicly available. Therefore, one review author (RH) asked the JMHLW on 29 July 2010 to disclose all of the documents reporting the evidence base for the approval of oseltamivir for these indications. The JMHLW sent RH a letter of refusal dated 2 September 2010, with the explanation 'because the disclosure of such documents might hurt the right, position or other fair benefit in the competition of the

corporation concerned'. We waited for 6 months to take further action hoping that the required CSRs would be forthcoming from the manufacturers. When this did not happen, RH filed a suit to overturn the JMHLW decision with the Osaka (Japan) District Court on 28 February 2011. The District Court petition was rejected on 19 April 2013 and the Osaka High Court rejected it on 29 November 2013. No appeal to the Supreme Court was made because substantial CSRs had already disclosed from various sources.

Appendix 5 Modified Consolidated Standards of Reporting Trials statement-based extraction template for clinical study reports

Title and drug name

Include source documents used:

Modified CONSORT extraction template www.consort-statement.org/

Introduction CONSORT number

Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses

Insert text:

Methods

Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons

Insert text:

Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected

Insert text:

Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered

Insert text:

Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons

Insert text:

Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines

Randomisation:

Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned

Implementation	10	Who generated the random allocation sequence, who enrolled participants and who assigned participants to interventions

Insert text:

Blinding	11a	If done, who was blinded after assignment to interventions (e.g. participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions

Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes

Title and drug name

Include source documents used:

- 12b Methods for additional analyses, such as subgroup analyses and adjusted analyses

Insert text:

Results

Participant flow (a diagram is strongly recommended)

- 13a For each group, the numbers of participants who were randomly assigned, received intended treatment and were analysed for the primary outcome
- 13b For each group, losses and exclusions after randomisation, together with reasons

Recruitment

- 14a Dates defining the periods of recruitment and follow-up
- 14b Why the trial ended or was stopped

Insert text:

Baseline data

- 15 A table showing baseline demographic and clinical characteristics for each group

Numbers analysed

- 16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

Insert text:

Outcomes and estimation

- 17a For each primary and secondary outcome, results for each group and the estimated effect size and its precision (such as 95% CI)
- 17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Insert text:

Ancillary analyses

- 18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory

Insert text:

Harms

- 19 All important harms or unintended effects in each group

(for specific guidance see CONSORT for harms)

Insert text:

Other information

Registration

- 23 Registration number and name of trial registry

Protocol

- 24 Where the full trial protocol can be accessed, if available

Funding

- 25 Sources of funding and other support (such as supply of drugs), role of funders

Insert text:

First author

Date of completion

Conflicts of interest

Second author check

Date of check

Conflicts of interest

Appendix 6 Stage 1 of the 2012 A159 review

Two review authors assessed each study (with studies allocated randomly to three pairs of review authors). The lists of included studies (33 for oseltamivir, 30 for zanamivir, six for peramivir) were randomly created by the program Edgar II (www.edgarweb.org.uk/2011).²²⁶ Every study was openly allocated to each group according to its number.

We initially included six peramivir trials in the randomisation/allocation sequence but subsequently decided not to proceed further, as we were informed by the manufacturers that no CSRs would be available until after registration with the FDA (Bill Sheridan, BioCryst Pharmaceuticals Inc., 20 August 2010, personal communication). One review author (TJ) was assigned to the attempted reconstruction of CSRs from the FDA documents.

Two weeks before 'time lock' (see *Appendix 1*) we received the first batch of CSRs from the EMA (formerly EMEA), containing an additional four CSRs (including one complete four-module CSR) of studies we wanted to include. This time, random allocation was achieved by writing trial IDs on one set of tickets and asking an external researcher to allocate them to groups, the names of which had been written on another set of tickets.

Authors in pairs separately extracted data from the same CSRs of studies included in stage 1 of the review. When we had more than one copy of the same CSRs from different sources (e.g. CSRs submitted to a regulatory body and CSRs from a pharmaceutical company), we independently extracted data from each of the copies and then compared the results. We aimed to record and tabulate disagreements between data extracted from the same source and between different sources. We extracted data using a modified CONSORT statement-based extraction template (see *Appendix 5*).

The modified CONSORT-based extraction template aimed to assemble a concise version of the CSRs, which would include all important methods as well as define and extract all relevant outcomes. The CONSORT-based extraction template includes the features that would be expected to be found in a published trial report but in far greater detail. Our reconstructions do not include introduction or discussion sections. We extracted the following for each trial:

1. Background and objectives.
2. Methods: including trial design, important changes to methods after trial commencement (such as eligibility criteria), with reasons.
3. Participants: including eligibility criteria for participants and settings and locations where the data were collected.
4. Interventions: the interventions for each group with sufficient details to allow replication, including how and when they were actually administered.
5. Outcomes: prespecified primary and secondary outcome measures, including how and when they were assessed and changes to trial outcomes after the trial commenced, with reasons.
6. Sample size: how it was determined and explanation of any interim analyses and stopping guidelines.
7. Randomisation: including sequence generation and method used to generate the random allocation sequence.
8. Blinding: who was blinded after assignment to treatment groups.
9. Statistical methods: methods used to compare groups for primary and secondary outcomes and methods for additional analyses, such as subgroup analyses and adjusted analyses.
10. Results: participant flow, numbers of participants randomly assigned, losses and exclusions after randomisation, together with reasons. Baseline demographic and clinical characteristics for each group.
11. Outcomes: primary and secondary outcome results for each group.

12. Ancillary analyses: results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.
13. Harms: all important harms or unintended effects in each group.

One review author completed the CONSORT-based extraction on the template in full (see *Appendix 5*), with the name and date of completion and a statement of conflict of interests. A second review author checked the extraction. We extracted data, text, tables and figures directly from the relevant sections of the CSRs into the appropriate section of the template. We did not change the text in any way apart from clarifying abbreviations or spellings, but we highlighted some text. We used three types of text highlighting in the document.

- *Yellow* Where text, figures or tables need to be checked with further information (e.g. if an adverse event is referred to in appendices or a further CSRs module).
- *Red* Where text or comments were inserted by one or both review authors but required an additional opinion because of concerns that there is the potential for discrepancies in the CSRs.
- *Green* Any text or tables added by us to the template (e.g. a reconstructed table of adverse events).

Two review authors (CH and MT) independently piloted the reconstruction method on oseltamivir trial WV15671⁵⁸ with data from module 1 of the CSR from Roche and data submitted to UK NICE. We discussed the pilot reconstruction among the whole review team for clarification. At a face-to-face meeting we discussed the reliability and completeness of each reconstructed trial in the light of comments and other information from regulatory sources with a view to inclusion of the trial in stage 2. We resolved all of the differences in opinion by consensus. We reached decisions on whether or not a trial moved to stage 2 by consensus. We planned to record dissent when consensus was not possible.

Appendix 7 Applying inclusion criteria for the A159 2012 review

For the 2012 A159 review, two review authors (CDM and MT) independently scanned the titles and abstracts identified from the searches of the published literature. None of the identified items was a published version of a trial unknown to us. Four review authors (TJ, CH, MJ and RH) independently read all of the data relating to the studies on the list constructed during our search and selected studies that seemingly fulfilled our inclusion criteria. One review author (PD) compiled the assessments into a single sheet for another review author (CDM). One review author (CDM) resolved disagreements by discussion.

We assigned three categories to identified trials from our complete list:

1. definitely included
2. definitely excluded
3. trials for which we needed further information.

We excluded studies definitely not meeting inclusion criteria on the basis of available information (e.g. the title described the trial as a pharmacokinetic study). Where appropriate, we requested further information from the trial's sponsor, usually copies of the CSRs (minus participant identification) for each trial that was definitely included or for which we needed further information. We did not contact first/corresponding authors of published versions of the trials on the basis of our experience with the 2009 A047 review.

Appendix 8 Post-protocol hypotheses: methods and results

This text is carried over from the 2012 version of this review and is provided for record completeness

Methods

The hypotheses (expressed as null hypotheses) are listed below, in order of their generation (not necessarily of importance). Their rationale is explained further down the text.

Hypothesis 1. Incidence of certain harms is not associated with placebo content.

Hypothesis 2. Oseltamivir (or zanamivir) does not affect antibody production in treatment trials.

Hypothesis 3. Oseltamivir does not affect antibody production in post-exposure (or secondary prophylaxis) trials.

Hypothesis 4. The number of trial centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size).

Hypothesis 5. In oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection.

Hypothesis 1. Incidence of certain harms is not associated with placebo content.

Rationale. While reviewing the US Food and Drug Administration (FDA) critique of zanamivir, we noted the regulators' concern over the apparent drop in forced expiratory volume (FEV) following zanamivir inhalation ([FDA 1999a](#)), which appeared to be enhanced by the lactose powder excipient content of the active blister ([FDA 1999b](#)). The powder, which causes bronchospasm in susceptible individuals, was contained in both the active and the placebo blisters. This principle of using a matching placebo is of course correct but may have had the effect of increasing the incidence of bronchospasm (or asthma-related episodes) in both arms. This is clearly reported as a warning in the 1999 FDA label "Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation" ([FDA 2000b](#) p.10).

We reasoned by analogy and reviewed the medication content of the available clinical study reports of oseltamivir trials. The detailed information comparing content and physical characteristics and batch numbers is in [Table 11](#). Roche's use of the word 'matching' is not strictly correct as two principles present in the placebo capsules (dehydrocholic acid and dibasic calcium phosphate dihydrate) are not listed as being present in the active oseltamivir capsules. We could not locate the reason for such a choice in the clinical study reports but both substances may have gastrointestinal action if consumed in large enough quantities.

On this basis we formulated two **hypotheses**:

1a. There is no association between incidence of gastrointestinal harms and a placebo containing dehydrocholic acid in oseltamivir trials.

1b. There is no association between incidence of asthma-related events and a placebo containing lactose powder in zanamivir trials.

To test hypothesis 1a we assessed the oseltamivir trials for which we had clinical study reports Module 1 ([M76001](#); [WV15670](#); [WV15671](#); [WV15707](#); [WV15812/WV15872](#); [WV15730](#); [WV15819/WV15876/WV15978](#); [WV15758](#); [WV15799](#)) for gastrointestinal tract (GIT) harms including nausea, vomiting and diarrhoea as well as participants withdrawing from the studies due to adverse events. We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the χ^2 test and used Tau^2 to estimate between-study variance. To investigate whether placebo containing dehydrocholic acid may be associated with gastrointestinal harms we compared adverse event rates in placebo groups from the oseltamivir trials (where placebo contained dehydrocholic acid) with adverse event rates in the placebo groups from the zanamivir trials (where placebo did not contain dehydrocholic acid). This comparison was done informally using 1) data obtained from the FDA labels of oseltamivir and zanamivir ([FDA 2000b](#); [FDA 2011a](#)) as well as 2) the trials for which we have clinical study reports. As a sensitivity analysis we assumed a similar gastrointestinal adverse event rate in the placebo groups of the oseltamivir trials as was observed in the placebo groups of the zanamivir trials and then repeated the meta-analysis (as described above). We also speculated that withdrawals in the placebo groups due to gastrointestinal adverse events were possibly related to dehydrocholic acid and removed these for the sensitivity analysis.

For hypothesis 1b we assessed asthma-related events in nine zanamivir trials for which we had clinical study reports ([NAIA3002](#); [NAIB3002](#); [NAIA2005](#); [NAIB2005](#); [NAIB2007](#); [NAIB3001](#); [NAIA3005](#); [NAI30010](#); [NAI30009](#)). We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the χ^2 test and used Tau^2 to estimate between-study variance. To investigate whether placebo containing lactose powder may be associated with asthma-related events we informally compared event rates in placebo groups from the zanamivir trials (where placebo contained lactose powder) with event rates in the placebo groups from the oseltamivir trials (where placebo did not contain lactose powder). As a sensitivity analysis we assumed a similar asthma-related event rate in the placebo groups of the zanamivir trials as was observed in the placebo groups of the oseltamivir trials and then repeated the meta-analysis (as described above).

Hypothesis 2. Oseltamivir (or zanamivir) does not affect antibody production in treatment trials.

Rationale. All oseltamivir influenza treatment trials specify the primary efficacy analysis population as the influenza-infected population, not the randomised intention-to-treat (ITT) base population. The influenza-infected population (known as ITTI, or intention-to-treat-infected in clinical study reports) is determined post-randomisation based on the results of laboratory testing by culture and/or antibody rise (comparing paired sera from the same participant). The sample for culture and the first sample of sera are taken before commencement of trial product but the second or the third sera are taken after patients are treated with trial medication. It is vital that placebo and active groups of patients have the same odds of being classified as influenza-infected, otherwise any comparison between influenza-infected groups will be potentially affected by bias and will essentially be a non-randomised comparison. If trial medication affects the production of antibodies, the selection of the influenza-

infected population (which is partly based on antibody production) is confounded by taking the trial medication.

Roche have stated on multiple occasions ([Smith 2006](#); [Ward 2005](#); section 3.2.4.2 Serology [WV15799](#)) that ingestion of oseltamivir does not affect antibody production and the FDA supports this, stating that "In studies of naturally acquired and experimental influenza, treatment with TAMIFLU did not impair normal humoral antibody response to infection" ([FDA 2011a](#)).

However, we noticed unequal numbers of individuals in the influenza-infected population subgroup in numerous trials. In addition, Takahashi et al reported that oseltamivir significantly suppressed respiratory mucosal secretory immunoglobulin (Ig) A responses to antigen (Ag)-specific antibody (Ab) production and also the induction of Ag-specific IgA Ab-forming cells in an animal experiment ([Takahashi 2010](#)). If taking oseltamivir affects the production of IgG antibody as well, it may affect the selection of the influenza-infected population.

We are also unsure of the implication for immunisation with influenza vaccine. According to the FDA, no influenza vaccine interaction study has been conducted with oseltamivir ([FDA 2011a](#)).

To test the hypothesis we compared: (1) the odds of participants in the ITT population subsequently classified as influenza-infected; and (2) the odds of participants in the ITT population with a four-fold or more rise of antibody between the placebo and active arms of the trials. If ingestion of oseltamivir does not affect antibody production then we expect the odds of being classified as influenza-infected to be the same for the placebo and active arms. Therefore, we tested a null hypothesis that the odds of having a four-fold or more rise of antibody was the same for the placebo and active arms. We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the Chi^2 test and used Tau^2 to estimate between-study variance. The trials included in this analysis were the 10 oseltamivir treatment trials analysed by [Kaiser 2003](#) plus [WV15758](#) for oseltamivir and [NAIA3002](#), [NAIB3002](#), [NAIA2005](#), [NAIB2005](#), [NAIB2007](#), [NAIB3001](#), [NAI30009](#) for zanamivir. These are all the treatment trials for which we have clinical study reports Module 1. In an additional analysis we also assessed the oseltamivir trial conducted in China by Shanghai Roche Pharmaceutical Ltd for which we have a partial clinical study report ([ML16369](#)).

Hypothesis 3. Oseltamivir does not affect antibody production in post-exposure (or secondary prophylaxis) trials.

Rationale. According to the clinical study report of [WV15799](#), the trial programme assessing the effects of oseltamivir in post-exposure prophylaxis (PEP) consisted of two trials: [WV15799](#) and [WV16139](#). The Module 1s of both trials together with copious FDA notes on trial [WV15799](#) were available to us at 'time lock'. However the PEP trial [WV16139](#) was not standard care or placebo-controlled and so we excluded it from the review.

[WV15799](#) was a double-blind, cluster-randomised trial in which contact clusters of index cases were randomised to oseltamivir 75 mg a day or placebo for seven days. The trial formed an integral part of the "pivotal" trials package for the supplementary

application and review for prophylaxis use of oseltamivir 75 mg in people aged more than 13 years of age, submitted to the FDA on 22 May 2000, approved on 20 November 2000 ([FDA 2000c](#)). In the clinical study report Module 1 the manufacturer claimed that the trial provided evidence of the drug's capacity to prevent influenza in contacts by interrupting its transmission from index cases. Since all index cases were left untreated except for a paracetamol rescue pack, it is hard to see how such a claim can be made. The interruption of transmission claim has two components: reduction of viral spread from index cases (measured by nasal shedding of influenza viruses) and prevention of onset of influenza in contacts. This latter claim was based on the definition of (prevented) influenza cases: a mixture of symptoms signs and 'laboratory confirmation' (i.e. viral culture from the upper airways and/or at least a four-fold rise in antibody titres measured between baseline and two to three weeks later). The results of the trial later formed the basis for claims of the drug's effectiveness in interrupting transmission from person to person ([WHO 2007](#)) and allow time before the arrival of vaccines in the event of a pandemic. The interruption of transmission claim provided a powerful rationale for stockpiling oseltamivir (see for example vol 8, p.61-62 [NICE 2000](#): "Ro 64-0796 successfully interrupts the transmission of influenza within households ... and suggests that Ro 64-0796 [oseltamivir] would control the spread of influenza in other closed communities associated with high risk of transmission, such as nursing homes" ... "Ro 64-0796 also effectively interrupted virus transmission within households.")

The interruption of transmission indication was accepted by agencies such as the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC), but the US FDA refused to register and allow publicity based on any further indication beyond treatment and prophylactic effects on symptoms ([FDA 2000f](#)). Review of the evidence from the study protocol and Module 1 together with the FDA criticism explains the rationale for the FDA not supporting the manufacturers' claims. The design of the trial did not allow for comparison of the effects of treating index cases with oseltamivir versus placebo (as all index cases were not medicated) and a repeat viral culture was not performed for all participants. Viral culture was performed at baseline for all participants and thereafter only in participants with influenza-like illness symptoms (see Schedule of assessment for the contact case, [WV15799](#), and the FDA Medical Officer report ([FDA 1999c](#))). Any participants presenting at follow-up with symptoms of influenza had throat and nasal swabs taken in order to confirm the presence or absence of influenza infection ([FDA 2000c](#)), thereby missing out on potential asymptomatic infected people. However, a recent review of transmission studies has found no convincing evidence of spread from pre-symptomatic or asymptomatic subjects ([Patrozou 2009](#)), which might explain the FDA's caution in sanctioning any such claim for oseltamivir.

Our review of the clinical study report's Module 1 identified further problems with the conduct and reporting of the trial and discrepancies both within the clinical study reports and between the study and its protocol. In the protocol (version H) there is no mention of viral shedding measurement. This appears to be a post-protocol addition, which would explain the unsystematic nature of the viral excretion measurement remarked on by the FDA (i.e. taken from symptomatic contacts only). The primary population of analysis is the so called ITTIINAB population (contacts of ITT influenza-infected index cases who had negative virology at baseline). Although defined in the protocol, the selection and presentation of results for the intention-to-

treat contacts of the influenza-infected index case not infected at baseline (ITTIINAB) population has the effect of excluding 57% of the placebo (200/456) and 59% of the oseltamivir (205/497) participants. The effect of selection on the clustering was not formally tested in a sensitivity analysis. Nor is the potential weakness of such a choice discussed in the [WV15799](#) clinical study report. We carried out an analysis using Fisher's exact test, which showed that there was no statistical evidence that the placebo and oseltamivir groups' cluster sizes were distributed differently based on households with an infected index case ($P = 0.56$) (Table 2). By analysing the population by influenza status of the index case, instead of unit of randomisations (all index cases), the beneficial effects of the cluster-randomisations are potentially lost, introducing unknown biases into the analysis. In addition, the generalisability of the conclusions may not be easily applied to clinical practice where testing of suspected influenza cases is often not practical. Cross-checking the definition of ITTIINAB with that reported in the protocol of the other PEP trial, [WV16193](#) (excluded from this review) yields a different definition (PDF page 589) "The primary outcome in this study ([WV15799](#)) was the incidence of influenza occurring among contacts of influenza-infected index cases (the intent-to-treat-index-infected population)".

Throughout the clinical study report of trial [WV15799](#) there are many other apparently contradictory statements on important aspects of the trial, for example, on how many viral swabs and paired sera tests were carried out. The text at page 50 of the Module 1 reports that "For 21 of the 26 contacts with laboratory-confirmed clinical influenza in the ITTIINAB population the diagnosis was confirmed by culture" but Table 19 shows the 26 contacts as shedding virus at days two to eight. The same table reports that 178 placebo contacts and 201 oseltamivir contacts were negative for virology (which suggests that they were tested) at days two and eight. However, viral testing only took place at baseline and thereafter only in symptomatic participants. The number of contacts in which influenza was diagnosed only by serology is unclear but it appears to be five (26 minus 21). These inconsistencies highlight one of the fundamental conceptual problems in understanding the whole oseltamivir prophylaxis trial programme: the mode of action of the drug. Our interpretation of the text suggests that oseltamivir does not prevent infection and does not affect influenza antibody response. As stated above, the claim that oseltamivir does not affect antibody responses has been made by the manufacturers. However, an antibody response is part of the definition of influenza. We are unsure how it is possible that oseltamivir could prevent influenza by stopping symptoms appearing and antibodies rising while at the same time leaving antibody production unaffected.

It is for this reason that we decided to test whether administration of oseltamivir for PEP affected the production of antibodies to influenza viruses. The distribution of change in antibodies from baseline to follow-up was compared between the arms of the trials for contacts of the index cases. Analysis was performed using Wilcoxon two-sample test separately for each type of antibody in each trial. An additional analysis of proportion of contacts having a four-fold or greater rise in influenza-specific antibody titre in antibodies was compared between groups using the χ^2 test. Antibody data were not available for index cases, who were left untreated. In [WV15799](#), antibody testing may have been undertaken at day 1, day 8 and at day 21 ± 4 days for all contacts. Day 8 blood samples for influenza antibody analysis were stored to measure influenza antibody levels only in those contacts who did not attend

the follow-up visit (day 17 to 25). Analysis was based on data from the ITTIINAB population at pages 59-60 and Appendix 60 of the clinical study report's Module 1.

Hypothesis 4. The number of trial centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size) and **Hypothesis 5.** In oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size).

Rationale. The proportion of ITT population in the treatment trials of NIs that are subsequently diagnosed as infected with influenza is higher (~ 50% to 80%) than is usually seen in the course of the winter season in routine clinical care, although high peaks can occur for a very limited period. We know that in some treatment trials, such as [WV15670](#) and [WV15671](#), centres were activated to "recruit subjects during an influenza outbreak in the locality, detected using standardised surveillance techniques." We postulated that unreported procedures may also have been used in the trials to obtain these high proportions of influenza to ILI cases. Two procedures that may have been used are: 1) use of rapid influenza tests to screen out patients based on negative results; 2) dropping of centres that recruited low proportions of infected patients. The use of rapid testing of patients prior to randomisation has been reported in at least one of the zanamivir treatment trials ([NAIB3001](#)), in oseltamivir trial [WV15670](#) as a means of excluding infection with H5N1 in the Hong Kong Centre, as a pilot surveillance in suburban London during the 1998 to 1999 winter ([NICE 2000](#) vol.1) and in most oseltamivir paediatric trials to exclude respiratory syncytial virus (RSV) infection. In addition, the schedule of testing varies by trial for the oseltamivir trials with swabbing performed either before randomisation or after randomisation. In at least one oseltamivir treatment trial ([WV15730](#)) it was reported that no viral culture was performed at centres from South America ([FDA 1999c](#)). As a result of these observations we reformulated **Hypothesis 4** as follows: the number of centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was primary outcome effect size) in oseltamivir treatment trials and **Hypothesis 5** as in oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection.

To test **hypothesis 4**, we used Spearman's rank method to estimate the correlation between average number of patients recruited per centre and the proportion of placebo patients subsequently diagnosed with influenza infection. The placebo patients were used for the proportion of patients subsequently diagnosed with influenza infection because, as we show later in the review, there is evidence that oseltamivir interferes with antibody production and antibody response was used to diagnose influenza infection. We did not analyse the number of centres dropped from studies because information on this variable was not available in Module 1s of the clinical study reports for the included trials (information on patients recruited to each centre is reported in Module 2 which we do not currently have access to).

Hypothesis 5 was generated to attempt to explain the seemingly high proportion of influenza-infected influenza-like illness cases in treatment trials. However, we did not formally test this hypothesis as there was only one clinical study report reporting randomisation first then swabbing second ([WV15819/WV15876/WV15978](#)) (see also [Appendix 9](#)).

Results

The results of our post-protocol analyses are also reported in Figure and/or Table format.

Hypothesis 1a tested in a sensitivity analysis whether the incidence of gastrointestinal harms may be associated with exposure of participants to a placebo containing dehydrocholic acid. The data obtained from the oseltamivir trials clinical study reports is shown in Table 15.

Overall, the crude adverse event incidence in the placebo groups of the oseltamivir trials was 5.5% for nausea, 3.6% for vomiting and 7.0% for diarrhoea. This compares with crude incidence in the nine zanamivir treatment trials' placebo groups of 4.1% for nausea and vomiting (reported as a combined outcome in the clinical study reports) and 2.8% for diarrhoea. Two studies ([WV15670](#); [WV15671](#)) compared three treatment groups: oseltamivir 150 mg bid, oseltamivir 75 mg bid and placebo. To maintain the blinding in these trials, each participant took two pills twice daily. Therefore the participants in the oseltamivir 75 mg bid group took one placebo tablet twice daily. We note that in trial [WV15671](#) there was evidence of a dose-response effect of placebo on incidence of diarrhoea: oseltamivir 150 mg bid (5.9%), oseltamivir 75 mg bid (8.7%) and placebo (11.8%) ($P = 0.036$). However, there was no evidence found of a similar trend in trial [WV15670](#) ($P = 0.88$). We were unable to carry out a similar analysis for paediatric treatment trial [WV15758](#) because a detailed content of the placebo preparations is not available (see [Table 11](#)).

Random-effects meta-analysis of the data in Table 15 provided the following results.

Nausea: increased odds of adverse events due to oseltamivir (OR 1.62, 95% CI 1.17 to 2.26, $P = 0.004$).

Vomiting: increased odds of adverse events due to oseltamivir (OR 2.32, 95% CI 1.62 to 3.31, $P < 0.001$).

Diarrhoea: decreased odds of adverse events due to oseltamivir (OR 0.72, 95% CI 0.53 to 0.97, $P = 0.03$).

Withdrawal from treatment due to adverse events: no evidence of a difference between treatment groups (OR 1.08, 95% CI 0.66 to 1.76, $P = 0.75$).

We carried out a sensitivity analysis by assuming placebo rates of gastrointestinal adverse events in oseltamivir trials based on those observed in placebo groups of similar zanamivir trials. Overall rates of nausea, vomiting and diarrhoea in placebo groups of zanamivir treatment trials for adults and adolescents were 3%, 2% and 4% compared to oseltamivir treatment trials for adults and adolescents where rates were 6%, 3% and 10% respectively based on FDA-reported data ([FDA 2000b](#); [FDA 2011a](#)). Conversely, other common adverse events such as headaches, cough and dizziness had similar incidences of 2% to 3% in the placebo groups of zanamivir and

oseltamivir treatment trials ([FDA 2000b](#); [FDA 2011a](#)). In the treatment trials of children the rates of nausea, vomiting and diarrhoea in placebo groups of zanamivir treatment trials were 2%, 3% and 2% compared to oseltamivir treatment trials of children where rates were 4%, 9% and 11% respectively. Our conservative estimate is that the oseltamivir placebo increased rates of nausea two-fold (risk ratio (RR) = 2), vomiting (RR 1.5) and diarrhoea (RR 2.5) compared to the placebo arms in zanamivir trials. Based on the adult and adolescent trials we could conservatively speculate that the substances in the oseltamivir trials placebo increase nausea, vomiting and diarrhoea by 100% (6%/3%), 50% (3%/2%) and 150% (10%/4%) respectively. This could also be considered a conservative assumption because it is plausible that the lactose powder used as the placebo in the zanamivir trials also induced gastrointestinal symptoms, especially in patients that were lactose intolerant. Adjusting the actual rates of these events in the oseltamivir trials placebo groups to be consistent with the zanamivir trials placebo group rates (as reported by the FDA ([FDA 2000b](#); [FDA 2011a](#))) and re-running the random-effects meta-analysis we obtained the following results.

Nausea: increased odds of adverse events due to oseltamivir (OR 3.33, 95% CI 2.44 to 4.54, $P < 0.001$; test for heterogeneity $P = 0.33$).

Vomiting: increased odds of adverse events due to oseltamivir (OR 3.46, 95% CI 2.51 to 4.78, $P < 0.001$; test for heterogeneity $P = 0.37$).

Diarrhoea: increased odds of adverse events due to oseltamivir (OR 1.86, 95% CI 1.39 to 2.50, $P < 0.001$; test for heterogeneity $P = 0.50$).

The estimated effect sizes for nausea and vomiting have increased based on the sensitivity analysis. The effect on diarrhoea has reversed, indicating oseltamivir is possibly associated with increased odds of this adverse event. The results of our analysis support an alternative interpretation to that of the FDA.

Finally, we carried out a sensitivity analysis of withdrawal from treatment due to adverse events by assuming no withdrawals due to gastrointestinal events in the placebo group. In total there were nine patients in the oseltamivir trials' placebo groups that withdrew due to gastrointestinal events. When these withdrawals are not included the following result is obtained based on random-effects meta-analysis:

Withdrawal from treatment due to adverse events: no evidence of a difference between treatment groups (OR 1.48, 95% CI 0.87 to 2.51, $P = 0.15$; test for heterogeneity $P = 0.40$).

We conclude that participants in placebo arms of oseltamivir treatment trials experience a higher rate of gastrointestinal adverse events compared to their zanamivir counterparts. As the zanamivir trials' inclusion criteria were similar to the oseltamivir trials (fever and two additional symptoms of influenza-like illness (ILI)) this observation cannot plausibly be explained by an incremental role of influenza infection in the genesis of such heterogeneity. It is possible that the difference in reported gastrointestinal adverse events in the placebo groups of zanamivir and oseltamivir trials is due to differences in the collection of these events. However, other common adverse events such as headaches, cough and dizziness had very similar rates in the placebo groups of zanamivir and oseltamivir trials. Despite the results of this sensitivity analysis it is impossible without a clear statement of dosage

and rationale of use to assess the role of dehydrocholic acid and possibly calcium phosphate in the causation of such a high incidence of gastrointestinal adverse events.

For **hypothesis 1b** the data obtained from the zanamivir treatment trials clinical study reports are shown in Table 16.

Over all the nine zanamivir trials the incidence of asthma (including asthma exacerbation) in the placebo groups was 2.1% compared to 0.9% in the placebo groups of the oseltamivir trials. Random-effects meta-analysis of the data in Table 16 provided the following results for the combined outcome of any asthma event:

Asthma: decreased odds of adverse events due to zanamivir (OR 0.54, 95% CI 0.34 to 0.86, $P = 0.01$).

We carried out a sensitivity analysis by assuming placebo rates of asthma-related adverse events in zanamivir trials based on those observed in similar oseltamivir trials. If we assume a rate of asthma events in the placebo groups of the nine zanamivir trials similar to that observed in the oseltamivir trials we obtain the following result based on random-effects meta-analysis:

Asthma: no evidence of a difference between treatment groups (OR 1.27, 95% CI 0.71 to 2.26, $P = 0.42$; test for heterogeneity $P = 0.68$).

We conclude that zanamivir trial placebo recipients appear to have a higher incidence of asthma-related events than their oseltamivir counterparts. Again, as the inclusion criteria were similar for both trial programmes this finding is not likely to be due to severity of influenza infections but associated with exposure to lactose powder and possibly to the active principle. This is a point remarked on by the FDA.

For **hypothesis 2** (oseltamivir (or zanamivir) does not affect antibody production in treatment trials) the relevant trials showed strong and consistent evidence that patients randomised to active treatment had reduced odds of being classified as influenza-infected (OR 0.83, 95% CI 0.73 to 0.94, $P = 0.003$) with no evidence of heterogeneity (heterogeneity Chi^2 test = 2.80 (df = 7) $P = 0.90$; estimate of between-study variance $\text{Tau}^2 = 0.00$) (see Table 14). There was also strong evidence that patients randomised to active treatment had reduced odds of having four-fold or higher rise in antibody titres (OR 0.79, 95% CI 0.70 to 0.90, $P < 0.001$) with no evidence of heterogeneity (heterogeneity Chi^2 test = 4.61 (df = 7) $P = 0.71$; estimate of between-study variance $\text{Tau}^2 = 0.00$) (see Table 14).

In contrast, the zanamivir trials showed no evidence that patients randomised to active treatment had reduced odds of being classified as influenza-infected (OR 1.05, 95% CI 0.90 to 1.24, $P = 0.52$) with no evidence of heterogeneity (heterogeneity Chi^2 test = 3.03 (df = 6) $P = 0.81$; estimate of between-study variance $\text{Tau}^2 = 0.00$).

These results have important implications for the oseltamivir treatment trials programme and for all ongoing trials. All influenza-infected populations are selected post-randomisation and post-trial termination on the basis of laboratory findings (all ITT participants being symptomatic at entry, with aetiology unknown). However, as oseltamivir appears to affect antibody production (or perhaps testing, or both), there

may be some participants in the oseltamivir group who were infected with influenza but not diagnosed by the antibody rise and were therefore not counted in the influenza-infected population. These may have subsequently been excluded from the efficacy analysis. It is also possible that the strength of the antibody production limit to qualify for an influenza infection-induced antibody rise (four-fold and above from baseline) had the effect of selecting the 'stronger' responders into the influenza-infected subgroup of the oseltamivir arm. This would mean that the best antibody producers were selected and this may have led to inflated treatment estimates of efficacy in influenza-infected populations.

To investigate this possibility we calculated the correlation between the odds of being classified as infected in the oseltamivir group compared to the placebo group and the size of the primary treatment effect (time to alleviation of symptoms in the ITTI population). In treatment trials all participants are recruited on the basis of symptoms of influenza-like illness. According to the mechanism of action proposed by the manufacturer, infected participants given oseltamivir up to 48 hours from symptom onset should have an antibody response which, given the effects of randomisation, should be similar to that of placebo recipients. Non-responders or weak responders should be spread evenly across the trial arms. All treatment trials of oseltamivir showing evidence of a treatment effect on the primary outcome of the study were included in the analysis. This included two trials for which we did not have clinical full study reports ([ML16369](#); [JV15823](#)). We included these trials to increase variation in the two variables used for the analysis. In addition, two trials were excluded: [WV15707](#) which had a total ITTI sample size of 12 participants; and [WV15812/WV15872](#), which was a treatment trial in chronically ill adults that showed no evidence of a treatment effect. Results showed strong evidence of a correlation (Spearman rank correlation = -0.83, $P = 0.01$) (Table 19). The correlation was highly negative, indicating that lower odds of being classified as ITTI in the oseltamivir group compared to the placebo group is associated with larger treatment effects for the primary outcome of the studies. In contrast, there was no evidence of a correlation between the odds of being classified as infected in the oseltamivir group compared to the placebo group (Table 19) and the size of the treatment effect in the ITT population (Spearman rank correlation = -0.23, $P = 0.66$). A limitation of this analysis is that data for the ITT population for two trials were not available ([WV15730](#); [JV15823](#)) (Table 19).

Thus, all influenza-infected comparisons are potentially confounded by the action of the drug (oseltamivir but probably not zanamivir) and are essentially non-randomised comparisons. Any analyses should be based on ITT populations in oseltamivir treatment trials. Analyses and data considered for inclusion in systematic reviews should be based on the ITT (or safety) populations only.

Our analysis of **Hypothesis 3** shows that the odds of having a four-fold rise in antibodies is 0.33 (95% CI 0.16 to 0.67) for the oseltamivir group compared to placebo (hence a much bigger effect compared to the treatment trials). Due to insufficient information provided in the clinical study report we were unable to take account of the clustering in this analysis, hence the confidence intervals are possibly under-estimated; however an analysis that takes into account clustering is unlikely to change the conclusions. These results show that oseltamivir prophylaxis is associated with lower odds of a four-fold rise in antibodies and this appears to be due to a

difference in the distribution of antibody rise in HIAAH3 antibodies but not HIAAH1 or HIB antibodies (see [Table 14](#)). In summary no conclusions can be drawn from the available evidence on the effects of the drug on viral transmission. The mode of action in prophylaxis appears mainly to be ascribed to symptom suppression or control. There is uncertainty around other possible effects of the drug especially given its interaction with the production of antibodies.

We rejected **Hypothesis 4** and are currently unable to test **Hypothesis 5**

We rejected **Hypothesis 4** as there was no evidence of correlation between average recruited subjects per centre and the proportion of placebo patients subsequently diagnosed with influenza infection (Spearman correlation = 0.26; $P = 0.53$). Two studies failed to reach their recruitment target ([WV15707](#) and [WV15730](#)) and two clinical study reports were made up of multiple trials due to the original trial's poor recruitment ([WV15819/WV15876/WV15978](#) and [WV15812/WV15872](#)). In addition the proportion of placebo patients subsequently diagnosed with influenza infection ranged from 63% to 75%, implying little between-trial variation.

We are currently unable to test **Hypothesis 5** as only one oseltamivir clinical study report (of three trials) reported randomisation first then swabbing second ([WV15819/WV15876/WV15978](#)). In this study the proportion of placebo patients that were confirmed as influenza-infected was 68.1%. This compares with the other seven clinical study reports where swabbing was carried out first and randomisation second and the proportion of placebo patients that were confirmed as influenza-infected ranged from 63.2% to 74.9% with mean 68.1%. Hence it seems that swabbing after randomisation made no difference in the treatment trial programme where this practice is reported. However, with only one clinical treatment study report randomising prior to swabbing available to us, the power to detect a difference in the proportion of placebo patients subsequently diagnosed with influenza infection is low. We hope to be able to retest this hypothesis as more data become available.

Appendix 9 Example of contents of a Clinical Study Report (from p. 1 of WV15670 report)

Final study report modules

This report consists of five modules. Those not supplied in this submission were obtainable from the sponsor on request.

Module 1: core report and study publications

Introduction.

Rationale.

Objectives.

Methodology.

Efficacy results.

Safety results.

Discussion/conclusions.

Appendices.

Module 2: prestudy documents and study methodology

Protocol and amendment history.

Blank CRF.

Subject information sheet.

Glossary of original and preferred terms.

Randomisation list RAP.

Certificates of analysis.

List of investigators.

List of responsible ethics committees.

Module 3: individual subject listings of demographic and efficacy data

Demographic data listings.

Previous and concomitant diseases.

Previous and concomitant medications.

Efficacy listings.

Module 4: individual subject listings of safety data

Laboratory parameters.

Vital signs data.

Module 5: statistical report

Appendix 10 List of excluded studies and reasons for exclusion

Study	Reason for exclusion
105934	Post-marketing study
107485	Dose-ranging study
108127	Non-randomised study
112311	Pharmaco-availability study
112312	Pharmaco-availability study
113268	Pharmaco-availability study
113502	Non-comparative study
113625	Pharmacokinetics study
113678	Non-comparative study
114045	Survey
114373	Not placebo/do nothing controlled
167-02	Dose-ranging Phase I in volunteers, no influenza exposure
167-03	Dose-ranging Phase I in volunteers, no influenza exposure
167-04	Dose-ranging Phase I in volunteers, no influenza exposure
167-05	Dose-ranging Phase I in volunteers, no influenza exposure
167T3-11	An open-label trial of 20 mg CG167 (zanamivir) in the treatment of influenza viral infection in children aged ≤ 5 and < 15 years old (open-label study). Non-randomised; the intervention group was compared with a survey group; 18-page summary available with no title
ADS-TCAD-PO206	Not placebo/do nothing controlled
BP21288	Pharmacokinetics study
C94-009	Pharmacokinetics study
C94-085	Pharmacokinetics study
GCP/95/045	Pharmacokinetics study
JNAI-02	Unknown study. Only ID traced
JNAI-03	Unknown study. Only ID traced
JP15734	Pharmacokinetics non-comparative study
JP15735	Does not test treatment, prophylaxis or PEP and there was no exposure to influenza
JV16284	Open-label, no control
JV21490	No influenza circulation, Phase IV study with unusual oseltamivir dosages
M76006	Not placebo/do nothing controlled
ML17279	CSR bears no title. Study of community pharmacist availability
ML17713	Non-comparative study

Study	Reason for exclusion
ML19340	Text in French. Community pharmacist availability study
ML20542	Not placebo/do nothing controlled
ML21954	Not placebo/do nothing controlled
ML22789	Not placebo/do nothing controlled
ML22872	Not placebo/do nothing controlled
ML22879	Not placebo/do nothing controlled
ML25018	Bioavailability study
ML25087	Not placebo/do nothing controlled
ML25094	Non-comparative study
ML25157	Pharmacokinetics study
ML25176	Pharmacokinetics study
ML25179	Not placebo/do nothing controlled
ML25265	Non-comparative observational study
ML25266	Pharmacokinetics study
MP20691	Pharmacokinetics study
MV20043	Transmission study
MV20050	Dose-ranging study
MV22926	Non-comparative study
MV22949	Pharmacokinetics study
MV22951	Pharmacokinetics study
MV22963	Pharmacokinetics study
MV22970	Pharmacokinetics study
NAI106784	Pharmacokinetics study
NAI108166	Pharmacokinetics study
NAI10901	Comparator is vaccine
NAI10902	Pharmacokinetics study
NAI40012	Instructional leaflet study
NAIA1009	Pharmacokinetics study
NAIA2010	Open-label, rimantadine-controlled, cluster randomised trial
NAIB1001	Pharmacokinetics study
NAIB1002	Pharmacokinetics study
NAIB1007	Pharmacokinetics study
NCT00297050	Dose-ranging study
NCT00416962	Not placebo/do nothing controlled
NCT00867139	Not placebo/do nothing controlled in immunocompromised people
NCT00957996	Peramivir study – does not have placebo/do nothing comparator
NCT01063933	Pharmacokinetics study

Study	Reason for exclusion
Not applicable (registry)	Unknown study. Only ID traced. Identified from Reddy D. <i>J Antimicrob Chemother</i> 2010; 65 (Suppl. 2):ii35–40 (doi: http://dx.doi.org/10.1093/jac/dkq014) table 2. http://jac.oxfordjournals.org/cgi/content/full/65/suppl_2/ii35/DKQ014TB2)
NP15525	Pharmacokinetics study
NP15717	Pharmacokinetics study
NP15718	Pharmacokinetics study
NP15719	Pharmacokinetics study
NP15728	Pharmacokinetics study
NP15729	Pharmacokinetics study
NP15743	Palatability study, open-label
NP15757	Pharmacokinetics study
NP15810	Pharmacokinetics study
NP15826	Pharmacokinetics study
NP15827	Pharmacodynamics study
NP15881	Palatability study in children
NP15901	Pharmacokinetics study
NP15912	Palatability study in children
NP16472	Not placebo/do nothing controlled
NP22770	Pharmacokinetics study
NP25138	Not placebo/do nothing controlled
NP25139	Not placebo/do nothing controlled
NP25140	Pharmacokinetics study
NV20234	Immunocompromised participants
NV20235	Immunocompromised participants
NV20237	Resistance study
NV22155	Not placebo/do nothing controlled
NV22158	Registry study
NV25118	Pharmacokinetics study
NV25182	Not placebo/do nothing controlled
NV25655	Open-label pharmacokinetics study
PP15974	Pharmacokinetics study
PP16351	Pharmacokinetics study
PP16361	Pharmacokinetics study
PV15615	Viral challenge study
PV15616	Viral challenge study
WP15517	Pharmacokinetics study
WP15525	Pharmacokinetics study

Study	Reason for exclusion
WP15647	Pharmacokinetics study
WP15648	Pharmacokinetics study
WP15676	Pharmacokinetics study
WP15979	Bioavailability study
WP16094	Pharmacokinetics study
WP16134	Bioequivalence study
WP16137	Bioequivalence study
WP16225	Bioequivalence study
WP16226	Pharmacokinetics study
WP16254	Pharmacokinetics study
WP16263	No influenza circulation, Phase IV study
WP16295	Open-label absorption study
WP17721	Pharmacokinetics study
WP18308	Pharmacokinetics study
WP20727	Pharmacokinetics study
WP20749	Not placebo/do nothing controlled
WP21272	Pharmacokinetics study
WP22849	Pharmacokinetics study
WV15731	No placebo arm
WV16139	Unknown study. Only ID traced. ID could be a typo
WV16193	Not placebo/do nothing controlled
ID, identity number.	

Appendix 11 Symptomatic influenza-like illness in prophylaxis trials

Introduction

Among the CSRs of prophylaxis studies that we included, no oseltamivir study and only one study of zanamivir (NAI 30034⁸⁶) reported the relevant primary outcome 'symptomatic ILI irrespective of positivity of laboratory testing'. In the zanamivir CSR (NAI 30034) no significant reduction was observed (9% vs. 10%). Furthermore, no definition was provided for ILI in the oseltamivir CSRs; however, individual patient data on symptoms of influenza were provided in module 3.

Methods

Examples of the definitions of categories for lab-confirmed influenza used in the oseltamivir trials (p. 33, CSR for WV15673–697,⁵⁹ p. 31, CSR for WV15825⁶⁸) are given below:

TABLE 25 Definitions of categories for subjects with laboratory-confirmed influenza virus infection

Category	Oral temperature	Constitutional symptoms	Respiratory symptoms
Clinical influenza	≥ 99 °F	One or more	One or more
Non-clinical influenza			
Non-clinical URTI			
Febrile URTI	≥ 99 °F	None	One or more
URTI without systematic disturbance	< 99 °F	None	One or more
URTI with systematic disturbance	< 99 °F	One or more	None
Febrile constitutional	≥ 99 °F	One or more	None
Asymptomatic influenza	< 99 °F	None	None
	≥ 99 °F	None	None
	< 99 °F	One or more	None

URTI, upper respiratory tract infection.

TABLE 26 Definitions of categories for subjects with laboratory-confirmed influenza virus infection

Category	Oral temperature	Constitutional symptoms	Respiratory symptoms
Clinical influenza	$\geq 99^{\circ}\text{F}$	One or more	One or more
Non-clinical influenza			
Non-clinical URTI			
Febrile URTI	$\geq 99^{\circ}\text{F}$	None	One or more
URTIs without systematic disturbance	$< 99^{\circ}\text{F}$	None	One or more
URTIs with systematic disturbance	$< 99^{\circ}\text{F}$	One or more	One or more
Febrile constitutional	$\geq 99^{\circ}\text{F}$	One or more	None
Asymptomatic influenza	$< 99^{\circ}\text{F}$	None	None
	$\geq 99^{\circ}\text{F}$	None	None
	$< 99^{\circ}\text{F}$	One or more	None

URTI, upper respiratory tract infection.

These are complex and confusing definitions, in which, for example, the definition for 'URTIs with systemic disturbance' is the same as one of the definitions for asymptomatic influenza in WV15673–697.⁵⁹ Furthermore, the definition for 'URTIs with systemic disturbance' in WV15825⁶⁸ and WV15673/WV15697⁵⁹ is different. No definition is provided for ILI without confirmation of influenza. Asymptomatic influenza includes those with some symptoms.

In the absence of a definition provided in the CSRs for ILI and the complex and confusing definitions of categories for lab-confirmed influenza, we classified ILI as two or more symptoms out of nasal congestion, headache, chills/sweats, sore throat, cough, fatigue, myalgia and fever. Fever was defined as reported in the original protocols for each trial. We counted the number of patients with ILI during the trial follow-up for each prophylaxis study of oseltamivir in adults.

Results

Oseltamivir did not reduce ILI (RR 0.95, 95% CI 0.86 to 1.06) (Figure 20). In additional analysis we found that fever is reduced (RR 0.62, 95% CI 0.42 to 0.93) (Figure 21), proportion with laboratory confirmation is reduced (RR 0.59, 95% CI 0.41 to 0.85) (Figure 22) but symptoms other than fever are not reduced (RR 0.96, 95% CI 0.86 to 1.07) (Figure 23).

Interpretation

These results suggest oseltamivir suppresses fever, reduces antibody response and viral shedding but does not reduce the risk of symptomatic illness.

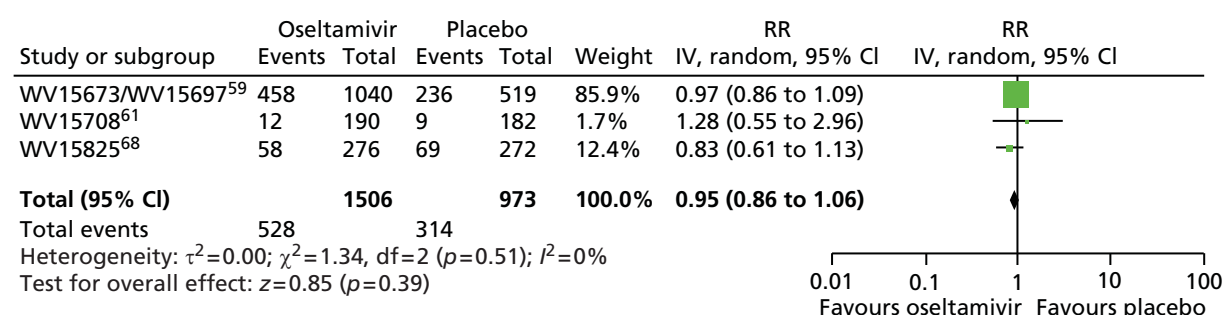


FIGURE 20 All symptomatic ILI in adult prophylaxis. ILI is classified as two or more symptoms out of: nasal congestion, headache, chills/sweats, sore throat, cough, fatigue, myalgia and fever (with or without lab confirmation). IV, inverse variance.

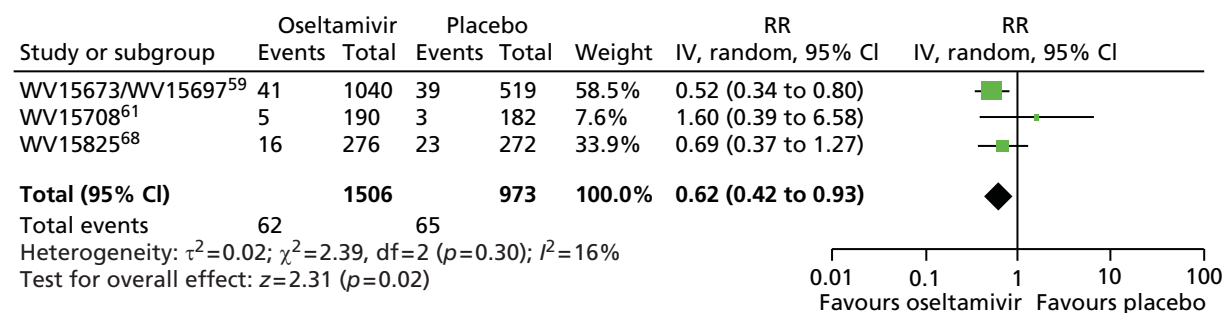


FIGURE 21 Fever in adult prophylaxis. Temperature $\geq 100^\circ\text{F}$ (WV15673/697⁵⁹) or $\geq 37.5^\circ\text{C}$ (WV15825/15708) as originally defined in the trial protocols. IV, inverse variance.

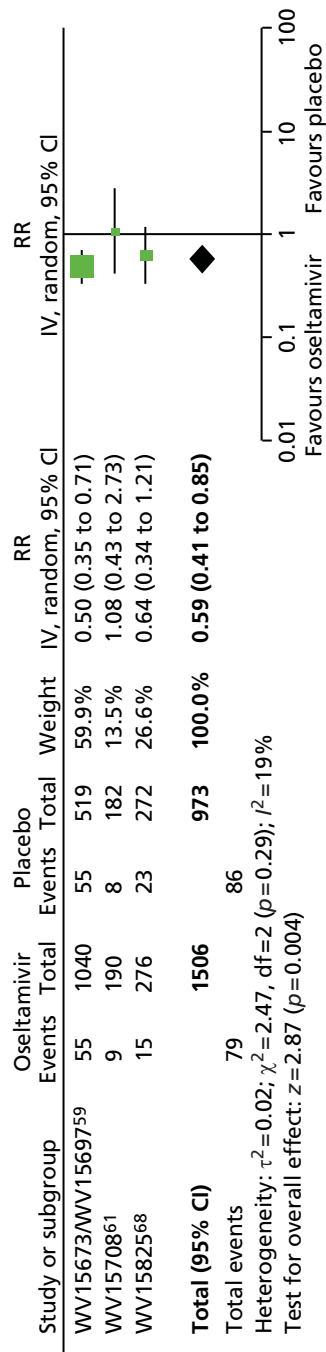


FIGURE 22 Lab confirmation of influenza (symptomatic and asymptomatic). IV, inverse variance.

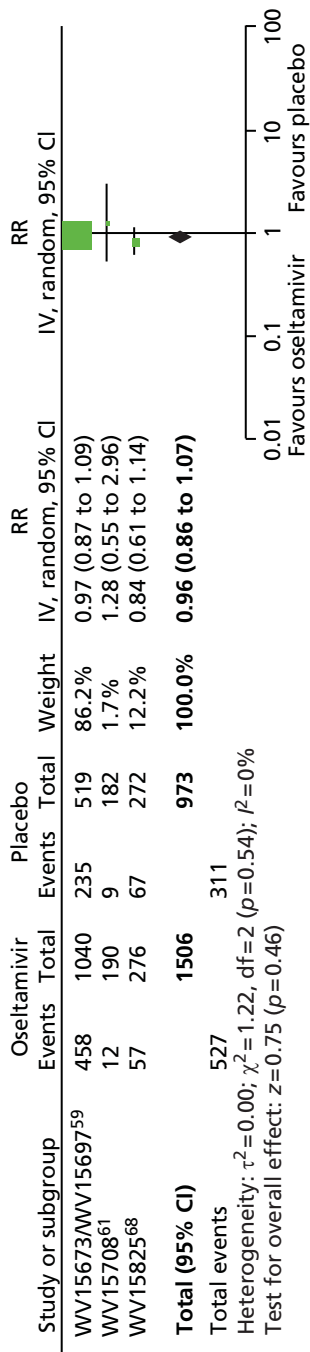


FIGURE 23 Two or more symptoms (other than fever) of ILI in adult prophylaxis. Other than fever defined as nasal congestion, headache, chills/sweats, sore throat, cough, fatigue and myalgia. IV, inverse variance.

Appendix 12 Oseltamivir observational studies review search strategies

Database: Ovid MEDLINE (1946 to February Week 1 2013)

Search strategy

1. Influenza, Human/
2. influenzavirus a/ or influenza a virus/ or influenza a virus, h1n1 subtype/
3. (influenza* or flu or h1n1).tw.
4. or/1-3
5. Oseltamivir/
6. (oseltamivir or tamiflu or neuraminidase inhibitor*).tw,nm.
7. Antiviral Agents/
8. antiviral*.tw.
9. or/5-8
10. 4 and 9
11. Hospitalization/
12. hospitali*.tw.
13. exp Mortality/
14. mortality.tw.
15. Death/
16. fatal outcome/
17. (death* or died or fatal*).tw.
18. Critical Illness/
19. (critical* adj2 ill*).tw.
20. or/11-19
21. 10 and 20
22. epidemiologic studies/
23. epidemiology.fs.
24. epidemiol*.tw.
25. exp case-control studies/
26. exp Cohort Studies/
27. cohort*.tw.
28. (("follow up" or "follow-up") adj2 (study or studies)).tw.
29. observational*.tw.
30. longitudinal*.tw.
31. retrospectiv*.tw.
32. prospectiv*.tw.
33. Cross-Sectional Studies/
34. (cross-section* or cross section*).tw.
35. (control* adj2 (group* or study or studies or patient* or case*)).tw.
36. or/22-35
37. 21 and 36

EMBASE (Elsevier)

#15 834

#15.34 #15.19 AND #15.33

#15.33 #15.20 OR #15.21 OR #15.22 OR #15.23 OR #15.24 OR #15.25 OR #15.26 OR #15.27 OR #15.28 OR #15.29 OR #15.30 OR #15.31 OR #15.32

#15.32 'control group':ab,ti

#15.31 'cross-sectional':ab,ti OR 'cross sectional':ab,ti

#15.30 'cross-sectional study'/de

#15.29 prospectiv*:ab,ti

#15.28 retrospectiv*:ab,ti

#15.27 longitudinal:ab,ti

#15.26 observational*:ab,ti

#15.25 (('follow up' OR 'follow-up') NEAR/2 (study OR studies)):ab,ti

#15.24 cohort*:ab,ti

#15.23 'cohort analysis'/de

#15.22 'case control study'/exp

#15.21 epidemiol*:ab,ti

#15.20 'epidemiology'/de

#15.19 #15.9 AND #15.18

#15.18 #15.10 OR #15.11 OR #15.12 OR #15.13 OR #15.14 OR #15.15 OR #15.16 OR #15.17

#15.17 (critical* NEAR/2 ill*):ab,ti

#15.16 'critical illness'/de

#15.15 death*:ab,ti OR died:ab,ti OR fatal*:ab,ti

#15.14 'death'/de OR 'fatality'/de

#15.13 mortality:ab,ti

#15.12 'mortality'/exp

#15.11 hospitali*:ab,ti

#15.10 'hospitalization'/de

#15.9 #15.3 AND #15.8

#15.8 #15.4 OR #15.5 OR #15.6 OR #15.7

#15.7 antiviral*:ab,ti

#15.6 'antivirus agent'/de AND [embase]/lim

#15.5 oseltamivir:ab,ti OR tamiflu:ab,ti OR 'neuraminidase inhibitor':ab,ti OR 'neuraminidase inhibitors':ab,ti

#15.4 'oseltamivir'/de

#15.3 #15.1 OR #15.2

#15.2 influenza*:ab,ti OR flu:ab,ti OR h1n1:ab,ti

#15.1 'influenza'/de OR 'influenza a'/de OR '2009 h1n1 influenza'/de OR 'influenza a (h1n1)'/de OR 'pandemic influenza'/de OR 'swine influenza'/de

Cumulative Index to Nursing and Allied Health Literature (EBSCOhost)

Friday, February 15, 2013 2:30:38 AM

Query Limiters/Expanders Last Run Via Results Action

S35	S21 AND S34
S34	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
S33	TI ((control* N2 (group* or study or studies or patient* or case*)) OR AB ((control* N2 (group* or study or studies or patient* or case*))
S32	TI (cross section* or cross-section*) OR AB (cross section* or cross-section*)
S31	TI prospectiv* OR AB prospectiv*
S30	TI retrospectiv* OR AB retrospectiv*
S29	TI longitudinal* OR AB longitudinal*
S28	TI observational* OR AB observational*
S27	TI (((“follow up” or “follow-up”) N2 (study or studies))) OR AB (((“follow up” or “follow-up”) N2 (study or studies)))
S26	TI cohort* OR AB cohort*
S25	(MH “Prospective Studies+”)
S24	(MH “Case Control Studies+”)
S23	TI epidemiol* OR AB epidemiol*
S22	(MH “Epidemiological Research”)
S21	S10 AND S20
S20	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S19	TI critical* N2 ill* OR AB critical* N2 ill*
S18	(MH “Critical Illness”)
S17	TI (death* or died or fatal*) OR AB (death* or died or fatal*)
S16	(MH “Fatal Outcome”)
S15	(MH “Death”)
S14	TI mortality OR AB mortality
S13	(MH “Mortality+”)
S12	TI hospitali* OR AB hospitali*
S11	(MH “Hospitalization”)
S10	S4 AND S9
S9	S5 OR S6 OR S7 OR S8
S8	TI antiviral* OR AB antiviral*
S7	(MH “Antiviral Agents”)
S6	TI (oseltamivir or tamiflu or neuraminidase inhibitor*) OR AB (oseltamivir or tamiflu or neuraminidase inhibitor*)
S5	(MH “Oseltamivir”)
S4	S1 OR S2 OR S3
S3	TI (influenza* or flu or h1n1) OR AB (influenza* or flu or h1n1)
S2	(MH “Influenzavirus A”) OR (MH “Influenza A Virus”) OR (MH “Influenza A Virus, H1N1 Subtype”)
S1	(MH “Influenza”) OR (MH “Influenza, Human”) OR (MH “Influenza, Pandemic (H1N1) 2009”)

Latin American and Caribbean Health Sciences Literature (BIREME)

(mh:"Influenza, Human" OR gripe OR "influenza humana" OR "gripe humana" OR influenza* OR flu OR h1n1 OR mh:"Influenzavirus A" OR mh:"Influenza A virus" OR mh:"Influenza A Virus, H1N1 Subtype") AND (mh:oseltamivir OR oseltamivir OR tamiflu OR "neuraminidase inhibitor" OR "neuraminidase inhibitors" OR "inhibe la neuraminidasa" OR "inibe a neuraminidase" OR mh:"Antiviral Agents" OR antivirales OR antivirais OR antiviral*) AND (mh:"Epidemiologic Studies" OR "Estudios Epidemiológicos" OR epidemiol* OR mh:"Case-Control Studies" OR "Estudios de Casos y Controles" OR "Estudos de Casos e Controles" OR "Case-Base Studies" OR "Case-Comparison Studies" OR "Case-Referent Studies" OR "Matched Case-Control Studies" OR "Nested Case-Control Studies" OR "Combined Case-Control Studies" OR "Grupos de Estudio" OR "Estudios de Comparación de Casos" OR "Estudios de Referencia de Casos" OR "Estudios de Casos y Controles por Apareamiento" OR "Estudios de Casos y Controles Anidados" OR "Estudios de Casos y Controles Combinados" OR "Grupos de Estudio" OR "Estudos de Comparação de Casos" OR "Estudos de Referência de Casos" OR "Estudos de Caso-Controlle com Emparelhamento" OR "Estudos de Caso-Controlle Aninhados" OR "Estudos de Caso-Controlle Combinados" OR mh:"Cohort Studies" OR "Estudios de Cohortes" OR "Estudios de Coortes" OR "Cohort Analysis" OR "Closed Cohort Studies" OR "Concurrent Studies" OR "Historical Cohort Studies" OR "Incidence Studies" OR "Análisis de Cohortes" OR "Estudios Cerrados de Cohortes" OR "Estudios de Concurrencia" OR "Estudios Históricos de Cohortes" OR "Estudios de Incidencia" OR "Análise de Coortes" OR "Estudos Fechados de Coortes" OR "Estudos Históricos de Coortes" OR "Estudos de Incidência" OR cohort* OR longitudinal OR retrospectiv* OR prospectiv* OR "follow up" OR "follow-up" OR "control group" OR mh:"Cross-Sectional Studies" OR "Estudios Transversales" OR "Estudos Transversais" OR "cross sectional" OR "cross- sectional") AND db:("LILACS")

Web of Science (Thomson Reuters)

#7	452	#6 AND #5 <i>Databases=SCI-EXPANDED, CPCI-S Timespan=All Years</i>
#6	1,897,044	Topic=(epidemiol* or cohort* or ("follow up" or "follow-up") NEAR/2 (study or studies)) or observational* or longitudinal or retrospectiv* or prospectiv* or "cross section*" or "cross-section*" or (control* NEAR/2 (group* or study or studies or patient* or case*)) <i>Databases=SCI-EXPANDED, CPCI-S Timespan=All Years</i>
#5	1527	#4 AND #3 <i>Databases=SCI-EXPANDED, CPCI-S Timespan=All Years</i>
#4	1,158,683	Topic=(hospitali* or mortality or death* or fatal* or died or (critical* NEAR/2 ill*)) <i>Databases=SCI-EXPANDED, CPCI-S Timespan=All Years</i>
#3	6592	#2 AND #1 <i>Databases=SCI-EXPANDED, CPCI-S Timespan=All Years</i>
#2	56,113	Topic=(oseltamivir or tamiflu or "neuraminidase inhibitor" or "neuraminidase inhibitors" or antiviral*) <i>Databases=SCI-EXPANDED, CPCI-S Timespan=All Years</i>
#1	86,524	Topic=(influenza* or flu or h1n1) <i>Databases=SCI-EXPANDED, CPCI-S Timespan=All Years</i>

Appendix 13 Template of letter sent to corresponding authors of included studies

Dear Dr. X*,

We read with interest your paper:

(citation)*

We are conducting a systematic review of observational studies of antivirals for influenza and are contacting you in the hope of obtaining a copy of the patient data you analyzed, as we would like to conduct a further analysis of these data considering the time-dependent nature of antiviral exposure. Would this be possible? We would of course acknowledge your help in any papers or reports arising from this research. We recognize the need to protect patient privacy and hope that the data can be de-identified before sharing. Our protocol can be obtained from the following website:

Mark Jones, Rokuro Hama. Effect of oseltamivir on mortality in treatment of 2009A/H1N1 influenza patients. PROSPERO 2012:CRD42012002245 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002245

The variables we are particularly interested in for each patient are:

Patient ID

Hospital ID

Age and Sex of patient

Underlying Co-morbidities

Date of onset of symptoms (fever, or other symptoms in the case of no fever)

Date of first presentation at a medical facility

Date of admission to hospital

Antiviral treatment: start date (with time), type (oseltamivir/zanamivir/other/none), dose, duration

Antipyretic treatment: date, type (paracetamol/ibuprofen/aspirin/other NSAID) and dose

Corticosteroid treatment: date, type and dose

Date of admission to ICU

Date (with time) of start of artificial ventilation

Hospital outcome (death/discharge/unknown)

Date of death/discharge

Any other variable that is associated with hospital outcome

Yours sincerely,

CDM

Appendix 14 Reasons for exclusion of studies based on full manuscripts

Reason for exclusion	Number of studies	Citations ^a
Most (or all) patients received antiviral medication	77	1–57, 59–61, 63, 67, 68, 71–73, 102–111
Overlap with other included studies	10	58, 62, 64–66, 69, 70, 74–76
Did not provide a breakdown of numbers of patients dying by oseltamivir exposure	12	77–88
Fewer than five deaths	12	89–100
Not a clinical study	5	101, 112–115
Other reasons	8	116–123

^a These citations refer to the reference numbers in this appendix and not the main reference list.

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Appendix 15 Illustration of time-dependent bias using individual patient data from the Canadian study

We illustrate the effect of time-dependent bias using the data from one of the included studies. Of 578 patients with a survival time, 540 received oseltamivir [of which 105 (19%) died] compared with 38 who did not receive an antiviral [of which 12 (32%) died]. A simple chi-squared test gives weak evidence of a difference in survival ($p = 0.072$) and Cox regression, assuming that treatment exposure uniformly occurs at hospital admission provides evidence of reduced risk of death for patients receiving oseltamivir (HR 0.52, 95% CI 0.29 to 0.95; $p = 0.033$). See *Table 27* for a life table and *Figure 24* for a Kaplan–Meier plot of the data assuming treatment exposure occurred at hospital admission.

An alternative analysis that takes into account the fact that treatment with oseltamivir does not occur at hospital admission but rather occurred at a mean of 0.62 days (range 0–45 days) after hospital admission shows a markedly different result. Cox regression assuming time-dependent treatment exposure gives no evidence of reduced risk of death for patients receiving oseltamivir (HR 0.87, 95% CI 0.48 to 1.61; $p = 0.66$). See *Table 28* for a life table and *Figure 25* for a survival plot of the data using the method of Simon and Makuch.²²⁷

The life tables and survival plots are shown for the first 11 days, as this is where most of the mortality occurred. When standard survival analysis is used there is an implicit assumption that treatment exposure begins at baseline, which, in this case, is hospital admission. Therefore, at baseline there were 540 patients at risk in the oseltamivir group and 38 patients at risk in the no-treatment group (see *Table 27* and see *Figure 24*). This incorrect assumption is what leads to time-dependent bias.

In the alternative analysis the timing of exposure to treatment is taken account of correctly by considering how many patients were exposed or unexposed to treatment on a daily basis. If the data were available the computation could be done more accurately, for example on an hourly basis. *Table 28* shows that in fact there were only 423 patients exposed to oseltamivir in the first 24 hours of hospital stay. By simple subtraction we also know that 155 patients had no exposure to oseltamivir during the first 24 hours of hospitalisation. This more accurate data then leads to more accurate estimates of the cumulative mortality. If we were to use hourly data then we would obtain more accurate estimates and reduce time-dependent bias further.

Severity of illness and competing risks analysis

Of 578 patients, 517 had an APACHE II score recorded, with the proportion missing being greater for the untreated patients than the treated patients (37% vs. 9%; $p < 0.0001$). Mortality was not significantly higher in the patients with missing APACHE II score (25% vs. 20%; $p = 0.35$). In those with an APACHE II score recorded there was no evidence of a difference between treated and untreated patients [untreated mean (SD) 19 (10)¹² vs. treated mean (SD) 21 (10);¹⁰ $p = 0.39$]. Owing to the large difference in proportion missing between untreated and treated patients combined with similar observed scores in the two groups, unadjusted competing risks analysis was conducted using the method of Fine and Gray.¹⁸⁰ Results show insufficient evidence of a difference in mortality (HR 0.84, 95% CI 0.41 to 1.73; $p = 0.64$) or discharge (HR 1.41, 95% CI 0.73 to 2.74; $p = 0.31$).

TABLE 27 Time from admission to death by time-fixed treatment status

Days since admission	Number at risk (AV)	Number dead (AV)	Cumulative mortality (%) (AV)	Number at risk (no AV)	Number dead (no AV)	Cumulative mortality (%) (no AV)
1	540	4	0.7	38	3	7.9
2	536	14	3.3	35	3	15.8
3	519	4	4.1	32	0	15.8
4	507	2	4.5	31	0	15.8
5	498	3	5.0	29	0	15.8
6	485	4	5.8	27	1	18.9
7	467	6	7.0	26	1	22.0
8	449	4	7.9	25	0	22.0
9	441	4	8.7	23	1	25.4
10	422	8	10.4	22	0	25.4
11	394	7	12.0	22	1	28.8
12	375	6	13.4	20	0	28.8

AV, antiviral.

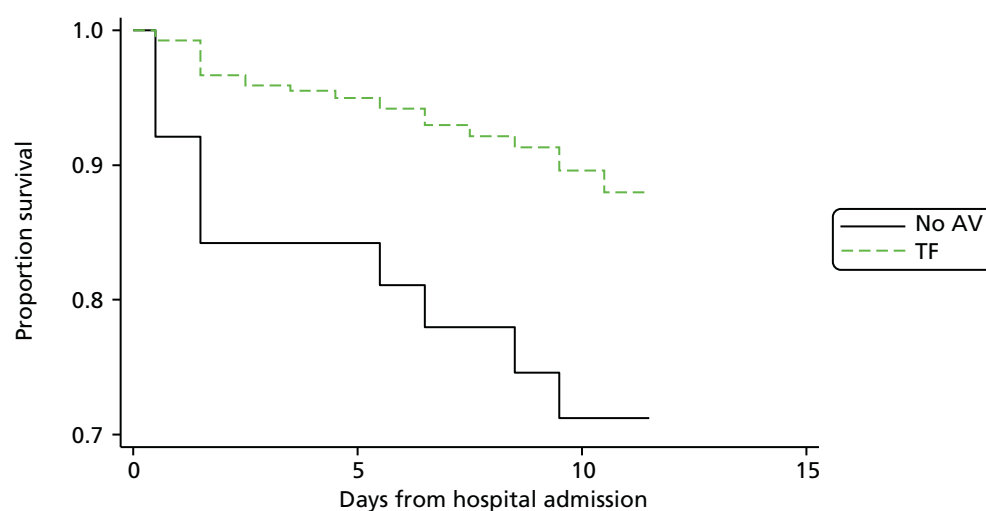
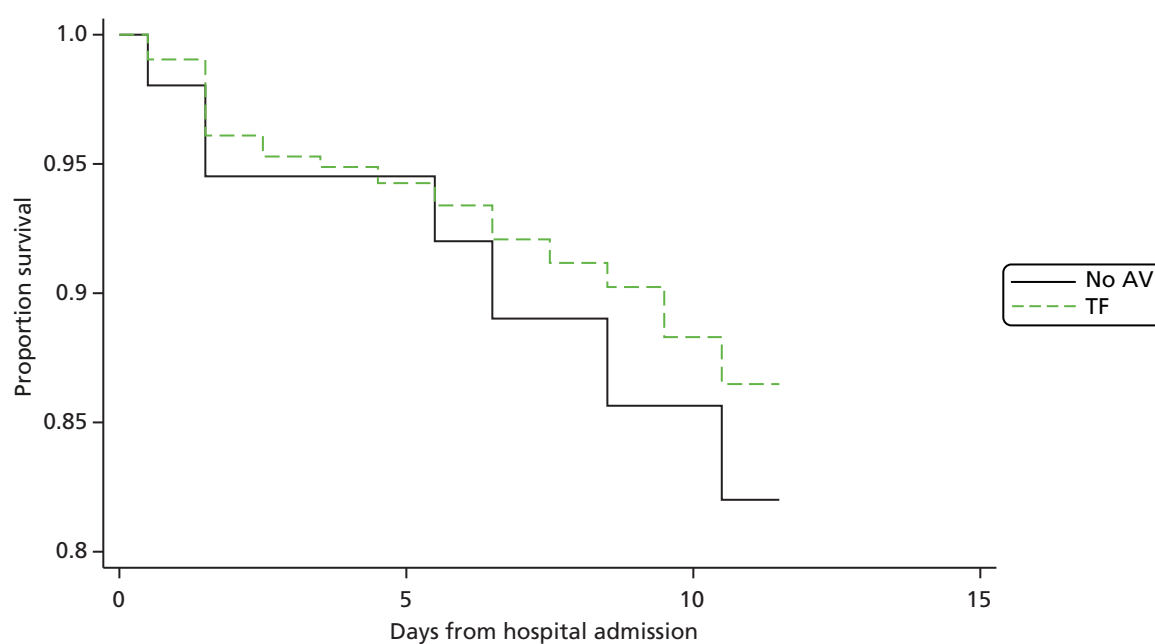
**FIGURE 24** Kaplan-Meier plot of time to death. AV, antiviral; TF, Tamiflu (oseltamivir).

TABLE 28 Time from admission to death by time-dependent treatment status

Days since admission	Number at risk (AV)	Number dead (AV)	Cumulative mortality (%) (AV)	Number at risk (no AV)	Number dead (no AV)	Cumulative mortality (%) (no AV)
1	423	4	1.0	155	3	2.0
2	484	14	3.9	87	3	5.5
3	487	4	4.7	64	0	5.5
4	485	2	5.1	53	0	5.5
5	481	3	5.7	46	0	5.5
6	472	4	6.6	40	1	8.0
7	459	6	7.9	34	1	11.0
8	442	4	8.8	32	0	11.0
9	434	4	9.7	30	1	14.4
10	415	8	11.7	28	0	14.4
11	388	7	13.5	28	1	18.0
12	370	6	14.8	25	0	18.0

AV, antiviral.

**FIGURE 25** Survival plot for time-dependent treatment exposure. AV, antiviral; TF, Tamiflu (oseltamivir).

Appendix 16 Feedback

1 From Michael Power, Sowerby Centre for Health Informatics at Newcastle, 15

December 2010

Summary

From: Michael Power <michael.power@schin.co.uk>

Date: 15 December 2010 18:51

Subject: Neuraminidase inhibitors for influenza - HTA project

To

Hi

I picked up Carl's Twitter request for comments on your draft protocol "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data". So, here are my two comments on the content.

The title confused me: I expected it to be a review of unpublished trials to complement your review of published trials. It would be longer but clearer if you could call it "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports for published and unpublished trials".

The section "How the intervention might work" could be reorganized along the lines of:

- 0) Metabolism: oseltamivir phosphate (OP), Tamiflu, is the pro-drug of oseltamivir carboxylate (OC), the effective form. OP dissociates in the gastrointestinal tract to form oseltamivir (OT) which is absorbed and metabolised into OC by hepatic carboxylesterase (h-CE).
- 1) Reducing the ability of the virus to penetrate the mucus in the very early stage of infection (Bhatia 2007; Matrosovich 2004; Moscona 2005; Ohuchi 2006).
- 2) Inhibiting neuraminidase, which enables influenza viruses to exit host cells (Liu 1995; Moscona 2005).
- 3) Central depression by OT (Hama 2008) may cause hypothermia (Ono 2008).
- 4) Inhibition by NIs of human sialidase may cause abnormal behaviour (Li 2007).

You have obviously put a huge amount of work and expertise into developing the protocol, and have an even bigger task ahead to complete the review. Congratulations for taking this on.

Best wishes

Michael

Reply

Thanks for the constructive comments.

We have re-titled the Protocol to address this concern (and that of feedback from GSK, see below);

We have re-examined the "How the intervention might work" section but made only small adjustments in the interest of keeping this section short;

We are not sure what problems you might have had printing the pdf file, and hope they are resolved with this new version.

Contributors

Chris Del Mar

2 From Juan C. Vergara, Intensive Care, Hospital Cruces, 48901 Barakaldo, Spain, 24**February 2011****Summary**

From: JUAN CARLOS VERGARA SERRANO <JUANCARLOS.VERGARASERRANO@osakidetza.net>

Date: 24 February 2011 12:48

Subject: oseltamivir

To:

I've read your Intervention Protocol: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data. And may be you can be interested in this letter I wrote to de BMJ: <http://www.bmj.com/content/340/bmj.c789.extract/reply>

1. Early use of oseltamivir does not reduce swine flu mortality, Juan C. Vergara, MD. Intensive Care Unit, Hospital Cruces. 48901 Barakaldo. Spain

As you say, in July the National Pandemic Flu Service started providing oseltamivir to anybody who telephoned with a plausible set of symptoms. From 23rd July to 1st December, the National Pandemic Flu Service (NPFS) in the UK, has provided more than one million courses of antiviral medication. By that time the Spanish Health Secretary General, José Martínez Olmos, at the Congress of Deputies, announced that only 6.000 patients (most of them hospitalised) had received oseltamivir in Spain. At the end of January there have been 411 deaths reported due to pandemic (H1N1) 2009 in the UK, and about 300 in Spain. That means 6.7 and 6.5 deaths per million, respectively. These data create serious doubts about the real utility of early use of oseltamivir in preventing deaths from Influenza A H1N1.

<http://www.nhsdirect.nhs.uk/article.aspx?name=SbSwineflu>

http://www.congreso.es/public_oficiales/L9/CONG/DS/CO/CO_411.PDF

Competing interests: None declared

Yours sincerely;

J. C. Vergara

Reply

Thank you for your interest.

Contributors

Chris Del Mar

3 From Dr Helen Steel, GSK, UK, 30 March 2011

Summary

GSK comments on Cochrane Collaboration protocol: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data

General:

The term '**unpublished data**' is used extensively in the protocol. However, it does not appear to be clearly defined either in the protocol or in Jefferson's comment in the 15 Jan 2011 edition of the BMJ. Additionally, the term '**unpublished data**' is misleading. It appears the Cochrane Group use this term interchangeably with Clinical Study Reports, regardless of whether a primary manuscript is available for a given study. We suggest this is clarified or preferably replaced, especially since the term appears extensively in the protocol including the title. Readers are likely to use the terms 'unpublished data' and 'unpublished trials' (trials for which no primary publication appears in the scientific press) interchangeably. A suggested replacement is 'Clinical Study Reports' since this term is not easily misinterpreted and is clearly defined in Jefferson's BMJ comment.

The 'scope of clinical trial data' are defined in Jefferson's BMJ 15 Jan 2011 comment, as mentioned above (i.e. definitions for clinical study reports, raw data, unpublished trial, published trial, regulatory data). It would seem important that these and any other definitions introduced in the protocol are included in the protocol.

Description of Intervention

This section incorrectly describes Relenza as 'nebulized zanamivir'. Relenza is formulated in Rotadisks containing foil blisters with a powder mixture of zanamivir and lactose. Relenza is administered by oral inhalation using a breath-activated device called the Diskhaler. Earlier clinical studies explored several methods of administration, including nebulized and intranasal routes but marketing approval in nearly all countries is currently available only for oral inhalation via Rotadisk/Diskhaler.

Types of Studies

To meet the objective of providing a comprehensive review of neuraminidase inhibitors in preventing and treating influenza, it would seem appropriate that clinical trials from all sources (including sponsors other than industry) be included in this meta-analysis. Please clarify if this is your intent.

Outcome Measures

More details should be provided on the outcome measures section in the final protocol.

For example, broad outcome measures are stated in the protocol but specific endpoints are not provided. The primary and secondary endpoints of the meta-analysis should be clearly defined in the final protocol.

e.g.1. A stated primary outcome in the treatment studies is 'symptom relief'. Does this refer to 'the time to alleviation of symptoms' or 'reduction in symptom score' or another endpoint? Time to alleviation of clinically significant symptoms was the primary endpoint used in the majority of GSK treatment studies.

e.g.2. Another stated primary outcome is 'Harms'. Please provide the specific endpoints. Will this refer to 'incidence of most common AEs' or 'incidence of common SAEs', 'incidence of complications' or another endpoint? It is not clear if 'harms' are the same as 'compliharms'. It is not clear what specific events will comprise compliharms.

Prophylaxis studies: Several types of prophylaxis studies were conducted by GSK: household prophylaxis (post-exposure prophylaxis), community prophylaxis and outbreak control in nursing homes, and as such the

designs and/or endpoints are different. It is possible to measure 'prevention of onset of influenza in contacts' in these studies but not 'reduction in viral spread from index cases' in the majority of prophylaxis studies.

Hospitalisations: As studies were generally conducted in the setting of acute uncomplicated influenza, limited hospitalisation data were collected, and are available only for some studies.

Extracting compliharms: There is a statement that 'AEs are reported for all participants while complications are only reported for infected subjects'. This statement is not accurate for GSK trials. AEs are reported for all study participants. However, AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness. Without knowing the specific safety endpoints, it is unclear whether this will affect the outcome of some of the harms analyses.

Data collection and analysis:

The protocol indicates that clinical study reports will be requested (minus participant identification). In fact many documents for each study will need to be redacted not just to remove participant identification but any personally identifiable information including author and investigator identification.

Missing Data. The protocol states "*At the participant level (i.e. within a trial) we will not make any assumptions about missing data.*" This is not possible, because an analysis of data that is collected in a trial can only be done in the context of assumptions about potential mechanisms that led to data being missing (e.g., missing completely at random, or missing at random).

Meta-analysis Method. Little detail is given in the protocol. The protocol states that "*Whether or not heterogeneity is detected, we will perform a random effects meta-analysis. Random-effects methods will be used to compare the dichotomised outcomes (RR and absolute risk reduction (ARR) for efficacy and safety).*" There are several different Random Effects methods available (Bayesian or frequentist, DerSimonian & Laird or Maximum-likelihood or REML), and different approaches to handling rare events (various "corrections" to include trials with zero counts). Furthermore, would random-effects methods also used to compare the continuous outcomes?

Fixed-effects Model. The protocol also states that fixed-effects models will be used in a sensitivity analysis. No details are given with regard to which fixed-effects models will be used. There are several fixed-effects models available including Inverse Variance, Mantel-Haenszel, and Peto's method. The appropriate method used should also depend on the outcome measures (dichotomous vs. continuous; relative vs. absolute). The approach and choice of models for sparse data and rare events should be provided. Furthermore, various methods in the framework of fixed-effects model may be explored to evaluate the robustness of the results.

Hazard Ratio. The protocol states "*We will convert medians of treatment groups into (log) hazard ratios (estimating the variance of these) to enable meta-analysis of time to event outcomes.*" Although hazard ratio (HR) is a standard analysis and widely recommended approach for time-to-event data in clinical trials, the HR analysis may not be suitable for the Relenza studies with relatively short follow-up time because the assumption of proportional hazards required for the proportional hazards model may not hold. GSK did not follow this approach for the original analysis due to the concern stated above. Further the clinical and regulatory interest centred on differences in the time to alleviation not in the relative hazard between treatments. The above issues would be best addressed by using subject level rather than summary data, which GSK have offered to provide to the Cochrane Group.

Analysis Populations. The protocol does not specify which populations will be used for the various analyses, for example, intent-to-treat or influenza-positive or other. We believe that influenza positive population is appropriate, especially for the efficacy analysis using time to alleviation of influenza symptom as a primary endpoint consistent with the prescribing information for Relenza.

Study Duration. No details are given in the protocol with regard to how studies with different follow-up times will be handled.

Trials with no Events. No details are given in the protocol with regard to how to deal with trials in which there are no events (such as death). By excluding studies with no events will make the event appear more common than it actually is. There are various techniques: Bayesian approach, continuity correction, combining similar trials to avoid having any components of the analysis that have no events.

Sensitivity Analyses. Sensitivity analyses using different outcome measures, statistical models and/or continuity correction factors to assess the robustness of the results are strongly encouraged.

Reply

General:

'unpublished data'. We agree that this term is confusing, and are attracted to the proposal of using 'clinical study reports' instead.

We have attempted to ensure all terms are clear.

Description of intervention

Description of zanamivir (Relenza): we have corrected 'nebulized zanamivir' to 'powder inhalation'.

Types of studies

Yes, we intend to comprehensively review clinical trials from all sources (including sponsors other than industry). This intent is clear from the subsection *'Electronic searching'* under the **'Search methods for identification of studies'** section.

Outcome measures

Our specified outcomes are those of interest to patients, and their clinicians and policy-makers. They are therefore likely to be broader than the more specific endpoints selected by trialists. The purpose of Cochrane Reviews are usually to set clinically relevant review questions, and search the literature (or other sources) for answers to them. Sometimes answers to some questions are not available, and this is also documented. Where possible we report outcomes as pre-specified in the trial protocols, or as pre-specified in the review protocol, or otherwise reported as a post-hoc analysis.

e.g. 1. 'symptom relief' may refer to 'the time to alleviation of symptoms' or 'reduction in symptom score', or any other endpoint (including 'area under the curve of symptom score and time').

e.g. 2. 'Harms' include common adverse events (AEs) as well as serious AEs. We agree about the confusion of harms and complications, and have tried to capture the totality of these with the neologism 'compli harms' to avoid classification errors between their different labellings.

Prophylaxis studies: We understand that it is possible to measure 'prevention of onset of influenza in contacts' in some GSK studies but not 'reduction in viral spread from index cases' in others.

Hospitalisations: We understand that hospitalisation data may only be available for some studies. However patient hospitalisation is usually classified as a serious adverse event therefore we expect to identify hospitalisations (not reported separately) in that way.

Extracting compli harms: Your statement that "AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness" underlies the complexity of analysing AEs and complications (our 'compli harms'). We have noted in the protocol that the limitation of complications only reported for the infected patients is relevant to the Roche trials only.

Data collection and analysis:

We are interested that not only subject identification would be required to be removed from any documents of clinical study reports but also information personally identifying authors and investigators. We wonder why.

Missing data. We have removed this statement.

Meta-analysis method. DerSimonian & Laird method will be used. Note that in the case of zero cells (e.g. no events in one group) the RevMan software (which we will use for the analysis) automatically adds 0.5 to each cell of the 2×2 table for any such study. There are no continuous outcomes specified in this review.

Fixed-effects model. Mantel-Haenszel method will be used except in the case of sparse data, in which case Peto's method will be used (as recommended in the Cochrane Handbook).

Hazard ratio. We note the concerns with this outcome hence we will also consider analysis of this outcome as a continuous outcome noting that the data are likely to be skewed. We will use the inverse-variance random-effects method for this analysis.

Analysis populations. All analysis will be using the intent-to-treat population as this is the most methodologically rigorous and clinically relevant.

Study duration. We have specified in the protocol, where appropriate, that we will report outcomes for the on-treatment and off treatment time periods. If data are not available in the clinical study reports for any time period of the study then we will write to the relevant manufacturer to request the missing data.

Trials with no events. As stated above the RevMan software automatically adds 0.5 to each cell of the 2×2 table for any such study.

Sensitivity analyses. We note this point and agree. Where appropriate, a realistic sensitivity analyses will be conducted.

Contributors

Chris Del Mar

4 Feedback from Wolfgang Becker-Brueser, 30 January 2012

Summary

Dear Tom Jefferson,

I read your review about NI for prevention and treating influenza with interest. It's an important work. In the chapter "Why it is important to do this review" I found a small mistake concerning the worldwide stockpiling of oseltamivir which is mentioned to be "CHF 7.6 billion worth of oseltamivir (JACK 2009)". This would be an enormous amount "prior (!) to the emergence of influenza A/H1N1 in 2009". But Andrew JACK wrote in the cited Financial Times (May 13, 2009): "Governments around the world had stockpiled 220m treatments to date, swelling sales since the start of 2003 to SFr7.6bn, largely on the basis of preparation for a pandemic virus that has yet to appear." So 7.6 billion SFr represent sales and not stockpiling.

Wolfgang Becker-Brueser (physician and pharmacist)

Reply

Thank you. The extent of stockpiling is a closely guarded secret this is why these are estimates. We will probably never know.

Contributors

Tom Jefferson MD

5 From Frederick G. Hayden, M.D., 02 February 2012

Summary

I am writing to comment on the recently updated meta-analysis by Jefferson and colleagues published through the Cochrane Collaboration and to request clarifications on several points, as well as to suggest some additional analyses that would be helpful in terms of taking greater advantage of this useful database. While I fully support access of Jefferson and other interested investigators to all of the published and unpublished data from the RCTs of oseltamivir and zanamivir for further analyses, this analysis only focuses on RCTs in ambulatory patients with uncomplicated influenza (the vast majority of whom were previously healthy) and on the period before the 2009 H1N1 pandemic. Consequently, I would urge these investigators to extend their efforts to other populations and datasets examining the risks and benefits of using neuraminidase inhibitors (NAIs) for treatment and prophylaxis. Furthermore, the authors should acknowledge the limitations of their analyses more explicitly and avoid inappropriate extrapolation to populations and influenza events that the RCTs did not adequately address. Differences in disease pathogenesis related to virus and host factors, as well as time to treatment, have important effects on the utility of antiviral agent interventions. My specific comments and recommendations for additional analyses follow:

1. Use of Intention to Treat (ITT) and ITTI-Infected Groups. The exclusive focus in the current treatment analysis on the ITT population is a readily rectified shortcoming. Outcomes in all three groups of relevance (ITT, ITT-infected, and ITT-noninfected) should be presented, so that readers can examine both clinical effectiveness and efficacy for the key endpoints, as well as events in those without documented influenza. Because NAI treatment would not be expected to provide any benefit in non-influenza illness, not presenting the ITT-infected outcomes in the analysis underestimates possible beneficial drug effects. Assessment of the non-infected group provides a valuable control and also enables a determination of whether there was a potential drug-disease adverse interaction of NAI treatment in non-influenza patients. Of note, our earlier pooled analysis of physician-diagnosed lower respiratory tract complications leading to antibiotic use found a significant benefit of oseltamivir in the influenza-infected patients but not in those enrolled in whom influenza infection was not detected by culture or serology [Kaiser 2003].
2. Sample size considerations. Severe outcomes of influenza infection are sufficiently uncommon in previously healthy people that even large RCTs or combining multiple RCTs would be very unlikely to detect them with confidence. The same point applies to very uncommon endpoints like microbiologically documented bacterial complications and rare adverse effects of treatment. Consequently, conclusions that there is no evidence (from trials) that NAIs reduce the risk of pneumonia, hospitalisations, deaths are overstated, as the evidence considered in this analysis is insufficient to properly address these questions.

The US CDC has estimated age-related influenza-related hospitalisation and mortality rates for both seasonal epidemics and the 2009 pandemic [Shrestha 2011]. Jefferson and colleagues should use such event estimates and others to make calculations of the necessary sample sizes to detect reductions in these severe outcomes with NAI therapy in a controlled RCT across a range of clinically relevant effect sizes (e.g., 20%, 35%, 50% reductions). In a related fashion, they should also provide more quantitative estimates for their ability to detect such outcomes with their existing database and comment more precisely on their power to capture particular endpoints.

3. Complications in ambulatory patients. Other clinically relevant endpoints in these previously healthy and at-risk persons warrant investigation. With regard to influenza-related complications, the most frequent in previously healthy children and adults are respiratory tract infections (otitis media, bronchitis) leading to antimicrobial use. These are usually not severe and typically not microbiologically documented with respect to etiologies but physician-diagnosed complications leading to antibiotic use is an outcome that has important clinical and public health implications (i.e., cost, antibiotic resistance, side effects) and also is sufficiently frequent to demonstrate effects of antivirals. We showed such a benefit in adults in our earlier pooled analyses

of the then available RCT data on inhaled zanamivir [Kaiser 2000] and oral oseltamivir [Kaiser 2003]. The oseltamivir effect was confirmed in a recent meta-analysis [Hernan 2011], and another recent Cochrane report confirms an effect on otitis media in children [Wang 2011].

Given the large amount of data available to the investigators, it would be a valuable contribution to also explore the clinical outcomes in greater detail and to clarify the use of terms like severe outcomes. Although uncommon in the populations enrolled in these RCTs, endpoints such as radiographically documented pneumonia, microbiologically documented infections, and hospitalisation or death are clear and should be listed separately in those with or without proven influenza infection. Because of the importance of hospitalisations as an endpoint, it would be helpful to examine not only all-cause hospitalisations but also relevant subgroups based on likely causation (e.g., events in which influenza was documented or likely implicated including exacerbations of co-morbidities vs others like accidents, elective surgeries, conditions unlikely to be influenza-related). In addition to these events, exacerbations of underlying conditions (e.g., asthma, COPD, diabetes, CHF) are of medical importance in influenza outpatients with co-morbidities and should be examined.

4. Data from observational studies. Typically the patients who are most at risk of severe outcomes (older people, infants and young children, those with underlying chronic conditions) are not included in RCTs. In this regard, the current analysis is limited to placebo- or active-controlled RCTs largely done in previously healthy persons and does not consider the multiple observational studies from different countries that have consistently showed protective effects against severe outcomes like pneumonia and hospitalisation, particularly in those with co-morbidities, as well as reduced mortality if patients have been hospitalised. A considerable amount of new treatment data was generated in many countries during the 2009 H1N1 pandemic that found timely NAI treatment to be associated with a lower risk for intensive care admission and death (reference list available upon request).

While such data and analyses are weaker than RCT data and subject to bias, these observational studies address key endpoints in at-risk and seriously ill populations, including patients admitted to a hospital at the time of initiating therapy, that the available RCTs cannot and do not address. Furthermore, the standard of care has evolved such that placebo-controlled RCT in such patient groups would not be acceptable to investigators or ethics committees. The decision by Jefferson and colleagues not to consider and critically analyse the large amount of observational data with modern techniques means that they are not incorporating key information and many important patient groups in which the available data suggests medically important benefits from early NAI therapy. Such findings from observational data can inform antiviral treatment in more severely ill patients when no other data are available. As discussed above, not to include observational data means that conclusions of no effect on uncommon events or no severe adverse events being detected are almost inevitable. This should be made explicit in the design and the conclusion of the current report.

4. Influenza diagnosis and serologic results. The Jefferson report raises questions about the possible inhibitory effects of oseltamivir therapy on influenza-specific serologic rises and introduction of bias into the outcomes analysis. Further analyses might help to assess these possibilities. They should compare the primary endpoint of illness alleviation between the oseltamivir and placebo subgroups that were culture-positive (irrespective of serologic findings) at enrolment, and separately those that were culture-negative but had serologic evidence of infection.

Of note, one prior study of oseltamivir treatment in pandemic 2009 H1N1 patients, although not in seasonal influenza patients, suggested that early treatment could reduce antibody responses [Cowling 2010]. Jefferson and colleagues should examine the age-related frequencies of HAI seroconversions and the GMT titre rises in those with influenza-culture positive illness and separately in those with such HAI rises in absence of culture positivity. Of course, if still available, it would be interesting to test the culture-negative enrolment samples by RT-PCR.

The RCT data were generated over multiple seasons in which different influenza A and B viruses were circulating. Influenza B neuraminidases are generally less susceptible to oseltamivir carboxylate and several observational studies indicate that oseltamivir is less effective in influenza B- than influenza A-infected children

[Sugaya 2007; Sato 2008]. It would be useful to examine the primary outcome in relation to virus type (A vs. B) and if possible A subtype (H3 vs. H1) in those with documented infections to expand on this point.

5. Other treatment endpoints of interest. Since those enrolled in the RCTs were outpatients, it would be useful to explore other endpoints that reflect patient recovery and impacts on the healthcare system (e.g., nonscheduled return visits for complications or adverse events). Perhaps more important than the time to alleviation endpoint used in the registrational trials might be the times to resumption of usual activities and return to pre-morbid status.

The authors raise the possibility that oseltamivir might have non-specific antipyretic effects, and one animal model study has also suggested possible adverse immunomodulatory effects of oseltamivir in RSV infection [Moore 2007]. Consequently, it would be interesting to examine the course of fever resolution (a much earlier event than cough resolution) and of symptoms in oseltamivir- and placebo-treated patients with and without documented influenza infections. In addition, it would be valuable to examine the correspondence (or lack thereof) between influenza virologic measures (e.g., enrolment virus titre, time to culture negativity, change in viral titres over time) and symptom resolution measures in both oseltamivir and placebo groups.

Various cost-effectiveness analyses on NAI therapy in low-risk populations have been published with widely divergent outcomes, largely depending on the input assumptions. Using this large database, a more refined analysis that incorporates both the direct and indirect (productivity losses) costs of influenza would be informative.

6. Adverse events with treatment. With regard to drug tolerability, it is important to examine not only the frequencies of reported adverse events but also assess indicators of their severity and interference with compliance (e.g., symptom days, patient reported severity, premature cessation of study drug).

Comparisons of AEs in the placebo groups across zanamivir and oseltamivir studies need to be interpreted with caution, since these studies were performed in different influenza seasons viruses and locations, with different protocols and case record forms, and by different investigators. Only one head-head RCT of treatment comparing these drugs has been published to date to my knowledge but the design did not include placebo only groups [Duval 2010]. In particular, comparisons in children (page 24) need to be age-adjusted as there were major differences in those enrolled into the zanamivir (5 years and older) and oseltamivir trials (1 year and older), and the frequencies of gastrointestinal manifestations are much higher in younger children with influenza and other acute illnesses.

7. Prophylaxis endpoints of interest. The analysis of prophylaxis outcomes and the associated discussion requires clarification. The statement on page 5 says: "The FDA has also not allowed an indication for interference of viral transmission within households (the key concept behind post-exposure prophylaxis)." The key concept behind post-exposure prophylaxis is prevention of illness in exposed persons, and the primary endpoint in most prophylaxis studies has been symptomatic, laboratory-confirmed influenza illness. FDA and other regulatory agencies have approved both NAIs for post-exposure prophylaxis in households and also for longer duration pre-exposure chemoprophylaxis [reviewed in Khazemi 2009].

The Jefferson analysis seems to focus exclusively on the effect of chemoprophylaxis in "preventing the spread" of influenza, with endpoints presumably determined by evidence of culture or serologically confirmed infection irrespective of illness. While this is one endpoint of interest in such studies, the primary outcome of medical interest is prevention of influenza illness in those exposed. There is abundant RCT data, as well as observational data from the 2009 pandemic, that both inhaled zanamivir and oral oseltamivir have both statistically significant and medically important effects on preventing influenza-specific illness. Of note, the development of serologic evidence of infection without illness is advantageous in those receiving chemoprophylaxis, as it likely is an immunizing event that protects against future infection and illness by that strain. In addition several oseltamivir RCTs have shown significant but lesser effects on influenza infection in prophylaxis recipients [Welliver 2001; Hayden 1999]. The authors should present all of the relevant endpoints in their analysis of the prophylaxis trials.

8. Adverse effects with prophylaxis. The prophylaxis studies are particularly useful in assessing drug tolerability as symptoms of acute illness present in treatment studies are not confounders and there is a more prolonged duration of drug exposure. However, it is essential to examine not only the frequencies of reported adverse events but also indicators of their severity and possible interference with compliance (e.g., symptom days, patient reported severity, premature cessation of study drug).

For example, the Jefferson posting states that "Similarly, a published prophylaxis trial (Hayden 1999a, known by its trial ID WV15673/WV15697) describes headache as having "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)." but indicates that Japanese regulatory documents reached a different conclusion. My own review of the adverse event tabulations from our 6-weeks prophylaxis study (tables provided by the sponsor) indicates that the proportions of subjects reporting headache (not otherwise specified) that might have been related to study drug (unrelated reports excluded) during the treatment phase were similar across the placebo (N=116, 22.4%), oseltamivir 75 mg once (N=124, 23.8%), and oseltamivir 75 mg twice (N=132, 25.4%) daily dose groups [Hayden 1999]. Most of these reports indicated mild or moderate intensity and were self-limited. As indicated in the published paper [Hayden 1999], study withdrawals for AEs or illness occurred infrequently across these same groups (N=10, 1.9%; N= 8, 1.5%; N= 7, 1.3%). Of note, the specified causes for AE-related withdrawals included three reports of headache associated with other symptoms in the placebo group. In contrast, there were no reports of headache as reason for the withdrawals receiving oseltamivir; gastrointestinal complaints accounted for withdrawals in 4 of 8 oseltamivir 75 mg and 3 of 7 oseltamivir 75 mg twice daily recipients. The total numbers of patients with premature study withdrawal for any reason was 21 (4.0%), 17 (3.3%), and 16 (3.1%) across the three groups, respectively. Overall, severe AEs were reported in 82 (15.8%) of placebo, 75 (14.4%) of oseltamivir 75 mg, and 77 (14.8%) of oseltamivir 75 mg twice daily recipients. We were unable to include these details in the paper because of space limitations but my interpretation remains that no excess of clinically relevant oseltamivir-related headache occurred during this study. This type of detailed AE analysis incorporating severity measures provides necessary context in interpreting the possible importance of AEs.

9. Peer review. The questions raised and opinions expressed in this and earlier Cochrane reports on NAIs by Jefferson and colleagues have resulted in debate and sometimes confusion among practitioners and policy makers regarding the appropriate use of NAIs in seasonal and pandemic influenza responses. Given the importance of these issues, it would be helpful for any future updates to have proper independent review before posting or publication by the Collaboration, as the Cochrane methodology of publication and then independent peer review is not well understood by many people.

Thank you for the opportunity to provide comments. I look forward to seeing the responses from Dr. Jefferson and his colleagues on these points.

Sincerely,

Frederick G. Hayden, M.D.
Stuart S. Richardson Professor of Clinical Virology
Professor of Medicine
University of Virginia School of Medicine
Charlottesville, Virginia, USA

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Submitter has modified conflict of interest statement: Disclosures to BMJ (Updated 4 June 2012)

Dr. Hayden received lecture and/or consulting honoraria from GSK until 2002 and from Roche until 2005. Gilead Sciences from 1996-1999 and Roche from 1999-2005 provided grant support to the University of Virginia for oseltamivir studies on which he was PI. Similarly GSK provided grant support to the University of Virginia for zanamivir studies from 1994-2001. Dr. Hayden served as medical officer in the Global Influenza Programme from 2006-2008 with funding provided to the University of Virginia through the National Institute of Allergy and Infectious Diseases (NIAID). Since 2008 to present the University of Virginia has received funding from the Wellcome Trust for his part-time work as influenza research coordinator at the Trust and

through NIAID for his work as consultant the Southeast Asia Infectious Diseases Clinical Research Network. From 2008-11 the University also received honoraria for his participation in the Neuraminidase Inhibitor Susceptibility Network which received funding from Roche and GSK. Since 2008 to present, Dr. Hayden has been an unpaid consultant to multiple companies engaged in the development or marketing of influenza antivirals including Roche and GSK.

Dr. John Treanor reports receiving compensation as a member of the scientific advisory boards of Novartis and Immune Targeting Systems, and has performed consulting work for Pfizer. Within the last 3 years, his group has been funded to perform laboratory assays or conduct clinical trials for Sanofi, GlaxoSmithKline, Protein Sciences Corp, Wyeth, PaxVax, Ligocyte, and Vaxinnate.

Dr. Kaiser reports no financial disclosures.

Frederick G. Hayden

Reply

Response to Dr. Hayden's comments of 2 February 2012.

We thank Dr. Hayden for his detailed feedback. However nothing he writes allays our basic concerns that:

- (1) despite the 16,000 pages we analysed, we currently only have access to a very limited dataset hence cannot carry out many of the analyses Dr. Hayden suggests;
- (2) analysing the "influenza infected" population in Roche oseltamivir trials, as Dr. Hayden proposes, will lead to misleading results because the treatment groups are not comparable for this population;
- (3) the observational studies Dr. Hayden urges us to consider are generally of poor quality and only represent the small proportion of patients who are hospitalised with influenza;
- (4) the Kaiser et al (2003) analysis is seriously flawed;
- (5) data have been selectively reported.

Below, we provide point-by-point responses to Dr. Hayden's concerns. (Please note that point 4 appears twice, to follow the numbering in Dr. Hayden's letter.)

1. Use of intention to treat (ITT) and ITTI-infected [sic] groups

We agree, in principle, to conduct analysis using the ITT-infected (ITTI) sub-population provided that it is appropriately selected by the results of testing completed before the start of the trial (for example by using only the results of viral culture or rapid testing before randomisation).

However we argue that this is not possible in Roche oseltamivir trials. In these trials, the selection of "infected" or "non-infected" was dependent on the results of serology that is affected by "use" and "non-use" of oseltamivir. And the selection of those with "serology-positive results" appears to have given advantage to the oseltamivir group. Hence the method of selecting the ITT-Infected population in the trials has fundamental flaws and therefore the results are less reliable than those obtained using the ITT population.

2. Sample size considerations

The Kaiser et al analysis has a number of fundamental problems. First, analyses were performed on the ITT-infected sub-population which we have shown to be non-comparable between treatment groups. Second, the authors analysed an outcome that was different to that pre-specified in the trials. In the trials, complications included otitis media and sinusitis but in the Kaiser et al paper these were not included. This is an example of selective reporting or "cherry picking". Third, complications were not objectively or consistently measured in the trials. Fourth, outcomes such as pneumonia and bronchitis could be either reported as a complication or as an adverse event according to a classification criteria we do not understand and is not discussed in the Kaiser et al paper. And finally the data from the 10 trials was not meta-analysed, rather, it was combined as if generated from one single trial.

We could potentially address most of these limitations (except for the third) but we have not been given access to the data despite repeated requests to the manufacturer. However we were able to compare hospitalisations as those data were available to us for the ITT population.

We found no evidence of effect on hospitalisations based on seven studies with a median placebo group event rate of 0.84% (range 0% to 11%): odds ratio (OR) 0.95; 95% CI 0.57 to 1.61, $P = 0.86$). This result is quite different to that reported by Kaiser et al based on the (non-comparable) ITT Infected population.

In terms of power analysis, to detect a significant difference at this level of difference of 0.84% (placebo) vs 0.80% (oseltamivir), with alpha of 0.05 and power of 0.8, a RCT with approximately 800,000 participants is required.

3. Complications in ambulatory patients

As we have illustrated above the Kaiser et al (2003) analysis has fundamental flaws that we cannot address because the manufacturer refuses to provide us with the data necessary to conduct a proper analysis.

Analysis of the "population with proven influenza infection" (ITT-infected population) is not appropriate (see above). Data for the analysis of "population without proven influenza infection" are not available to us.

As we have shown above, the power to detect a difference in all-cause hospitalisation is very small hence to do a subgroup analysis on this outcome seems unwarranted.

The pharmacological/toxicological adverse effects of oseltamivir can be classified into two major types [3]. One is sudden type occurring during the hypercytokinemic state in the early phase of infection including sudden death [3,4], accidental death after abnormal behaviours and vomiting induced by the central depressing action of unchanged oseltamivir [4]. The second are delayed type of reactions including recurrence or exacerbation of influenza and/or other infection, diabetes, bleeding, renal impairment and delayed type neuropsychiatric reactions related to inhibition of the host's neuraminidase [3]. Sudden type adverse effects should be collected and analysed only during the early phase of influenza (for example, vomiting was only significantly increased within one day of treatment in the paediatric RCTs). However, delayed type adverse effects should be collected and analysed for a longer period to detect those reactions after a full course of treatment (for example the increase of pneumonia in the off-treatment period in the paediatric RCTs).

A recently published proportional mortality study has indicated that oseltamivir increases sudden type of death (odds ratio: 5.9) compared with zanamivir users by analysing all death cases among approximately 20 million 2009A/H1N1 influenza patients in Japan. This effect was also true for the comparison of oseltamivir users with non-users of antivirals [4].

4. Data from observational studies

Observational studies during the 2009 H1N1 influenza outbreak have assessed the effects of oseltamivir on a selected population of hospitalised patients. These represent a very small proportion of the total population who get influenza. While subgroup analyses are important, it is important to not lose sight of the fact that the use and governmental stockpiling of oseltamivir is for its routine use in asymptomatic and symptomatic members of the community. Our review thus considers the evidence base that applies to the vast majority of people.

In addition, the studies Dr. Hayden appears to be referring to are retrospective observational studies in which apparent treatment effects may be the result of an effective treatment but could also be due to confounding effects. Unfortunately there is no way to determine which of these possibilities is true. That is why drug regulators require evidence from RCTs to determine whether or not a drug is approved for use. According to the analysis by Jones and Hama [5], apparent protective effects against severe outcomes like pneumonia, hospitalisation and mortality are possibly derived from survivor treatment selection bias (or immortal time-bias). This is not an issue for randomised controlled trials because follow up begins at the time of randomisation which is the same for patients allocated to active drug and patients allocated to placebo. However in the case of

observational studies treatment can begin at varying times (up to several days) after the onset of symptoms. Therefore a naive comparison that compares a binary outcome, such as death (or other adverse event), or time to an event (survival time) is at high risk of survivor treatment selection bias (also referred to as immortal time bias or simply time dependent bias). This bias can occur, for example, because patients who die early are not given the opportunity to receive treatment. In addition patients who are extremely sick may not be given the opportunity to receive antivirals because other treatments and procedures take priority. This bias can be addressed with an appropriate analysis however this has not been done in any of the observational studies of antiviral use for influenza that we have seen.

4. Influenza diagnosis and serologic results

We do not have access to the data required to conduct all these analyses.

5. Other treatment endpoints of interest

We do not have access to the data required to conduct these analyses (time to resumption of usual activities and return to pre-morbid status) using the ITT population.

By mentioning the evidence and possible mechanism of action for oseltamivir, we are arguing that fever alleviation and symptom reduction may not be caused by the reduction of viral load but may be the result of inhibition of host's immune functions including induction of cytokines and antibody production by inhibition of the host's neuraminidase in addition to central depression by oseltamivir.

Analysis of the population with documented influenza infection (ITT-Infected population) is not valid (see above). Hence we are unable to conduct a valid analysis in the influenza positive population and data for the influenza negative population has not been provided.

Antibody titre is one of the ways of selecting only subjects infected with influenza. However we have shown that the production of antibodies was consistently lower in the oseltamivir group compared to the placebo group in the treatment trials. Therefore the use of antibody production to confirm influenza in prophylaxis trials is not valid. Moreover comparison of the proportion with confirmed infection between the oseltamivir group(s) and the placebo group will provide misleading results.

Nor are "virus titre", "time to culture negativity" or "change in viral titres over time" a true measure of viral load, because oseltamivir as a neuraminidase inhibitor may conceal positivity by inhibiting the influenza virus from leaving the surface of host respiratory cells (which are covered by a mucous layer on the surface of the cells).

6. Adverse events with treatment

In principle we agree. However, there are many data that show the classification of severity is questionable: for example, we believe that *psychosis* or *hallucinations* should be classified as "severe" but this has not always been followed. Therefore, we are planning to propose using new classification methods for the analysis of adverse events in the next update of our review.

We agree that comparisons of adverse events in the placebo groups across zanamivir and oseltamivir studies need to be interpreted with caution.

We agree that the spectrum and severity of adverse events/reactions are different among age groups. Therefore, we propose analysing adverse events/reactions stratified by age, if possible, according to the data in the Clinical Study Reports or individual patients' data in the next step of our systematic review.

7. Prophylaxis endpoints of interest

As described on page 7 of our systematic review, the primary outcome measures for prophylaxis studies are:

influenza (both symptomatic and asymptomatic and laboratory-confirmed) and influenza-like illness (ILI);

hospitalisation and complications;

interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts);

harms.

We did not meta-analyse data from the prophylaxis trials in this systematic review because the substantial documents for prophylaxis trials were obtained after the time lock of 12 April 2011.

Due to the problems we have illustrated above on using virus titre to confirm influenza infection we plan to amend the primary endpoint for prophylaxis trials to influenza-like illness (ILI).

There is some fear that those with serologic negative infection without symptoms may be more easily infected with influenza virus in the future, because evidence from animal experiments shows that IgA antibody in the respiratory mucosa is reduced (to about 20% of the control group), while reduction of those of systemic IgG antibody (HI antibody) was slight and not statistically significant [6].

8. Adverse effects with prophylaxis

We agree that the prophylaxis studies are particularly useful in assessing drug tolerability.

As we discussed above ("7. Adverse events with treatment"), there are many data that show the classification of severity is questionable. For example, we believe that psychosis or hallucinations should be classified as "severe" but this has not always been followed. Therefore, we are planning to propose using new classification methods for the analysis of adverse events in the next step of the review.

We mentioned the statement "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)" as an example of reporting bias present in the paper (Dr. Hayden's reference no. 3; known by its trial ID WV15673/WV15697).

The numbers for headache are 47% (242/520) in high-dose oseltamivir group, 43% (335/520) in low-dose oseltamivir group and 39% (202/519) in placebo group. These proportions are not similar and show a significant linear trend of increase with oseltamivir dose ($P = 0.013$).

In addition, we would be grateful if Dr. Hayden were to supply the definition of "drug related headache among headaches reported as adverse events"? In particular, how was it decided whether a headache was drug-related or not? We cannot suggest signs or symptoms to distinguish oseltamivir-induced headache from placebo-induced headache.

We propose analysing adverse events in clinical study reports, including those for prophylaxis trials.

9. Peer review

We agree that there is confusion among policy-makers and practitioners but believe this to be justified: the data published and accessible to them appear to have some flaws that need to be resolved. We are encouraged by Dr Hayden's support for our obtaining all the data necessary to clear the confusion.

Cochrane systematic reviews are stringently peer-reviewed. Not only are they peer-reviewed by independent experts prior to publication but the protocols are also peer-reviewed before being undertaken, to reduce a priori biases. In addition, protocols are available for comment from outside the internal review process – Dr Hayden himself, or employees of Roche the manufacturer of oseltamivir, could have provided input about suggested alterations to the protocol which we would have been glad to receive. To this extent the peer-review process is more stringent than that employed by most other scientific journals.

RH, MJ, TJ, CDM, PD

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6 Additional feedback from Frederick G. Hayden, 10 August 2012

Summary

I am writing to respond to the comments and questions raised by Jefferson and his colleagues to my letter of 2 February 2012 about their report published through the Cochrane Collaboration. While the authors have provided helpful clarifications to many points, I remain concerned about their selective approach to data analysis and presentation. Resolution of these issues is important in anticipation of future analyses by Jefferson and colleagues or by others. Many of their responses indicate that analysis of the cohorts with proven influenza infection (ITT-infected) are not appropriate but further analyses of patient level data should be able to address their concerns (see below). Also they identify biases that could make oseltamivir look better but not those that could make it look worse than its effectiveness and tolerability likely are in reality. An impartial analysis would identify biases in both directions and attempt to deal with them in a balanced appraisal.

My specific comments and recommendations for additional analyses follow:

1. Use of intention to treat (ITT) and ITTI-infected groups. One obvious means of addressing the concern about selection bias in defining the ITT-infected (ITTI) population for analysis is to focus on those who were influenza virus-positive (irrespective of serologic results) at enrolment. These individuals (ITTI-virus) represented approximately 70-85% of those enrolled into the ITTI cohorts across the various RCTs.

In addition, those who were included in the ITTI group solely on the basis of seroconversion could be analysed separately to assess overall comparability in terms of symptom resolution and complications to those who were both virus-positive (ITTI-virus) and showed serologic rises. This might also help determine whether inclusion of data from virus-negative seroconverters would affect overall findings.

In contrast to the Cochrane statement that "And selection of those with "serology-positive results" appears to have given the advantage to the oseltamivir group", it might alternatively be disadvantageous (bias toward the null) or neutral in effect. If oseltamivir is most beneficial in preventing lower respiratory tract (LRT) complications leading to antibiotic use in those in whom it also prevents seroconversion, as one might expect if its overall treatment effect varies between patients based on timing of administration, individual pharmacokinetics or other factors, then its protective effect on complications will be underestimated because the benefits in those for whom it prevents seroconversion will not be counted. If, on the other hand, treatment works effectively only in those infected who seroconvert and has little or no effect in those in whom it prevents seroconversion, this would increase the apparent benefit. However, the only way in which this sequence seems possible would be if late treatment does not interfere with seroconversion but early treatment does AND late treatment is more effective than early. This is biologically implausible and inconsistent with the observed effects on time to treatment for other outcomes, in which early treatment is associated with greater effects. Alternatively, if oseltamivir treatment has a similar effect on LRT complications in infected who seroconvert and those who do not, this would reduce the numbers in the treated group with and without outcomes in a non-differential way.

In addition to a possible non-specific immunomodulatory effect of oseltamivir on serologic responses or possible confounding effect of prior inactivated influenza vaccine which might blunt antibody responses in those with proven influenza (1), one explanation for the apparently lower seroconversion rate in oseltamivir recipients would be that some oseltamivir recipients had low viral replication levels at enrolment that were quickly reduced by treatment and did not stimulate antibody rises, so that in these persons treatment prevented seroconversion. If one assumes that clinical outcomes are linked to viral replication levels as other reports suggest, such individuals would probably have shorter illness duration and also be less likely to develop LRT complications. Consequently, not counting them in the oseltamivir group would bias towards the null and under-estimate the effect of treatment on both illness resolution and complications. In this regard, comparing outcomes in the ITTI-virus seroconverters vs non-seroconverters would be of interest if sufficient numbers are available. Also, as stated previously, analysis of the serologic responses based on time from symptom onset to

enrolment, including both frequency of seroconversion and observed titres rises in the ITTI-virus group compared to placebo, might help address this possibility.

If I have interpreted their report correctly, the post-hoc analyses by Jefferson and colleagues found an absolute difference of 3.4% in overall infection rates between placebo (68.9%) and oseltamivir (65.5%) groups across the studies they analysed (Figure 5, Table 14). This difference presumably approximates the fraction of virus-negative, non-seroconverting but possibly influenza-infected subjects in oseltamivir group. To what extent this difference might bias outcomes is uncertain but its relatively modest size suggests that misclassification would not be a major confounder in either the ITTI or ITT-non-infected groups. Optimally in future studies more sensitive nucleic acid amplification testing will be used to detect infection by influenza and other respiratory viruses and facilitate more clear delineation of the groups of interest.

In summary, further analyses of the RTCs on oseltamivir and zanamivir, the outcomes in all groups of relevance (ITT, ITTI, ITTI-virus, and ITT-non-infected) are important and should be presented as fully as possible. As stated previously, separate assessment of the ITT-non-infected group provides a valuable control and also enables a determination of whether there was a potential drug-disease interaction of NAI treatment in non-influenza patients. As specific antiviral treatment would not be expected to provide benefit on illness resolution or complications in non-influenza illness, examining the ITT-non-infected groups allows this point to be tested directly. An analysis of 11 oseltamivir RCTs (2) confirmed lack of treatment effect on LRT complications in non-influenza-infected subjects compared to placebo. The failure to present outcomes in the ITT-infected or ITT-virus cohort underestimates possible beneficial drug effects, whereas full data presentation would enable readers to examine the event rates and magnitude of treatment effect sizes for key outcomes across all relevant groups for themselves.

2. Sample size considerations. The endpoint used in our pooled analysis of oseltamivir RCTs (3) was prospectively defined before the analysis was undertaken and was based on findings in our earlier study of zanamivir treatment effects (4) that indicated inhaled zanamivir reduced LRT illnesses leading to antibiotic prescriptions (RR, 0.60; 95% CI 0.42-0.85) but not upper respiratory tract ones (RR 0.90; 95% CI 0.63-1.27). The oseltamivir analysis used all studies available to us at the time, including unpublished clinical study reports, in order to avoid selection bias. The other endpoints of upper respiratory tract complications leading to antibiotic use (6.8% oseltamivir vs 5.9% placebo) and overall antibiotic use (14.0% oseltamivir vs 19.1% placebo; $P < .001$) were described in our 2003 paper (page 1760). Of note, the reductions in overall antibiotic use in influenza outpatients were similar for zanamivir (28%) and oseltamivir (27%) treatment. The limitations of the clinical diagnoses and retrospective approach used in these studies were described more fully in the earlier zanamivir paper (4). However, the simple pooled analysis we undertook in the oseltamivir paper did not correct for the higher proportion of influenza-infected, at-risk individuals in the placebo group, and this was a shortcoming. In any case, we pointed out this difference in the paper (page 1669) and presented the data by each group of interest (previously healthy or at risk) in Tables 3 and 4.

More importantly, our finding that early oseltamivir treatment reduced the likelihood of physician-diagnosed LRT complications leading to antibiotic use has been confirmed and extended (37% reduction in oseltamivir group; risk ratio 0.63 [95% CI 0.48, 0.82]) in a subsequent meta-analysis (that controlled for pre-enrolment risk status and included events from the time of enrolment) of the same 10 RCTs included in our paper and one additional one (2). Furthermore, this analysis found that the unpublished trials for which Jefferson and colleagues apparently do not have data were found to be no more favourable to oseltamivir than the published ones. When only the two published trials in previously healthy persons were considered, the reduction in the 24-day risk of LRT complications treated with antibiotics was 65% (risk ratio, 0.35; 95% CI 0.15, 0.82) in the oseltamivir arms.

3. Complications in ambulatory patients. Their comments on possible oseltamivir adverse events, including sudden death and neuropsychiatric adverse events (NPAEs), raises important points about the effects of influenza infection itself and possible drug-disease interactions. A well-documented relationship exists between NPAEs and influenza infection itself. Differing age-related patterns of influenza-associated encephalopathy/encephalitis and NPAEs have been reported in Japanese children and adolescents, and also age-

related differences exist in NAI prescribing patterns in Japan. Consequently, careful analysis is required to assess possible associations. It is important to point out that causal relationships between oseltamivir use and such events remain to be proven. Some analyses have indicated comparable or lower NPAEs rates in oseltamivir-treated compared to non-treated influenza patients (reviewed in (5)) and no higher rates of NPAEs have been found in hospitalised infants in the USA (6). Oseltamivir administration to those with influenza-associated NPAEs does not appear to worsen manifestations (7;8). Of note, the crude reporting rates for possible oseltamivir-associated NPAEs in Japan and USA were significantly lower during the 2009 pandemic than during preceding influenza seasons (9).

As pointed out by Jefferson and colleagues, the possibility of late-onset adverse events requires that sufficient follow-up be incorporated into study design to examine both possible adverse and beneficial effects. However, the low frequencies of such events would likely require much larger numbers of subjects than enrolled in most RCTs. One approach is retrospective examination of large databases that link healthcare visits, clinical diagnoses, and drug administration registries. For example, one cohort study involving over 150,000 subjects (49,238 oseltamivir recipients, 102,692 control patients) reported that oseltamivir treatment of presumed influenza was associated with lower risk of TIA or stroke in the subsequent six months (10). This kind of observational study approach has been undertaken for investigation of outcomes and possible adverse events following influenza immunisation and should also be extended to antivirals.

4. Data from observational studies. Jefferson and colleagues indicate that possible survivor treatment selection bias in observational studies can occur because patients who die early are not given the opportunity to receive treatment. However, there is also the opposite concern that sicker patients, especially in a rapidly evolving illness like influenza, are more likely to initiate therapy at any given time after symptom onset than less ill ones. This would be a conservative bias and reduce the likelihood of observing a treatment effect. Clinical experience during the 2009 H1N1 pandemic indicated that late NAI treatment in critically ill or non-surviving influenza patients was frequently due to delayed consideration of the diagnosis or failure to appreciate the potential value of starting treatment beyond two days after symptom onset in those with progressive illness or high-risk conditions. This occurred often despite some of these patients having had prior outpatient contact for their acute illness. Although the published reports indicate that most critically ill patients ultimately received antiviral therapy, delayed treatment commonly led to initiation of NAI administration as part of a salvage effort in a deteriorating patient. In part because of critical care support, even those patients who died in hospital usually survived into the second week of illness or later. Those analysing the large amount of observational data that has been generated in recent years, particularly in the context of the 2009 H1N1 pandemic, need to keep these clinical observations in mind. Of note, a recent analysis of critically ill pandemic H1N1 patients in California compared mortality in untreated patients who survived at least to the day after symptom onset when NAIs were first given to the NAI-treated ones and found that cases who received NAI up to 4 days after symptom onset were more likely to survive ($P < 0.05$ for each day 0-4) (11).

An independent report on the observational studies of influenza antivirals published up to November 2010 (12) conducted a meta-analysis of the few studies providing effects adjusted for confounders and, while acknowledging the low quality of the evidence based on the GRADE assessment approach, concluded that in high-risk populations, oral oseltamivir may reduce mortality (odds ratio, 0.23 [95% CI 0.13 to 0.43]) and hospitalisation (odds ratio, 0.75 [95% CI 0.66 to 0.89]). In addition, as reported in multiple studies of hospitalised pandemic 2009 A(H1N1) patients, including high-risk ones like pregnant women and those admitted with pneumonia, treatment with oseltamivir up to 4 days and in some studies later after illness onset has been associated consistently with better outcomes (11;13-21). Such observations have served to reinforce US CDC recommendations for using influenza antivirals as early as possible in those with severe or progressive illness, those hospitalised with suspected or proven influenza, and outpatients at higher risk for influenza complications (22). Furthermore, given that the circulating influenza viruses have continued to change, with the pre-2009 A(H1N1) seasonal viruses being entirely replaced by A(H1N1)pdm09 and now antigenically drifted A(H3N2) and B viruses, ignoring observational data means that only information concerning NAI treatment for influenza viruses that are now no longer circulating is being considered.

5. Other treatment endpoints of interest. The possibility that oseltamivir might have non-specific antipyretic or immunomodulatory actions unrelated to its antiviral effects has been raised in part on the basis of murine studies (23;24). These possibilities or other symptom-modifying effects could be addressed by comparison of the course of fever and individual symptom resolution between oseltamivir and placebo recipients for those enrolled in the RTCs who did not have laboratory evidence for influenza (ITT-non-infected). Of note, antipyretics were provided to participants in these trials, so that use of paracetamol (acetaminophen) needs to be included as a confounder in such analyses.

In the published pivotal RCTs of oseltamivir treatment in adults, the fever and symptom reductions observed in oseltamivir recipients were in addition to the effects of paracetamol (acetaminophen). One previous RCT in adults with uncomplicated influenza compared amantadine to aspirin and found faster fever resolution in aspirin recipients but slower resolution of other symptoms and higher rates of adverse effects leading to drug cessation (25). While fever resolution is an objective endpoint of interest, it is generally short-lived and of limited clinical importance relative to other endpoints like time to symptom alleviation, time to return to usual activities/premorbidity status, and complications reductions.

The comment by Jefferson and colleagues on measuring viral loads is confusing. Virologic endpoints like quantitative virus titres (infectious and in recent studies viral RNA), time to culture negativity, and changes in titres over time are essential to determining whether a putative influenza antiviral treatment is exerting an antiviral effect and the magnitude of that effect. Failure to detect an antiviral effect raises questions about issues like compliance, drug absorption and disposition, lack of potency, and resistance emergence. Examining such virologic measures also serves to confirm the likely mechanism of antiviral action of NAIs, inhibiting release from infected cells and spread in respiratory tract secretions to initiate subsequent rounds of replication. Several observational studies during the 2009 pandemic found that early antiviral treatment (<2-3 days from symptom onset) was associated with reduced duration of viral RNA detection (26-28). Consequently, in the context of the oseltamivir RCTs, it would be valuable to examine the correspondence between upper respiratory tract influenza virologic measures and symptom resolution and LRT complications in both oseltamivir and placebo groups.

7. Prophylaxis endpoints of interest. As indicated in my initial letter, the key efficacy endpoint for an influenza antiviral used for prophylaxis should be symptomatic, laboratory-confirmed influenza illness. Given the potential for other respiratory viruses to cause febrile respiratory illness, a focus on ILI as the primary endpoint will inevitably underestimate the protective effects of an influenza-specific chemoprophylactic agent. Of note, various definitions of symptomatic illness and ILI have been used in the influenza prophylaxis RCTs to date, so that further analyses using standardised definitions would be a helpful contribution. Other secondary endpoints of interest include laboratory documented infection (irrespective of symptoms), ILI, virus-positive ILI, and laboratory-confirmed illnesses not meeting the ILI definition. Laboratory confirmation based on both viral culture and in future studies viral RNA detection would take advantage of the greater sensitivity of RNA detection.

8. Adverse effects with prophylaxis. As detailed in the oseltamivir seasonal prophylaxis study protocols and report, the relationship between drug receipt and adverse events, including headache, in these trials (29) was determined by the study staff and investigators during the trial under blinded conditions before data lock. The assessment of causality in adverse events (unrelated, remote, possible, probable) as related to drug administration was made using pre-specified criteria in the protocol (see Appendix 1) on an individual basis by both interviewing the affected participant and considering various factors including past patterns of headaches, associated symptoms, duration and severity, timing in relation to study drug, and whether the symptom persisted during drug administration. Because of its background frequency in the population, headache is a very common event in longer term studies. When it is mild or transient despite continued drug administration, or when it occurs in context of other events (URI, trauma, stress), headache is unlikely to be drug-related. Using these criteria and the analysis report provided by the sponsor Roche, we observed headache (not otherwise specified, NOS) that was probably, possibly, or remotely related to study drug administration in 22.4% of placebo, 23.8% of once daily oseltamivir, and 25.4% of twice daily oseltamivir recipients during the 6 weeks of prophylaxis.

(29). The proportions were 10.2%, 8.7%, and 10.8%, respectively, for headache (NOS) that was possibly or probably related to study drug administration.

Headache is a good example of where it is essential to examine not only the frequencies of reported adverse events but also their severity and functional impact, including premature cessation of study drug. In our 6-week prophylaxis trial (29), severe headache (NOS) irrespective of relationship to study drug administration was reported in 5.0% of placebo, 3.3% of once daily oseltamivir, and 6.9% of twice daily oseltamivir, respectively. Overall premature study withdrawals were found in 21 (4.4%) of placebo, 17 (3.3%) of once daily oseltamivir, and 16 (3.1%) of twice daily oseltamivir recipients. In three placebo but no oseltamivir recipients, headache was listed as a contributory factor. However, headache was reported to be a factor leading to cessation of oseltamivir prophylaxis in one subject in another prophylaxis study (30) and was also reported at a higher frequency during 6-weeks prophylaxis in a nursing home-based RCT (5.5% placebo vs 8.3% oseltamivir)(31), so that further analyses are warranted.

9. Peer review. I thank Jefferson and his colleagues for their clarifications on the Cochrane peer review process, and as indicated above, I have provided my own suggestions on the design of future analyses by them and others. In addition, I have provided a list to the Cochrane Editorial Unit of several dozen potential expert reviewers for future protocols and reports on influenza antivirals.

Thank you for the opportunity to provide these responses and comments.

Sincerely,

Frederick G. Hayden, M.D.
Richardson Professor of Clinical Virology
Professor of Medicine
University of Virginia School of Medicine
Charlottesville, Virginia, USA

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Appendix 1 Definition of Adverse Event Relationship to Treatment

Probable

This category applies to those adverse events which are considered, with a high degree of certainty, to be related to the test drug. An adverse event may be considered **probable** if:

1. It follows a reasonable temporal sequence from administration of the study drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It disappears or decreases on cessation or reduction of dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias).
4. It follows a known pattern of response to the study drug.
5. It reappears upon re-challenge.

Possible

This category applies to those adverse events in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered **possible** if or when:

1. It follows a reasonable temporal sequence from the administration of study drug.
2. It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It follows a known pattern of response to the study drug.

Remote

In general, this category is applicable to an adverse event which meets the following criteria:

1. It does **not** follow a reasonable temporal sequence from administration of the study drug.
2. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It does not follow a known pattern of response to the study drug.
4. It does not reappear or worsen when the drug is re-administered.

Unrelated

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under **remote**, **possible**, or **probable**.

	Probable	Possible	Remote	Unrelated
Clearly due to extraneous causes	-	-	-	+
Reasonable temporal association with drug administration	+	+	-	-
May be produced by subjects clinical state	-	+	+	+
Known response pattern to suspected drug	+	+	-	-
Disappears or decreases on cessation or reduction in dose	+	-	-	-
Reappears on re-challenge	+	-	-	-

Reply

Reply to Hayden Letter 10 August 2012

Thank you for taking the trouble to provide further feedback to our responses to your first set of feedback comments.

You remain concerned about 1) "...selective approach to data analysis and presentation...", especially with respect to our concern that ITT-infected (ITTI) criteria are inappropriate; and 2) our identification of biases that may exaggerate the effectiveness of oseltamivir. You detail these concerns in more detail:

1. ITT and ITTI

You propose an analysis of ITTI in which patients are categorised not by an immune response (which we regard as potentially flawed because our interpretation of the data suggests the drug may interfere with the immune response) but instead by determining whether patients were seroconverting excreting influenza virus at enrolment.

This sounds sensible, and were the data of symptoms and baseline infectivity (by serology or even virus shedding) available to us in suitable format, we would include this analysis. By this, we would expect the randomisation of patients into the two groups to be independent of the initiation of the drug (that is the "influenza-positive" or "-negative") before the drug was administered, in case (as may be with the immune response) the drug interferes with virus excretion (as the manufacturer claims in some of its literature).

You also propose an analysis of those grouped by ITTI from serological conversion with those grouped by virus excretion. This also would be useful, to determine whether or not a bias exists in the current data (in either direction, as you point out – the possible mechanisms you outline are plausible).

However, your hypothesis "If oseltamivir is most beneficial in preventing lower respiratory tract (LRT) complications" IS one of the main issues to be confirmed.

As already described in our review, you reported a reduction of cytokine production in response to influenza infection by oseltamivir in humans:

Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *New England Journal of Medicine* 1999;341(18):1336-43

These findings suggest that reduction of antibody production cannot simply be assumed to be the result of reduced viral load.

2. Sample sizes

You describe in more detail the Kaiser 2003 pooled analysis of complications:

Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalisations. *Arch Intern Med* 2003;163:1667-72

This was central to the start of our unease, after it was pointed out to us (in this Feedback section!) by Hayashi that over half of the data in it were of unpublished trials. You state that the end-points were established a priori and not post hoc. You admit to shortcomings of the paper but point out that they were declared in the paper itself. You suggest that because the two published trials meta-analysed had no more favourable drug results than the unpublished, bias is less likely.

We think this is to misunderstand our central concern: we are unable to critically appraise the trials in the usual way because they are not available to us, nor, apparently, any other group unselected by the manufacturer. Incidentally we note that you yourself, even as an author, admit you were unable to locate the data for this paper on request, referring us instead to the sponsoring manufacturer, Roche:

Cohen D. Complications: tracking down the data on oseltamivir. *BMJ* 2009;339:b5387.

This inability by you (authors) or sponsoring manufacturer to provide data for independent scrutiny is disgraceful, a view shared by others, <http://bmj.com/tamiflu>.

3. Adverse effects of NIs

We find it interesting that you call these adverse events 'complications'. You point to our concerns about

neuropsychiatric adverse events (NPAEs), and (correctly) state that any association recorded in the literature "...remains to be proven..." with some references (all were retrospective studies and mostly sponsored by the manufacturer) that suggest that there is no increase over control groups. We have other references suggesting the opposite:

Hama R. Fatal neuropsychiatric adverse reactions to oseltamivir: case series and overview of causal relationship. *Int J Risk Safety Med*: 20 (2008): 5-36: <http://npojip.org/english/no11.html>

Nakamura K, Schwartz BS, Lindegårdh N, Keh C, Guglielmo BJ. Possible neuropsychiatric reaction to high-dose oseltamivir during acute 2009 H1N1 influenza A infection. *Clin Infect Dis*. 2010 Apr 1;50:e47-9.

Kruker AT, Krause M. ["Oseltamivir-induced delirium"]. *Ther Umsch*. 2010 Dec;67(12):613-5. German.

Chung S, Joung YS. Oseltamivir (Tamiflu) induced depressive episode in a female adolescent. *Psychiatry Investig*. 2010 Dec;7(4):302-4. Epub 2010 Nov 11.

The following are prospective cohort studies that aimed to analyse the association of NPAEs and administration of NIs, in particular oseltamivir.

Fujiwara F, Ikushima S, Hibi N et al. An analysis of risk factors of abnormal behavior in two seasons (07, 08) of influenza infection. Presentation at the 40th annual meeting of the Japanese Society for Paediatric Infectious Diseases held on 15 and 16 (2008)

Fujita T, Fujii Y, Watanabe Y, Mori M, Yokota S. A pharmacoepidemiological study on the relationship between neuropsychiatric symptoms and therapeutic drugs after influenza infection. *Jap J Pharmacoepidemiol* 2010; 15: 73-92.

This preliminary report on the analysis of randomised controlled trials of oseltamivir for prophylaxis contains our response to Roche's report discussing NPAEs and oseltamivir:

Jones M, Hama R, Jefferson T, Doshi P. Neuropsychiatric adverse events and oseltamivir for prophylaxis (letter). *Drug Safety*, 2012, 35 (12): 1187-90.

A proportional mortality study indicates that oseltamivir increases sudden death (odds ratio: 5.9) compared with zanamivir users in an analysis of all deaths among ~ 20 million 2009A/H1N1 influenza patients in Japan. This effect is also observed for the comparison of oseltamivir users with non-users.

Hama R, Jones M, Okushima H, Kitao M, Noda N, Hayashi K, Sakaguchi K. [Oseltamivir and early deterioration leading to death: a proportional mortality study for 2009A/H1N1 influenza](http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf). *Int J Risk Saf Med*. 2011;23(4):201-15. <http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf>

We have presented many of these studies in our previous reply to you, without response.

Of course the uncertainty about causation is true for many drug adverse events: our duty is to ensure that any such uncertainty is clearly articulated.

Nevertheless we entirely agree that "...observational studies ... undertaken for investigation of outcomes and possible adverse events following influenza immunisation ... should also be extended to antivirals." However, because this Cochrane review is limited to randomised data, such observational studies would be conducted outside this particular review.

4. Observational data

You point to our concerns about observational data in general for answering intervention questions. We acknowledge the plethora of observational data available, and even the meta-analysis of some of them. This does not detract from our continued concern that the best data for answering these questions are randomised, and to leave most of these data unavailable for independent scrutiny is unforgivable.

Moreover, the observational studies are regarded as poor in quality. A recent systematic review and meta-analysis of observational data for antivirals for the treatment of influenza concluded, "...therapy with oral oseltamivir and inhaled zanamivir may provide a net benefit over no treatment of influenza. However the confidence in the estimates of the effects for decision making is low to very low."

Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al. *Ann Intern Med*. 2012 Apr 3;156(7):512-24. doi: 10.1059/0003-4819-156-7-201204030-00411. Epub 2012 Feb 27. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies

Incidentally, we are interested in rigorously meta-analysing these data ourselves, and have put in a protocol to do just that. (Jones M, Hama R. Effect of oseltamivir on mortality in treatment of 2009A/H1N1 influenza patients. PROSPERO 2012:CRD42012002245. Available from:

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002245

The proportional mortality study (above), analysing all influenza deaths in Japan and estimating populations who took antivirals and did not take them as the denominators, provides far more reliable estimates of risk from drug exposures than retrospective analysis of surveillance cases without exposed populations (denominators). Contrary to your suggestion "...there is also the opposite concern that sicker patients, especially in a rapidly evolving illness like influenza, are more likely to initiate therapy at any given time after symptom onset than less ill ones...", no such tendency was detected in this study. Proportions of patients treated with antivirals within 12 hours from the onset of fever were significantly lower in the "not mild" cases (26.5%) than "mild" cases (35.4%) at the time when antiviral was prescribed [Table 2b]. However, no patients who deteriorated before the first presentation at medical facilities were treated with antivirals before deterioration [Table 2a], while 78% of "mild" cases and 55% of "not mild" cases were prescribed antivirals within 48 hours from onset of fever [Tables 2a and 2b]. These may be related to the lower positive results (45%) of rapid testing for influenza virus in the "not mild" cases than that in the "mild" cases (60%) at the first consultation:

Hama R, Jones M, Okushima H, Kitao M, Noda N, Hayashi K, Sakaguchi K. [Oseltamivir and early deterioration leading to death: a proportional mortality study for 2009A/H1N1 influenza](#). *Int J Risk Saf Med*. 2011;23(4):201-15. <http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf>

5. Other treatment endpoints of interest

Does oseltamivir have non-specific antipyretic or immune-modulatory actions unrelated to its antiviral effect?

We have already noted the hypothermic and immune-suppression effect of oseltamivir in humans, some from your own writing.

Hama R. Fatal neuropsychiatric adverse reactions to oseltamivir: case series and overview of causal relationship. *Int J Risk Safety Med* 2008;20:5-36

Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomised controlled trials for prevention and treatment. *JAMA* 1999;282:1240-6.

Your suggestion that antipyretic actions of oseltamivir be tested by comparing those randomised to oseltamivir against those not in the non-ITTI group is worth consideration (although the results might be difficult to interpret). Again, as mentioned above, it would be good to have access to sufficient data to allow this analysis and others we have outlined in the protocol.

We note your criticism about over-focusing on fever as a proxy for symptom resolution. We are of course interested in any good measure of the latter that is not only objective but also common to all trials. Nevertheless, despite your criticism, fever is a reasonable marker of 'illness' from infections such as influenza, and probably correlates reasonably well with symptom resolution (especially in the prophylaxis trials) and in the treatment trials (if fever is measured until complete resolution) – it is, after all, a cardinal symptom – and has the great advantage of being clearly measured.

You suggest that we test whether viral excretion correlates with symptoms of influenza. We agree that this would be an interesting analysis, were the data available to us (see above).

7. (Note there was no Point 6) Should we be focusing so much on influenza-like illness (ILI)?

Of course, if oseltamivir neither reduces antibody production to influenza virus nor conceals testing positivity, selecting only laboratory-confirmed influenza might be a reasonable end point for prophylaxis trials. However the facts suggest these cannot be assumed.

In any case, the Cochrane Collaboration is dedicated to finding the best available evidence to enable patients and their clinicians to make best-informed decisions. To that end, ILI is what the vast majority of clinicians and their patients will be facing. Therefore this is an end-point of direct relevance to them, and we make no apology for including it.

8. Adverse events in prophylactic trials

Thanks for this detailed information. Further analyses are indeed what we would like to undertake according to our protocol.

9. Peer review

Thanks for offering a list of your own colleagues to act as peer reviewers. We adhere to the principle of ensuring there is methodological expertise as well as content expertise. Your list will be useful to consider when finding peer reviewers.

As you may be aware, because this particular Review Group (Acute Respiratory Infections) has its Coordinating Editor as an Author on this review, the handling of the manuscript is managed by the Central Editorial Unit to minimise any potential conflict of interest.

Contributors

Chris Del Mar, Tom Jefferson, Rokuro Hama, Mark Jones, Peter Doshi, Carl Heneghan, Matthew Thomson.

7 Feedback from Adam Jacobs, 13 February 2013

Summary

Comment: The selection criteria in the review seem highly unusual. The authors describe a 2-stage process for including trials.

In the first stage, they require that the trial reports they analyse have "external consistency". As far as I can tell, this means that they must be able to verify the contents of the report from an external source.

This seems an extraordinarily high bar to set. I am not aware that it is part of standard Cochrane methodology. If it were applied across Cochrane reviews more generally, I imagine that very few Cochrane reviews would include any evidence at all, especially given that most Cochrane reviews are done perfectly happily with published papers, whereas this one had the advantage of clinical study reports, which are generally far more reliable and comprehensive than published papers.

It is almost as if the authors have gone out of their way to exclude the evidence, which does not help to answer important questions about the efficacy of neuraminidase inhibitors.

It is also noteworthy that no specific reasons were given for exclusion of studies from stage I of the process: we are only told that "insufficient information was available". In the interests of transparency, it would be better to know specifically what information was lacking.

May I suggest that the authors either explain the reason why they felt the need to use far stricter inclusion criteria than is normal in Cochrane reviews, or revisit their inclusion criteria so that the studies can be analysed.

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Adam Jacobs, Director, Dianthus Medical Limited

Reply

Adam Jacobs writes:

"The selection criteria in the review seem highly unusual. The authors describe a 2-stage process for including trials. In the first stage, they require that the trial reports they analyse have "external consistency". As far as I can tell, this means that they must be able to verify the contents of the report from an external source."

At page 11 of the review we provide the definition: "External consistency. Consistency of data as reported in regulatory documents, other versions of the same clinical study reports/unpublished reports and other references, to be established by cross-checking"

"This seems an extraordinarily high bar to set. I am not aware that it is part of standard Cochrane methodology. If it were applied across Cochrane reviews more generally, I imagine that very few Cochrane reviews would include any evidence at all, especially given that most Cochrane reviews are done perfectly happily with published papers, whereas this one had the advantage of clinical study reports, which are generally far more reliable and comprehensive than published papers".

And

"May I suggest that the authors either explain the reason why they felt the need to use far stricter inclusion criteria than is normal in Cochrane reviews, or revisit their inclusion criteria so that the studies can be analysed."

Our review is the first systematic review that we are aware of to be completely based on regulatory information. As our basic element of data synthesis was different, we had to develop new methods which we did transparently and are described in the review. It was a fact that we had received partial clinical study reports for the same trials from both Roche and EMA. We felt the need to ensure these reports were consistent. Whether our methods were an "extraordinarily high bar" or a reasonable bar or too low a bar is a judgement readers can make for themselves.

The background history which informed our methodology is explained in the review itself. At pages 4 and 5 of the review we write:

"In 2009, a reader posted a comment in response to the (then current) 2006 version of this review (Jefferson 2006). He pointed out that the review had endorsed the claim regarding a reduction in complications based on the uncritical inclusion of the Kaiser meta-analysis (Doshi 2009). The reader pointed out that only two of the 10 'Kaiser trials' had been published (Nicholson 2000; Treanor 2000) and the information provided by the Kaiser text about the remaining eight was insufficient for their appraisal. Our subsequent efforts to retrieve and review the eight unpublished trials (representing 2691 patients) were unsuccessful, raising the possibility that the findings of our previous review were not an accurate estimate of the benefits and safety of the drug. In addition, we found clear evidence of possible publication bias (see below) amid concern that some evaluations have not been available to scrutiny by the scientific community (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009)."

"This review is focused on healthy adults and children. It represents the amalgamation of two long-standing Cochrane reviews on the effects of NIs for influenza in healthy adults (Jefferson 2010a, also published as Jefferson 2009a) and children (Matheson 2007). The reviews were combined to pool our collective expertise and time in extracting and assessing data from clinical study reports, which in the case of some oseltamivir trials, report both adult and paediatric outcomes. Cochrane reviews of NIs in both children and adults generated intense interest from clinicians and media during the influenza outbreak declared a pandemic by the WHO in 2009. The Cochrane review of NIs in healthy adults highlighted the high risk of publication bias (Jefferson 2010a). In 2009, a reader posted a comment in response to the (then current) 2006 version of this review (Jefferson 2006). He pointed out that the review had endorsed the claim regarding a reduction in complications based on the uncritical inclusion of the Kaiser meta-analysis (Doshi 2009). The reader pointed out that only two of the 10 'Kaiser trials' had been published (Nicholson 2000; Treanor 2000) and the information provided by the Kaiser text about the remaining eight was insufficient for their appraisal. Our subsequent efforts to retrieve and review the eight unpublished trials (representing 2691 patients) were unsuccessful, raising the possibility that the findings of our previous review were not an accurate estimate of the benefits and safety of the drug. In addition, we found clear evidence of possible publication bias (see below) amid concern that some evaluations have not been available to scrutiny by the scientific community (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009).

Our attempts to reconcile published and unpublished evidence by contacting the manufacturer and study authors failed (the latter were unable to provide us with the necessary data; some were not in possession of the data and others may have been restricted by confidentiality agreements). Together with the *British Medical Journal* (BMJ) we ascertained that ghostwriters had been involved, which means the named authors may not have been in full control of the trial publications (Cohen 2009). We also identified several key differences in licensed indications for oseltamivir between regulatory systems (mainly between the US, Europe and Japan) and under-reporting of harms. The differences are detailed elsewhere (Doshi 2009) but of particular concern was the insistence of the FDA that oseltamivir has not been shown to reduce complications (FDA 2011a). The FDA has also not allowed an indication for interference of viral transmission within households (the key concept behind post-exposure prophylaxis). This undermined our confidence in published data and in the findings of our previous Cochrane reviews. In the background of all this were suggestions that NIs may not be as safe as

previously assumed, with associations between oseltamivir use and neuropsychiatric adverse reactions of particular concern (Hama 2008)."

Adam Jacobs writes:

"It is almost as if the authors have gone out of their way to exclude the evidence, which does not help to answer important questions about the efficacy of neuraminidase inhibitors."

A page 5 of the review we write:

"During the preparation of the 2010 review and of the current review, we realised that there were multiple sources and different levels of granularity of clinical trial data (see 'The Scope of Clinical Trial Data' table in Jefferson 2011). We decided that clinical study reports and regulatory comments were likely to provide the least biased, most complete and most insightful set of data for our review".

And

"We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled phase III treatment trials of oseltamivir have never been published. This includes M76001, the biggest treatment trial ever undertaken on oseltamivir (with just over 1400 people of all ages). Exclusion of unpublished data changed our previous findings regarding oseltamivir's ability to reduce complications of influenza (Doshi 2009; Jefferson 2009a)."

Our attempts at identifying and retrieving all available evidence from regulators and manufacturers since 2009 are documented at <http://bmj.com/tamiflu>.

Adam Jacobs writes:

"It is also noteworthy that no specific reasons were given for exclusion of studies from stage I of the process: we are only told that "insufficient information was available". In the interests of transparency, it would be better to know specifically what information was lacking."

In Table 9 (page 186) we list all studies included in Stage 1 and report details of what data for each were available to us. For, example for trial MV22940 we know that it is likely to be a randomised trial assessing effects of oseltamivir on post exposure prophylaxis but no other data are available to us. In these circumstances we cannot proceed to assessment until the information is available, as explained in the text of the review. However these studies are not excluded but are marked as pending assessment.

We invite Adam Jacobs to read the review and the references which document the history of the review, background and rationale for withdrawing the original review and developing the current version. We also invite Mr Jacobs to clarify what business relation his firm has if any with Roche, GSK and BioCryst Ltd.

It is possible that future Cochrane reviews will include an increasing proportion of regulatory information to minimize the effects of reporting bias. This type of speculation is however beyond the scope of the review.

Contributors

Cochrane Neuraminidase Inhibitors Review Team, 5 March 2013

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8 Feedback from Harri Hemilä, 06 May 2013

Summary

Comment: Oseltamivir (Tamiflu) shortens the duration of influenza-like illness by 13% (95% CI 8% to 18%)

In studies measuring dichotomous outcomes, relative risk (RR) is a standard measure for comparing study groups. The purpose of using RR is to adjust for baseline variability in the occurrence of disease. It is easier to compare two trials on the basis of their RR estimates than on the basis of their absolute effects.

The relative effect should also be calculated for continuous outcomes. Although the duration of disease may vary randomly in placebo groups, there are also biological reasons why diseases in different placebo groups differ in their severity and duration. For example, in Analysis 1.1 of this review, the duration of influenza-like illness in the placebo group of trial WV15671 is 35% shorter than in the placebo group of trial WV15819/WV15876/WV15978 ($Z = 6.5$; $P = <0.00001$; 125h/192h). Such very large baseline differences are not explained by chance. Differences in the study populations, influenza seasons, study protocols, etc. are plausible explanations for the baseline variation. The above-mentioned baseline difference is much greater than any of those between the oseltamivir (Tamiflu) and placebo groups in the five trials of Analysis 1.1. As for dichotomous outcomes, the baseline variability of continuous outcomes can be adjusted for by calculating the effect in percentages, i.e., the relative effect. Furthermore, the percentage effect is informative for an average reader because the reader may form an opinion on whether, for example, a 10% or 20% average decrease in the duration is worth the cost and effort of the treatment. Separate from the absolute effect in days, the percentage effect shows whether the effect is small or large.

Therefore the effect of oseltamivir should be calculated also as a percentage effect. I calculated the relative effects for the five trials listed in Analysis 1.1, pooled them using the fixed effect inverse variance method of RevMan, and found that the average effect of oseltamivir is a 13% (95% CI 8 to 18%) decrease in the duration of influenza-like illness.

Furthermore, the relative effect estimate makes it possible to compare the effects of treatments for related conditions. Influenza-like illness has substantial overlap with the common cold. In our Cochrane review on vitamin C and the common cold we calculated that ≥ 1 g/day of vitamin C shortens colds in adults by 8% (95% CI 4 to 12%) and in children by 18% (95% CI 9 to 27%) [1]. Another meta-analysis found that a high dose of zinc (>75 mg/day) as zinc acetate lozenges decreased the duration of colds by 42% (95% CI 35 to 48%) and as zinc lozenges made with other salts by 20% (95% CI 12 to 28%)[2]. The mechanism of the effect of vitamin C and zinc lozenges is not understood; however, there is no reason to assume that their effects are specific, for example, to the rhinovirus. If vitamin C and zinc lozenges have effects on diverse respiratory viruses, they might also have an effect on influenza viruses. In mice, influenza infection decreased vitamin C concentration in bronchoalveolar lavage fluid [3]. In mice, vitamin C deficiency increased lung pathology caused by influenza infection [4]. An early study with influenza patients reported that the occurrence of pneumonia was 80% lower (2 vs. 10 cases) in the vitamin C group, suggesting that vitamin C might also have an effect on influenza in humans [5,6]. If the effects of vitamin C and zinc lozenges on influenza-like illness are of the same magnitude as their effects on the common cold, then the effects of these treatments compare reasonably with oseltamivir. The comparison of the percentage effects of oseltamivir, vitamin C and zinc lozenges may be useful when considering how future research resources concerning the treatment of respiratory virus infections might be allocated. In this respect, the type of effect measure has a much wider importance than just its use in evaluating the effectiveness of oseltamivir as an issue of its own.

Thus the relative effect estimate adjusts for baseline variations between trials, it is informative for most readers because people are familiar with percentages, and it makes it easier to compare different treatments for related conditions. For these reasons I would like to encourage the authors to calculate and report the relative effect estimates for oseltamivir in the next revision of the review.

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I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Harri Hemilä

Department of Public Health, University of Helsinki

Reply

Thank you for your suggestion and comprehensive argument why you think it is important. Indeed in our 2006 and 2009 updates of A047 (the previous review on antivirals for influenza in otherwise healthy adults), we pooled hazard ratios and reported relative effects for time to alleviation of symptoms. However GSK, the manufacturer of zanamivir, made the comment that hazard ratios may not be appropriate due to non-proportional hazards. Therefore for A159 we reported absolute treatment effects for time to alleviation of symptoms but not relative effects. We agree with your argument and will report absolute and relative effects for time to alleviation of symptoms and other outcomes in the next update of 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children' due at the end of 2013.

Contributors

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ

9 Review amendments, 16 May 2013

Summary

As reported in the current version of our review, we will complete the review of regulatory information which arrived after our original time lock. We will assess additional evidence from oseltamivir Module 2s, evidence on adverse events following exposure to neuraminidase inhibitors (NIs) and clinically relevant outcomes.

A rationale and description of our methods follows.

Evidence from Module 2s (Ms2) of oseltamivir trials

1. Summary and background

This part of the document will describe our efforts to determine whether the additional information included within Module 2s (Ms2) of clinical study reports (CSRs) would change the risk of bias assessment, identify additional useful or relevant information, and conclusions of the overall body of evidence contained within our existing review. A second aim is to construct and test a tool that could be used to extract, organise and appraise study information contained in such modules.

The items which are most commonly found in the M2 of the oseltamivir trials are: Certificates of Analysis (a report on the colour, composition and content of active and control substance capsules, blank Case Report Forms (case notes for each participant), follow-up cards/diary cards (on which each participant recorded information such as symptoms), informed consent text and participant contract (to be administered to and signed by each participant), lists of investigators in the trial, investigation review board, ethics committees and study sites' addresses, the Reporting Analysis Plan (Roche's term for the Statistical Analysis Plan or SAP detailing the types of data analyses to be carried out), randomisation list (used to allocate participants and the study Protocol with its amendments when appropriate or available).

1.2 Methods

We received 12 CSR Ms2 from 31 studies requested from EMA by July 2011. Before we reviewed Ms2 we knew they contained protocols, with their amendments, certificate of analyses, blank case report forms, randomisation and participating centres' lists. However, we had no precise idea whether this was a comprehensive list or whether further items would be identified once we started reviewing. We also noted that the same info was reported elsewhere in the CSRs (for example in the core report) but in a different level of detail. A good example of this is the statistical analysis section of the core report which is a few pages long chapter, compared to the Statistical Analysis Plan (SAP), which is a self contained document included in M2. In addition we were not aware of the existence of any readily available tool to allow us to extract, organise and appraise the information contained in the Ms2.

As consequence we decided to develop our own tool. Our plan is to do this by identifying the types of items contained in the Ms2 available to us and their location in the Ms2. The outline content of all items identified will be checked in the Ms2 because of the potential for differing titles for the same item. For example we have already noticed that Research Analysis Plan (RAP) is sometimes called Data Analysis Plan (DAP) or Statistical Analysis Plan (SAP). Another example are the Protocol Amendment Histories and Protocol Modification History Document. These represented different ways of identifying the same item and need to be given a single identifier. Items such as Data Reporting and Analysis Manual (DRAM) are only cited in one M2. We will also conduct a pilot to identify with certainty which items are present more frequently. We will make a list of what we thought were most present and important items contained in the Ms2 and create a grid based on the sequence of development of the trial design and analysis plan. For example, we want to track whether the reporting of the trial study design in the relevant section of the protocol and its amendments (in M2) is consistent with that described in the core report (in M1). We will also make an initial extraction frame to reconstruct the timeline of

the study documents, summarising the number of protocol changes and their dates in sequence. This has the purpose of giving an overview of the main timeline points of the key items of study design and analysis.

We will then pilot our extraction sheet and make changes following discussion with all authors. We will extract the data in the same groups we worked in the original review.

We will define the impact of adding M2 information by measuring the change in risk of bias (ROB) assessment in our review as well as reporting our summary description and appraisal of each trial before and after addition of the data and comparing it with the manufacturer's assessment.

The detailed questions addressed by our analysis are:

Does addition of M2 to M1 change the risk of bias evaluation compared to M1 alone?

Does reading M2 and M1 in CSRs change the risk of bias evaluation compared to using published papers?

Is the current risk of bias tool adequate for assessing trials based on reading M2 then M1 in the CSRs?

Does reading M2 and M1 in the CSRs identify additional useful relevant information for systematically reviewing a trial programme?

We will primarily use descriptive methods to answer the questions. To answer question 1 we will compare the risk of bias in our 2012 review with risk identified after addition of M2 information to our current review using a 3 by 3 contingency table. We will repeat this procedure to answer question 2, by comparing risk of bias in our 2009 *BMJ* review to our current assessment. This analysis will be based on the subset of trials that were published and included in our 2009 review.

To answer question 3 we will list all the components of other risk of bias in the current review and compared these with previous reviews (2012 and 2009).

To answer the final question we will provide a summary of the items that were identified in our assessment of the trials using the new M2 tool. This will allow us to summarise discrepancies between what was planned in the protocol, what was carried out (RAP, protocol amendments), what was reported in M1, and what was reported in the published papers. The focus would be on the trial programme of research i.e. issues that appeared consistently over the trials.

Adverse events

2. Summary and background

This document outlines how we will conduct the analysis of adverse events as part of the wider Cochrane review of neuraminidase inhibitors (NIs) for prophylaxis and treatment of influenza in healthy adults and children (A159).

We use the term 'adverse events' throughout this document rather than harms or adverse reactions as these latter terms imply causality which may or may not be appropriate.

In keeping with the methods of our previous review we will not use data from journal publications for this proposed analysis. We now have access to multiple clinical study reports (CSRs) for both oseltamivir and zanamivir. To our knowledge this is the first time some of these data have been available outside manufacturers and regulators, and allows for the exploration of events in more detail than is possible using the limited information on safety reported in journal publications. This potentially allows us to address some of the concerns that have arisen in the post marketing period about the possible relationship between neuraminidase inhibitors, oseltamivir in particular, and neuropsychiatric and other harms. The documents available to us contain listings and summaries of adverse events recorded in the trials including narrative summaries of serious adverse events and adverse events leading to study withdrawal.

The adverse events are classified by relationship to the study drug and also, by intensity (mild, moderate, severe, life-threatening and death). The duration of events is reported and they are also lumped into body systems such as gastrointestinal, neurological, etc.

2.1 Methods

All CSRs of oseltamivir and zanamivir will be included in our analysis. CSRs for prophylaxis, for treatment of adults and for treatment of children will be analysed separately. Adverse events will be initially descriptively compared over the entire treatment and follow-up period but then potentially stratified by on-treatment and off-treatment periods if it appears there may be a difference between treatment groups.

2.2 Adverse events for comparison

2.2.1 Common events

For common events of any intensity with an overall incidence of 2% or more we will compare the incidence between treatment groups. The cut-off of 2% is based on a power analysis where assuming 4000 patients in total (this is approximately how many patients we have access to in oseltamivir treatment trials of adults as well as in oseltamivir prophylaxis trials of adults), we will have 80% power to detect an odds ratio of 1.75 with 5% level of significance.

2.2.2 Uncommon events

Due to a lack of data to compare uncommon events we will compare events lumped into body systems between treatment groups. If we find evidence of a difference in incidences between groups lumped into a body system we will conduct further analysis if appropriate. This further analysis is to determine whether the difference in incidence is due to any common events included in that body system. For example, in the case of neurological body system, if we found evidence of a difference between treatment groups we would remove all common neurological events such as headaches and repeat the analysis.

2.3 Severe, serious events and events leading to study withdrawal

As well as the analysis described in section 2.2 above we will also conduct a subgroup analysis of just the events with severe intensity, serious events and events leading to study withdrawal. We will use the same definitions of "severe" and "serious" as specified in the CSRs. However we will check the classifications using all the information available in the CSRs including line listings of events, narratives provided for serious events and also for events leading to study withdrawal. Any disagreements with the original classifications will be recorded and any reclassifications will be assessed in a sensitivity analysis. Given it is unlikely there will be sufficient events to conduct separate statistical analysis at the level of body system we will compare the overall distribution of events by body system between treatment groups.

2.4 Incidence of adverse events in the CSRs

As a further check on the validity of the data on adverse events contained in the CSRs we will conduct descriptive comparisons of the incidence of adverse events in the prophylaxis and treatment trials.

This is because of the unclear methods of collecting and classifying adverse events in the trials. A potential adverse event could have been classified as a symptom of influenza, an efficacy outcome (such as complication of influenza) or an adverse event. Hence an informal comparison of the incidence of adverse events in the trials where participants had influenza (or influenza-like-illness) and the trials where participants did not have influenza may help show where adverse events could have been under-reported. We will take into account factors such as age of participants and duration of treatment exposure for these informal analyses. In addition if it is clear that an adverse event was not reported as an adverse event but was included elsewhere in the CSR (e.g. in the efficacy section), we will include that data in our adverse event analyses.

We will also construct a table showing the definitions specified in each CSR for classifying potential adverse events as adverse events, complications or symptoms of influenza.

2.5 Antibody titre

We have already reported that antibody production was lower in the oseltamivir group than in the placebo group in the systematic review of treatment trials of oseltamivir (2012). We will update this analysis by including additional oseltamivir trials as well as assess antibody production in the zanamivir trials.

We will assess antibody production in the prophylaxis trials of oseltamivir and zanamivir by the following methods.

We will first identify the participants who had influenza-like illness (ILI) or pyrexia. If the proportion is similar between active group and placebo group, the proportion of participants who had four times or higher increase of antibody will be compared between groups.

2.6 Dose-response analysis

A number of trials included two or more active treatment arms with different doses of study medication given to participants in each of the arms. For these trials we will investigate the dose-response relationship for common adverse events (as defined above).

2.7. Details of analysis

Initial analysis will be descriptive only where we will report the numbers and percentages of events by treatment group. If there is a potential difference in the pooled percentages between treatment groups (e.g. if there is more than a two standard error difference between percentages) then we will conduct formal meta-analysis. If indicated we may also conduct additional analyses taking into account event intensity and/or duration.

2.8 Limitation and exploratory analysis

The methods presented above are those that we have pre-specified prior to formal analysis of the data. A limitation of these methods is that we may fail to detect differences in rare adverse events because these events will be compared along with other types of events within body systems. Therefore in the process of conducting our formal analysis we may generate further hypotheses or conduct additional exploratory analyses. If this is the case then we will clearly label these analyses as exploratory and interpret the findings accordingly.

Types of outcome measures

3. Background

For most people, influenza is a self-limiting illness. However the disease can at times lead to serious complications such as pneumonia and hospitalisations, and if treatment with neuraminidase inhibitors can reduce the risk of severe outcomes, this would be an important public health benefit. Another potentially important public health benefit would be the ability of antivirals to interrupt person to person transmission of influenza. Current evidence for these outcomes is scarce or inconclusive. A positive balance of effects on complications and viral spread versus harm profile is the main reason for using NIs in a public health context, especially the orally administered oseltamivir.

All analysis will be based on the intention-to-treat (ITT) or safety populations as our prior review discovered compelling evidence that the ITTI (the subpopulation deemed to be influenza-infected) populations were not balanced between treatment groups in the Roche oseltamivir trials. In addition, estimates from the ITT population will be more generalisable to clinical practice where routine testing for influenza is not common in many countries (and even where used, remains of variable accuracy). Analysis will be conducted separately for prophylaxis trials, treatment trials of adults and treatment trials of children.

The list of outcomes given below includes all potential outcomes that we believe are clinically important. However a number of them may not be formally comparable in this review because there are insufficient numbers of events (e.g. mortality) or they were not adequately measured or reported (e.g. drug resistance).

3.1 Outcome measures for treatment studies

Complications~
Harms*
Symptom relief
Hospitalisation
Viral excretion
Drug resistance
Mortality

3.2 Outcome measures for prophylaxis studies

Influenza-like-illness^
Complications~
Harms*
Hospitalisation
Viral excretion
Drug resistance
Mortality

~Complications (secondary illnesses) include pneumonia, bronchitis, otitis media, sinusitis or other respiratory tract infection after influenza-like illness. Initially we will construct a table to illustrate the design methodology used for each study. The table will include the following variables:

Study/trial ID

Where complications are first defined in the CSR (e.g. "as secondary endpoint in 3rd version of protocol six months into trial and two months prior to trial unblinding")

Definition of "complication" including types of events, population and time period at risk

How complications were measured (see diagnosis methods criteria shown below)

Availability of complications data for the ITT population

We will then stratify our analysis by method of diagnosis with three possible criteria:

- a. Lab-confirmed diagnosis (e.g. based on radiological or microbiologically confirmed evidence of infection).
- b. Clinical diagnosis without laboratory confirmation (diagnosed by a doctor after a clinical examination)
- c. Other type of diagnosis such as self-reported by patient

*A separate section provides the details of our proposed analysis of harms.

^The main outcome of interest is any symptomatic influenza-like-illness (ILI). However, we will also conduct separate analyses of influenza (symptomatic and asymptomatic) and non-influenza ILI.

Reply

TJ

Contributors

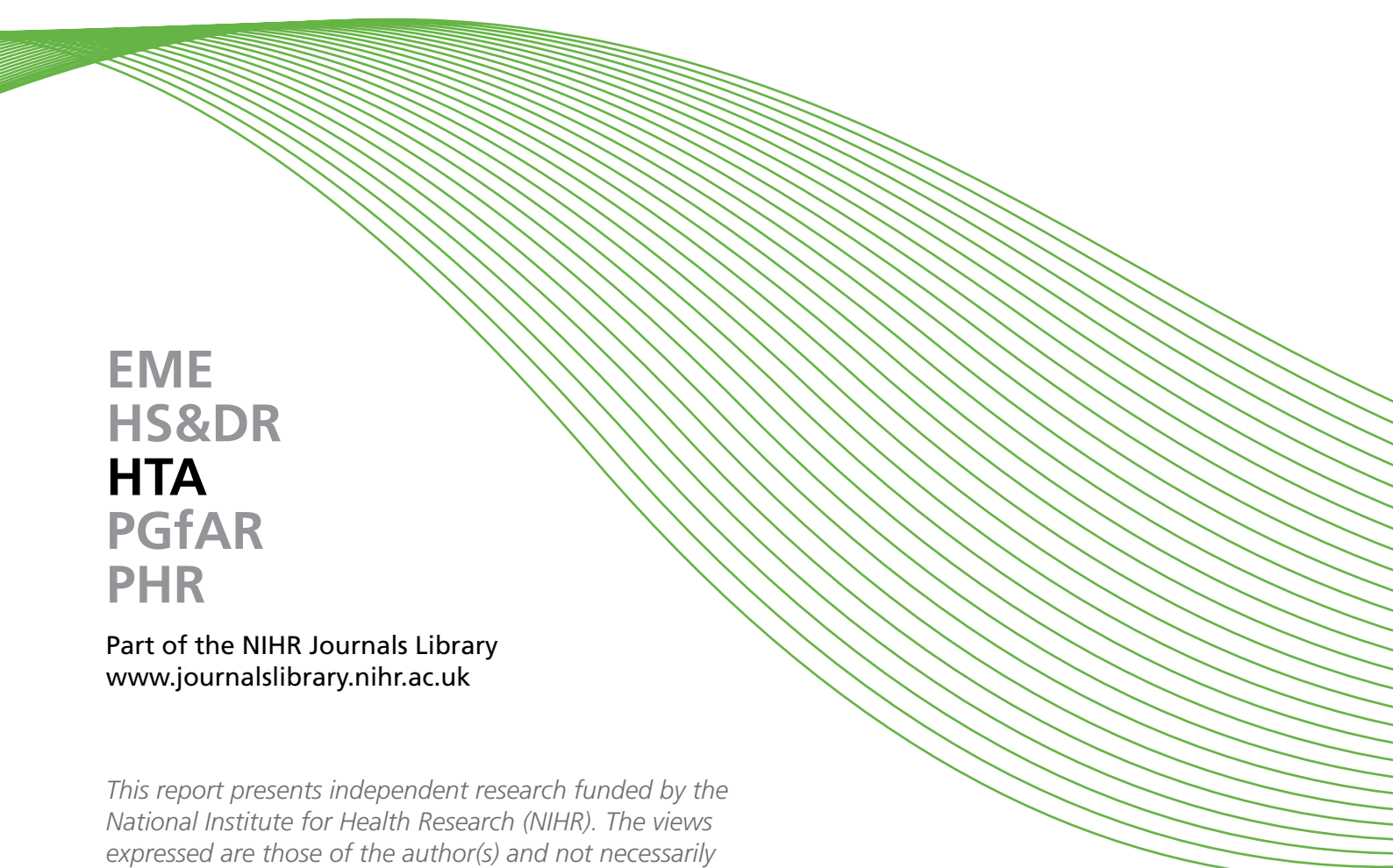
Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ

10 From Peter Gross, Hackensack University Medical Center, USA, 17 April 2014**Summary**

Comment: Can Cochrane compare their results on influenza neuraminidase inhibitors with the reduction in symptoms when penicillin is given for strep throat? I think they may be comparable. That would be an important perspective.

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and depth.

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Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors, 2014–2015

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ABSTRACT

The World Health Organization (WHO) Collaborating Centres for Reference and Research on Influenza (WHO CCs) tested 13,312 viruses collected by WHO recognized National Influenza Centres between May 2014 and May 2015 to determine 50% inhibitory concentration (IC₅₀) data for neuraminidase inhibitors (NAIs) oseltamivir, zanamivir, peramivir and laninamivir. Ninety-four per cent of the viruses tested by the WHO CCs were from three WHO regions: Western Pacific, the Americas and Europe. Approximately 0.5% (n = 68) of viruses showed either highly reduced inhibition (HRI) or reduced inhibition (RI) (n = 56) against at least one of the four NAIs.

Of the twelve viruses with HRI, six were A(H1N1)pdm09 viruses, three were A(H3N2) viruses and three were B/Yamagata-lineage viruses. The overall frequency of viruses with RI or HRI by the NAIs was lower than that observed in 2013–14 (1.9%), but similar to the 2012–13 period (0.6%). Based on the current analysis, the NAIs remain an appropriate choice for the treatment and prophylaxis of influenza virus infections.

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1. Introduction

The first class of influenza antiviral drugs to be approved, the adamantanes (namely amantadine and rimantadine), continue to be ineffective for the treatment of influenza due to resistance conferred by a S31N amino acid substitution in the M2 protein of virtually all currently circulating A(H1N1)pdm09 and A(H3N2) viruses. The neuraminidase inhibitor (NAI) class of influenza antivirals first came to market in 1999 and now encompasses four compounds – oseltamivir (Tamiflu®), zanamivir (Relenza®), peramivir (Rapivab®) and laninamivir (Inavir®) – that differ in their chemical structure, bioavailability and mode of administration. In the majority of countries, only oseltamivir and inhaled zanamivir are approved, with oseltamivir being the most widely used. Together with oseltamivir and zanamivir, peramivir and laninamivir are approved and used in Japan, and peramivir is also approved in China, the Republic of Korea and the USA. The use of influenza antivirals differs around the world; countries such as Japan and the USA use the greatest volumes and regularly treat influenza virus infected patients presenting at general practitioners or hospital outpatient clinics, while other countries primarily use the drugs to treat severely ill hospitalised patients. Aside from the treatment of seasonal influenza, several countries around the world have stockpiled large volumes of influenza antivirals for use in a pandemic situation. Other influenza antivirals that target other viral proteins or host factors, such as nitazoxanide, favipiravir and fludase, are currently in late-phase clinical trials but as yet have not been approved for use in patients with uncomplicated influenza infections. As such there remains a strong reliance on the NAIs, specifically oseltamivir, for the treatment of severely ill patients.

Surveillance for viruses with reduced NAI susceptibility is important to inform pandemic preparedness strategies and ensure that treatment and clinical management guidelines remain appropriate. Here we describe the third global update of NAI susceptibility for viruses collected through the World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS) for the period May 2014 to May 2015 (subsequently referred to as 2014–15).

Emergence of viruses with reduced NAI susceptibility is not unprecedented and has been observed over the last decade both on a local and global scale. For example, in late 2007 former seasonal A(H1N1) viruses acquired the neuraminidase (NA) H275Y amino acid substitution which conferred oseltamivir resistance, impacted clinical effectiveness (Kawai et al., 2009a, 2009b), and spread globally in less than 12 months (Dharan et al., 2009; Hurt et al., 2009; Lackenby et al., 2008; Meijer et al., 2009). More recently, clusters of A(H1N1)pdm09 viruses containing NA H275Y substitution have been detected at a local level (Hurt et al., 2011; Takashita et al., 2015a). Two of these clusters, in Hokkaido, Japan and Pennsylvania, USA were described in our last annual report of NAI susceptibility for the 2013–14 period (Takashita et al., 2015b). These events show that some former seasonal A(H1N1) and A(H1N1)pdm09 viruses containing the NA H275Y amino acid substitution are able to replicate and transmit as efficiently as normal wild-type viruses. The presence of other permissive amino acid substitutions are thought to restore the usual deteriorating effect of the NA H275Y substitution on viral fitness (Butler et al., 2014; Abed et al., 2015).

2. Overall analysis of phenotypic antiviral susceptibility data from WHO CCs

As part of the WHO GISRS network, over 140 WHO National Influenza Centres (NICs) (http://www.who.int/influenza/gisrs_laboratory/national_influenza_centres/en/) receive and conduct

preliminary analyses on influenza viruses collected within their countries. A representative number of these viruses are then forwarded to at least one of five WHO Collaborating Centres (WHO CCs) (Atlanta, USA; Beijing, China; London, United Kingdom; Melbourne, Australia; and Tokyo, Japan) (http://www.who.int/influenza/gisrs_laboratory/collaborating_centres/en/) for more detailed virus characterisation.

Where available, patient-specific data including age, gender, geographic location, healthcare setting, influenza antiviral treatment history and immune status (immunocompromised or immunocompetent) are included in the analysis. Availability of antiviral treatment data was limited for many of the samples tested but for all viruses showing reduced inhibition by any NAI this information was sought retrospectively. Because the majority of viruses analysed were collected from patients at the time of disease onset (i.e. prior to any commencement of antivirals), the data provides insights on the NAI susceptibility of circulating viruses as opposed to the risk of emergence of viruses with reduced susceptibility in NAI treated patients.

Viruses were typically passaged once or twice in MDCK or MDCK-SIAT1 cells by WHO CCs before being analysed by phenotypic NA inhibition assay to assess NAI susceptibility. The NAI assays utilised the fluorescence-based substrate 2'-(4-Methylumbelliferyl)- α -D-N-acetylneuraminic acid, sodium salt hydrate (MUNANA) as previously described (Potier et al., 1979), but with minor modifications in each laboratory (Takashita et al., 2015b). All five WHO CCs tested for susceptibility to oseltamivir and zanamivir, while the Atlanta, Melbourne and Tokyo WHO CCs also tested isolates for susceptibility to peramivir and laninamivir.

As in the two previous global analysis reports (Meijer et al., 2014; Takashita et al., 2015b), to facilitate pooled analysis of the IC₅₀ phenotypic data (the concentration of drug required to inhibit standardised amount of NA activity by 50%) generated in the five WHO CCs, data were converted into relative fold-change values based on WHO CC, assay technique and subtype/lineage of virus. Box-and-whisker plots based on log transformed IC₅₀ fold-change data were generated using Tukey's method. Using the standardised definitions for reporting NAI susceptibility data (WHO, 2012), viruses were classified as showing either normal inhibition (NI), reduced inhibition (RI) or highly reduced inhibition (HRI) based on their fold differences compared to the median of viruses from the same type/subtype/lineage showing NI. Briefly, influenza A viruses are classified as RI if they have a 10- to 100-fold higher IC₅₀ or HRI if they have a >100-fold higher IC₅₀ than the relevant median. For influenza B viruses RI viruses have a 5- to 50-fold higher IC₅₀ while HRI viruses have a >50-fold higher IC₅₀ than the relevant median.

Data presented here includes analysis of viruses collected between week 21/2014 (May 19th, 2014) and week 20/2015 (May 17th, 2015). During this period, the number of viruses collected and submitted to WHO CCs peaked during the Southern and Northern Hemisphere winter seasons in weeks 27 (2014) and 2 (2015) respectively (Fig. 1A). Over the 2014–2015 period, a total of 13,312 viruses were tested for NAI susceptibility by the WHO CCs, a 25% increase compared to the number tested in the equivalent 2013–2014 period (Takashita et al., 2015b). The majority of viruses were A(H3N2) (6876; 51.6%) and B/Yamagata-lineage (3594; 27.0%), with lower proportions of A(H1N1)pdm09 (2115; 15.9%) and B/Victoria-lineage viruses (727; 5.5%) (Fig. 1B). In comparison, the predominant influenza virus type/subtype collected and tested in the 2013–2014 period was A(H1N1)pdm09 (48%). As has been observed in previous studies, the majority of viruses tested came from the Western Pacific WHO region (56%), followed by the Americas (29%) and Europe (9%). Only small proportions of viruses were received and tested from the WHO regions of Eastern

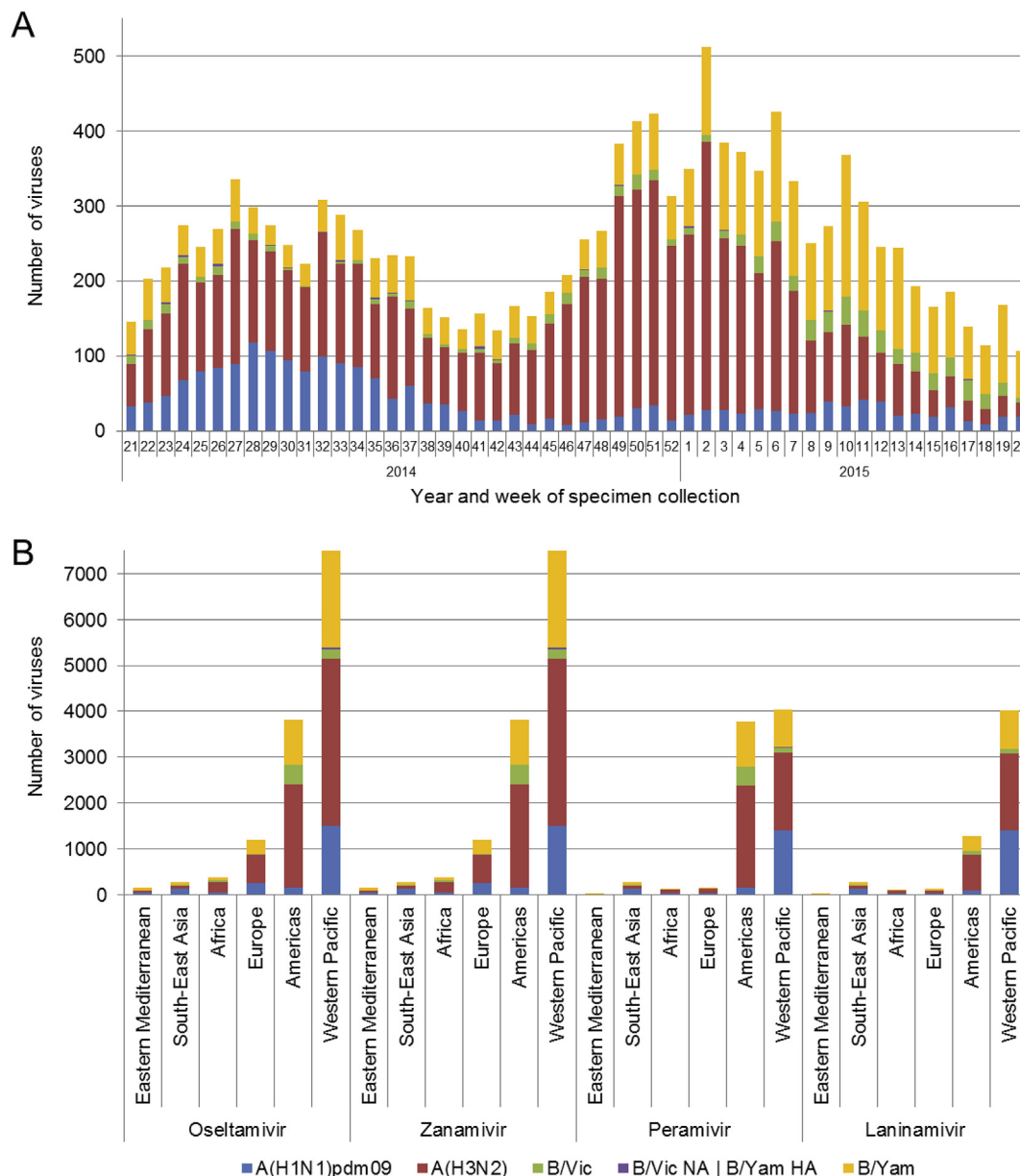


Fig. 1. Influenza viruses collected and tested for phenotypic neuraminidase inhibitor (NAI) susceptibility during 2014–2015. A) Week of specimen collection and virus type/subtype/lineage; for specimens tested, peaks in specimen collection during the Southern Hemisphere winter and during the Northern Hemisphere winter were observed. B) Number of viruses tested for phenotypic susceptibility to the four NAIs by World Health Organization region. B/Yamagata-lineage haemagglutinin:B/Victoria-lineage neuraminidase reassortants are shown separately.

Mediterranean (1%), South-East Asia (2%) and Africa (3%) (Fig. 1B).

Of the 13,312 viruses tested, 68 (0.5%) showed RI or HRI by one or more of the NAIs, a lower proportion than observed during the 2013–14 period (204/10,641; 1.9%) (Figs. 2 and 3; Tables 1 and 2). The NA genes from the 68 RI/HRI viruses were sequenced and 50 were found to contain amino acid substitutions compared to corresponding consensus sequences from wild-type viruses showing NI (Tables 1 and 2). NA genes were sequenced using standard procedures which differed slightly between laboratories. An example protocol from the Melbourne WHO CC is described in Deng et al. (2015) with specific NA segment primers from that procedure listed in Supplementary Table 1. Unfortunately many of the clinical specimens, from which the RI/HRI viruses with NA substitutions were recovered, were unavailable for sequence analysis ($n = 30$), but of those that were, 18 contained the same NA

amino acid substitution present in the isolate, while two did not, suggesting that those substitutions arose during cell culture (Tables 1 and 2).

3. A(H1N1)pdm09 viruses showing RI or HRI

Of 2115 A(H1N1)pdm09 viruses tested, 11 (0.5%) showed RI or HRI by one or more of the NAIs (Fig. 2; Table 1). Of these, six viruses were NA H275Y variants, showing HRI by oseltamivir (559- to 856-fold greater than the median) and RI/HRI by peramivir (94- to 212-fold greater), while retaining NI by zanamivir and laninamivir (Fig. 2; Table 1). The NA H275Y variant viruses were collected from patients within Australia ($n = 3$), Hawaii, Ukraine and France. Three of the patients were treated with oseltamivir prior to sample collection, two of whom were immunocompromised (Table 1).

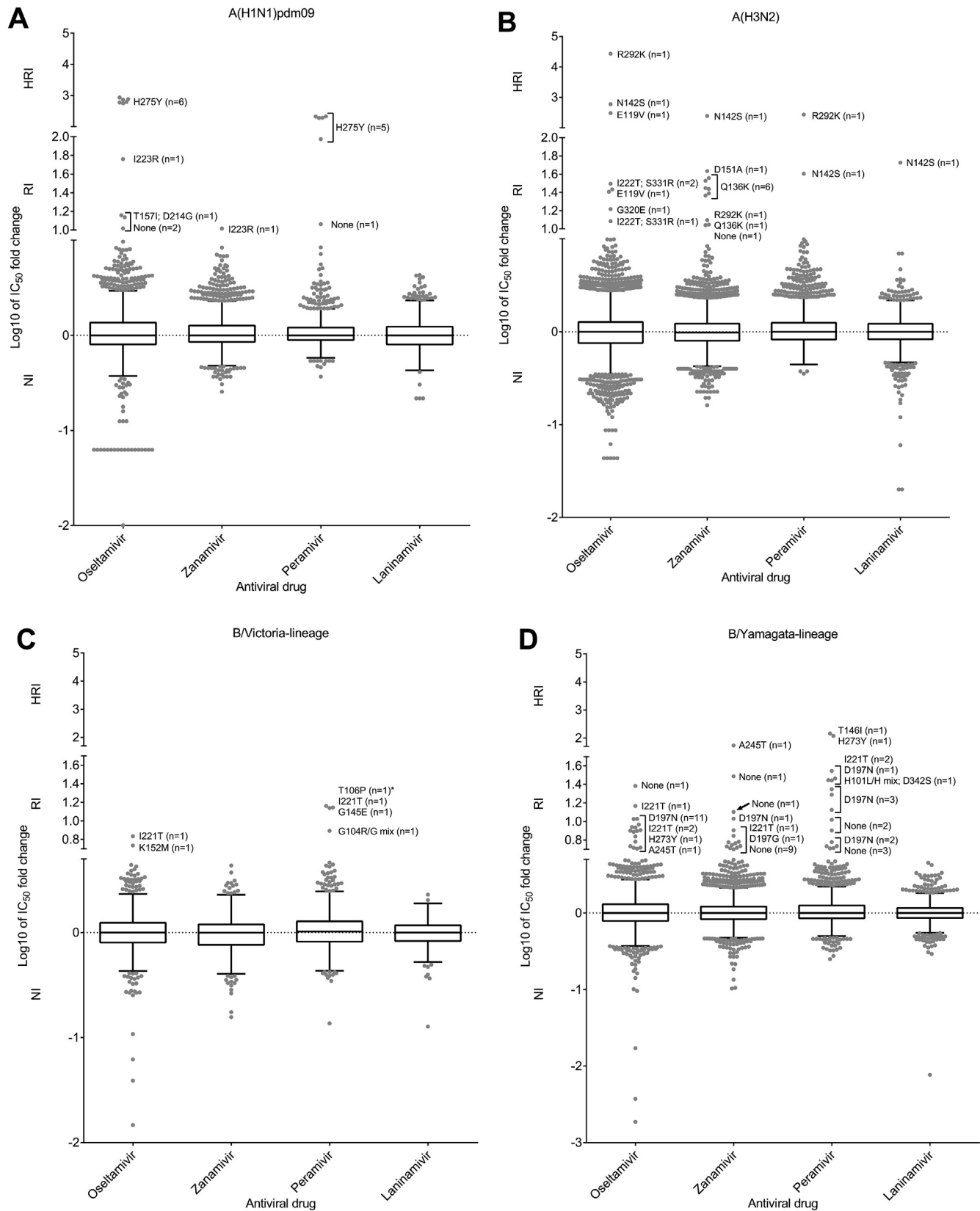


Fig. 2. Column-scatter plots of log-transformed 50% inhibitory concentration (IC_{50}) fold-change values. Data are presented by virus subtype or lineage (A, A(H1N1)pdm09; B, A(H3N2); C, B/Victoria-lineage; D, B/Yamagata-lineage) and neuraminidase inhibitor (labelled on the X-axis: oseltamivir, zanamivir, peramivir, laninamivir). Panel C also contains B/Yamagata-lineage haemagglutinin:B/Victoria-lineage neuraminidase reassortants, of which the one with amino acid substitution is indicated with an asterisk (*) in the peramivir column. The boxes indicate the 25–75 percentile and the whiskers stretch to the lowest and highest value within 1.5 times the interquartile region value from both the 25 and 75 percentile values respectively (Tukey's definition). The Y-axes have been split into 3 compartments according to the World Health Organization Antiviral Working Group recommended thresholds for normal inhibition (NI) (A viruses <10-fold; B viruses <5-fold), reduced inhibition (RI) (A viruses 10- to 100-fold; B viruses 5- to 50-fold), and highly reduced inhibition (HRI) (A viruses >100-fold; B viruses >50-fold). For RI and HRI viruses that have been sequenced the determined NA amino acid substitutions are shown; amino acid position numbering is A subtype and B type specific. All viruses were tested for susceptibility to oseltamivir and zanamivir but not all, including some variants, were tested against peramivir and laninamivir.

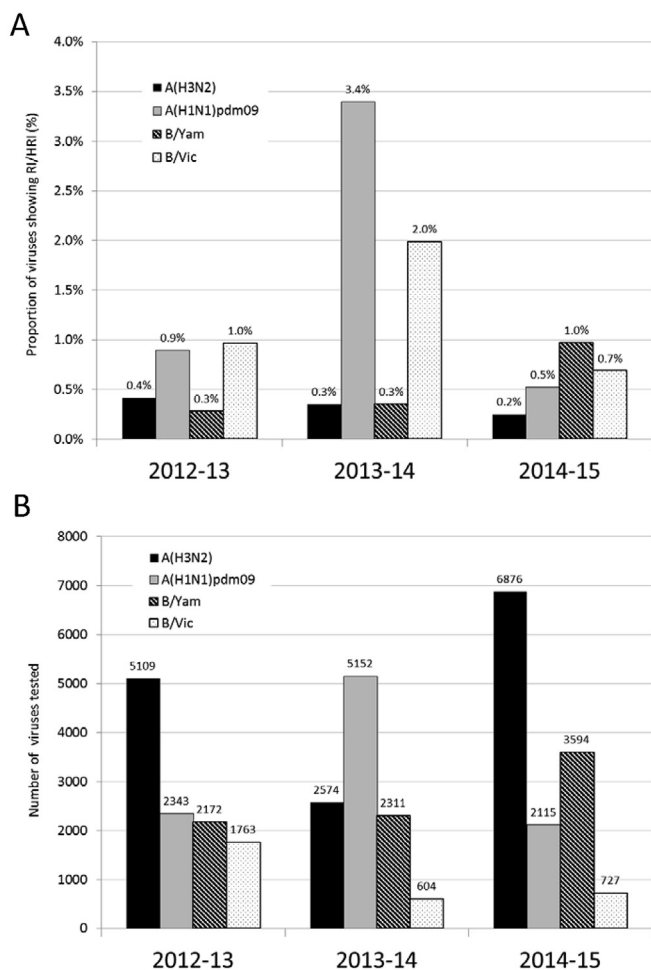


Fig. 3. A) Proportions of viruses showing RI or HRI by neuraminidase inhibitors over the 2012–2015 period. B) Number of viruses tested in NA inhibition assays. Data compiled from the global studies reporting on viruses isolated during 2012–13 (Meijer et al., 2014), 2013–14 (Takashita et al., 2015b) and 2014–15 (this study).

Compared with the 2013–2014 period, when 169 NA H275Y variants were detected (3.3% of the number tested) from predominantly Japan, China and USA, there was a substantial reduction in the detection of these variants in the 2014–2015 period, although this may be due to the lower number of A(H1N1)pdm09 viruses circulating.

A single A(H1N1)pdm09 virus with a NA I223R amino acid substitution was isolated from a patient in Bolivia (Fig. 2, Table 1). This virus showed RI by oseltamivir (58-fold greater IC_{50} than the median) and zanamivir (10-fold greater) but retained NI by peramivir and laninamivir (Fig. 2, Table 1). Of the remaining four viruses with RI by one or more of the NAIs, one contained dual T157I/D214G NA amino acid substitutions, while sequence analysis of the other three A(H1N1)pdm09 viruses failed to identify any NA substitutions that were either novel or associated with RI by NAIs (Fig. 2, Table 1).

4. A(H3N2) viruses showing RI or HRI

Seventeen (0.2%) out of 6876 A(H3N2) viruses showed RI or HRI by one or more of the NAIs. Seven of these contained NA Q136K amino acid substitution that confers RI by zanamivir (Fig. 2, Table 1). This substitution has typically been reported to arise during cell culture propagation (Little et al., 2015) but

unfortunately, for the seven isolates with this substitution, none of the respective clinical specimens were available to determine if this was the case. Three A(H3N2) viruses contained dual I222T/S331R amino acid substitutions that resulted in RI by oseltamivir (Fig. 2, Table 1). As single substitutions, neither I222T nor S331R alone confers sufficient IC_{50} rises to be classified as RI, but as a combination they synergistically raised oseltamivir IC_{50} by 12- to 31-fold (Table 1).

Five viruses with RI/HRI due to various NA amino acid substitutions were isolated from patients undergoing NAI treatment (Table 1). Two patients shed viruses containing NA E119V amino acid substitution that conferred RI/HRI by oseltamivir (25- to 303-fold) (Fig. 2), one received oseltamivir while the other (from Japan) received oseltamivir and peramivir and was immunocompromised (Table 1). Another immunocompromised patient from Japan, who was infected with A(H3N2) influenza and treated with oseltamivir and peramivir, shed viruses containing NA R292K amino acid substitution which conferred a massive 27,416-fold increase in oseltamivir IC_{50} as well as conferring HRI by peramivir (271-fold) and RI by zanamivir (12-fold) (Fig. 2; Table 1).

A NA D151A amino acid substitution was detected in an isolate that had RI by zanamivir (43-fold), but sequencing showed that the substitution was not present in the clinical specimen, thereby suggesting that it had arisen during cell culture, as has been reported previously for this substitution (Okomo-Adhiambo et al., 2010). Two other A(H3N2) viruses with less commonly identified NA amino acid substitutions were also detected in 2014–15. The first was a virus from the USA that contained NA N142S amino acid substitution that unusually conferred HRI or RI by all four NAIs (HRI to oseltamivir and zanamivir and RI to peramivir and laninamivir), while the second virus contained NA G320E amino acid substitution that caused RI by oseltamivir (17-fold) (Fig. 2; Table 1).

5. B/Victoria-lineage viruses showing RI or HRI

Five (0.7%) of the 727 B/Victoria-lineage viruses (which included 35 B/Yamagata-lineage HA:B/Victoria-lineage NA reassortants) showed RI or HRI by one or more of the NAIs. Three viruses exhibited RI by peramivir and had IC_{50} values that were 8- to 14-fold higher than the median, and contained single NA amino acid substitutions of T106P, G104R/G and G145E respectively (Fig. 2; Table 2). A virus from Honduras with NA I221T amino acid substitution showed RI by both oseltamivir (7-fold) and peramivir (14-fold) and a virus from Bangladesh contained NA K152M amino acid substitution that resulted in a 5-fold increase in oseltamivir IC_{50} (Fig. 2; Table 2). Unfortunately, no information about antiviral treatment or the immune status of the patients was available for these five cases.

6. B/Yamagata-lineage viruses showing RI or HRI

Of the 3594 B/Yamagata-lineage viruses tested, 35 (1.0%) had RI or HRI by one or more of the NAIs. Twelve of these viruses contained NA D197N amino acid substitution that conferred 4- to 11-fold increases in oseltamivir IC_{50} , 2- to 11-fold increases in zanamivir IC_{50} and 5- to 29-fold increases in peramivir IC_{50} (Fig. 2; Table 2). Three NA D197N variants were from Australia, three from the USA, five from China and one from the Ukraine (Table 2). Interestingly, the three viruses from Australia had identical HA and NA sequences and two of these (B/South Australia/2/2015 and B/South Australia/5/2015) were from a father and son who lived together. While there was no epidemiological link to the third Australian case, it is noteworthy that the specimen collection date differed by only 7 days from that which yielded B/South Australia/2/2015 virus. One of the NA D197N variants from China (B/Tianjin-

Table 1Virus and patient characteristics of 28 influenza A viruses showing RI or HRI, tested by WHO CCs.^a

Virus	n	IC ₅₀ fold-change compared to reference median IC ₅₀ values ^b				NA-substitution ^c		Patient setting	Antiviral treatment prior to specimen collection
		Oseltamivir	Zanamivir	Peramivir	Laninamivir	Virus isolate	Clinical specimen		
A(H1N1) pdm09; N = 2115	6	559–856	0.9–1.9	94 – 212	1.5–2.6 (5)	H275Y	H275Y (4) Not available (2)	GP/Outpatient (1) Hospital (3) Unknown (2)	Yes, oseltamivir (2) Yes, antiviral unknown (1) No (2) Unknown (1) No
	1	14	7.0	1.6	1.3	T157I, D214G	No sequence available, poor quality data	GP/Outpatient	
	1	58	10	7.2	2.2	I223R	I223R	Unknown	Unknown
	2	10–14	2.2–8.4	3.7 (1)	3.6 (1)	None	Not available (1) Not sequenced (1)	GP/Outpatient	No (1) Unknown (1)
	1	1.6	2.0	12	1.9	None	Not sequenced	Hospital	No
A(H3N2); N = 6876	7	0.3–1.1	11–36	2.9–9.0 (2)	2.0–3.6 (2)	Q136K	Not available	Hospital (5) Unknown (2)	Unknown
	3	12–31	2.9–7.2	1.6–2.4	2.5–3.6	I222T, S331R	I222T, S331R	GP/Outpatient	No
	2	25–303	1.5–2.3	1.5–2.1	1.1–2.2	E119V	E119V	Hospital (1) Unknown (1)	Yes, oseltamivir (1), oseltamivir and peramivir (1) Unknown
	1	595	244	40	53	N142S	N142S	Unknown	Unknown
	1	2.9	43	9.9	6.9	D151A	Substitution not present	GP/Outpatient	Yes, zanamivir
	1	27 146	12	271	2.7	R292K	R292K	Hospital	Yes, oseltamivir and peramivir
	1	17	8.4	3.3	1.9	G320E	Not available	Unknown	Unknown
	1	7.9	11	nd	nd	None	Not available	GP/Outpatient	Yes, oseltamivir

^a Between brackets the number of viruses for which data was reported if less than the number reported in column 'n'. RI = reduced inhibition; HRI = highly reduced inhibition; nd = not done; None = no amino acid substitutions compared to viruses with NI phenotype.

^b RI and HRI fold-change values are displayed underlined and in bold typeface.

^c Amino acid position numbering is A subtype specific.

Table 2Virus and patient characteristics of 40 influenza B viruses showing RI or HRI, tested by WHO CCs.^a

Virus	n	IC ₅₀ fold-change compared to reference median IC ₅₀ values ^b				NA-substitution ^c		Patient setting	Antiviral treatment prior to specimen collection
		Oseltamivir	Zanamivir	Peramivir	Laninamivir	Virus isolate	Clinical specimen		
B/Victoria-lineage; N = 727 ^d	1	1.1	2.9	14	0.7	T106P ^d	Not available	Unknown	Unknown
	1	4.2	0.8	7.8	0.7	G104R/G mix	Not available	Unknown	Unknown
	1	0.7	0.7	14	0.4	G145E	Not available	Unknown	Unknown
	1	5.4	0.6	1.9	1.1	K152M	Not available	Unknown	Unknown
	1	6.8	3.7	14	1.4	I221T	Not available	Unknown	Unknown
B/Yamagata-lineage; N = 3594	12	4.4–11	2.2–11	5.4 – 29	1.6–3.3 (6)	D197N	D197N (4) Not available (7) Not sequenced (1)	GP/Outpatient (4) Hospital (5) Unknown (2)	No (3) Unknown (8)
	3	7.9–15	4.1–5.4	28–35	1.7–1.9	I221T	I221T (1) Not available (2)	GP/Outpatient (1) Hospital (1) Unknown (1)	No (1) Unknown (2)
	1	1.7	1.8	28	1.2	H101L/H mix, D342S	Not available	Unknown	Unknown
	1	2.0	1.0	145	0.8	T146I	Substitution not present	GP/Outpatient	No
	1	3.3	5.4	nd	nd	D197G	Substitution not present	GP/Outpatient	Yes, oseltamivir
	1	5.2	1.0	120	0.6	H273Y	H273Y	Unknown	Unknown
	1	8.1	55	nd	nd	A245T	Not available	Hospital	Unknown
	15	0.8–24	0.2–31	0.8 – 10	1.3–4.2	None	Not available	GP/Outpatient (7) Hospital (1) Unknown (7)	No (1) Unknown (14)
				(14)	(14)				

^a Between brackets the number of viruses for which data was reported if less than the number reported in column 'n'. RI = reduced inhibition; HRI = highly reduced inhibition; nd = not done; None = no amino acid substitutions compared to viruses with NI phenotype.

^b RI and HRI fold-change values are displayed underlined and in bold typeface.

^c Amino acid position numbering is B type specific.

^d 35 of these viruses are B/Yamagata-lineage haemagglutinin (HA) – B/Victoria-lineage neuraminidase (NA) reassortants; because the NA defines the IC₅₀ values these viruses are listed in the B/Victoria-lineage category. One of these viruses had NA T106P.

Hedong/834/2015) was collected in the same time period as the Australian viruses and the HA and NA sequences of these four viruses clustered closely in the phylogenies (Supplementary Fig. S1). Two Chinese NA D197N variants, collected in September and October 2014 (B/Anhui-Baohe/1680/2014 and B/Shanghai-Pudongxin/11568/2014), also had identical HA and NA sequences. From phylogenetic analyses of these variants over the last five years, we also identified an early 2014 cluster of six Japanese viruses with NA D197N substitution that had identical HA and NA sequences, further suggesting that these viruses can spread in the

community (Supplementary Fig. S1). For NA D197N variants where the respective clinical specimens were available (n = 4), all contained the amino acid substitution and none of the patients had been treated with an NAi. Three influenza B NA D197N variants (2 from the B/Yamagata-lineage and one from the B/Victoria-lineage) were detected through phenotypic analysis in the equivalent 2013–2014 period, one of which was collected from a patient being treated with zanamivir (Takashita et al., 2015b). Another B/Yamagata-lineage virus from Spain carried NA D197G amino acid substitution which conferred a 5-fold increase in oseltamivir IC₅₀;

unfortunately the clinical specimen yielding this virus isolate was not available (Fig. 2; Table 2).

Three viruses with NA I221T amino acid substitution that conferred RI by oseltamivir (8- to 15-fold), zanamivir (4- to 5-fold) and peramivir (28- to 35-fold) were collected from patients in Japan, Russia and China (Fig. 2; Table 2). Three other B/Yamagata-lineage viruses, all with different NA amino acid substitutions (T146I, H273Y and A245T), demonstrated HRI by either peramivir or zanamivir (Fig. 2; Table 2), but sequence analysis of the relevant clinical specimen revealed that the T146I substitution arose during cell culture. A further 15 B/Yamagata-lineage viruses showed RI by at least one of the NAIs but sequence analysis failed to reveal any unique NA amino acid substitutions that were considered to be associated with the change in IC₅₀ (Fig. 2; Table 2).

7. Frequency of RI and HRI conferring NA amino acid substitutions in sequence databases

The interrogation of public sequence databases to determine the frequency of NA amino acid substitutions that confer RI or HRI by the NAIs is a useful adjunct to the phenotypic data generated by the WHO CCs. Analysis of the Global Initiative on Sharing All Influenza Data (GISAID) (www.gisaid.org) and National Center for Biotechnology Information – Influenza Virus Resource (NCBI-IVR) (www.ncbi.nlm.nih.gov/genomes/FLU/FLU.html) databases showed that sequences from 7316 influenza viruses collected during the 2014–15 period had been deposited, of which 2440 (33%) were from viruses that had not been tested by the WHO CCs in the phenotypic analysis described above.

We analysed the NA sequences from the 2440 viruses (466 A(H1N1)pdm09; 1373 A(H3N2); 58 B/Victoria-lineage and 543 B/Yamagata-lineage) to determine the number that contained amino acid substitutions associated with reduced inhibition, as listed in the summary table provided by the AVWG on the WHO website (http://www.who.int/influenza/gisrs_laboratory/antiviral_susceptibility/avwg2014_nai_substitution_table.pdf). Of the 466 A(H1N1)pdm09 virus NA sequences, four contained the H275Y amino acid substitution (from France (n = 2), Norway (n = 1) and Spain (n = 1) that confers HRI by oseltamivir and peramivir, while the E119V amino acid substitution, which confers RI/HRI by oseltamivir, was present in one of the 1373 A(H3N2) NA sequences. Four NA sequences from the 543 B/Yamagata-lineage viruses contained the same D197N amino acid substitution that was detected in twelve variants tested in the phenotypic assay, and which conferred RI by oseltamivir, zanamivir and peramivir; in addition one NA sequence contained the H273Y amino acid substitution which confers HRI by peramivir.

8. Concluding remarks

Based on our current analysis, >99% of influenza viruses tested during 2014–15 were susceptible to all four NAIs, indicating that these antivirals remain an appropriate choice for the treatment and prophylaxis of influenza virus infections. Viruses with RI or HRI occurred across multiple regions and were not detected at higher frequencies in countries where NAI usage is greatest (i.e. Japan and the USA) (Supplementary Table 2). This is the third global update on influenza NAI susceptibility based on data generated by the WHO CCs' analyses of viruses received from NICs throughout the world. The overall frequency of viruses with RI or HRI by the NAIs was highest in 2013–14 (1.9%), compared to 2012–13 and the most recent 2014–15 period where the frequencies were 0.6% and 0.5% respectively (Fig. 3). The higher frequency of RI/HRI viruses in 2013–14 was due mainly to A(H1N1)pdm09 being the dominant influenza A subtype with an associated increased detection of

A(H1N1)pdm09 viruses with NA H275Y amino acid substitution, with clusters of cases being detected in Japan, the USA and China (Takashita et al., 2015b). Of the different types/subtypes, B/Yamagata-lineage viruses had the highest frequency of RI/HRI viruses in the 2014–15 period, of which variants with NA D197N amino acid substitution were the most prevalent. Given the close genetic similarity across the HA and NA of some NA D197N variants in Australia and China it is possible that some low level community transmission of these viruses had occurred, so close monitoring of influenza B viruses for this substitution will be important in upcoming influenza seasons.

Contributions

All WHO-AVWG members, WHO Headquarters and Regional Office Staff present during the 5th WHO-AVWG meeting held 25–26 June 2015 in Geneva were involved in discussions relating to this global update. AH drafted the manuscript and all authors contributed to editing the final manuscript. AH, DT, BE, RD, LG, HTN, ET, MT, DW and WH generated and provided the NAI sensitivity data and molecular analysis. AM performed analysis of the data from the WHO CCs, RL and SM-S performed the analysis of data from sequence databases and RD and BE generated the phylogenies presented in supplemental data.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.antiviral.2016.06.001>.

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Estimates of global seasonal influenza-associated respiratory mortality: a modelling study

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Contributors

ADI, M-AW, and JSB conceived the study. ADI contacted and engaged potential partners for collaboration in the global network, communicated progress of the global estimation, and requested feedback. ADI and KMR compiled, managed, cleaned, evaluated, and analysed country-specific data. ADI and KMR developed statistical models for country-specific data for some contributing countries and communicated and discussed findings with country-specific partners before finalising estimates to use in global models. HHC conceptualised and developed the global statistical model. ADI, KMR, HHC, and JSB drafted the manuscript, created the tables and figures, compiled feedback, and addressed all comments from coauthors. DJM, RP, ST, CC, JMG, DS, BJC, PW, JK, LWA, MP, MR-F, HY, LE, AK, GE, LVA, SPdS, SA, and UB developed country-specific statistical models to estimate influenza-associated mortality, analysed country-specific data, provided statistical feedback on global models, and provided feedback on manuscript drafts. All other authors listed as network collaborators provided data, reviewed country-specific results, or reviewed, contributed to, and approved final results, manuscript drafts, and this publication.

Declaration of interests

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Summary

Background—Estimates of influenza-associated mortality are important for national and international decision making on public health priorities. Previous estimates of 250 000–500 000 annual influenza deaths are outdated. We updated the estimated number of global annual influenza-associated respiratory deaths using country-specific influenza-associated excess respiratory mortality estimates from 1999–2015.

Methods—We estimated country-specific influenza-associated respiratory excess mortality rates (EMR) for 33 countries using time series log-linear regression models with vital death records and influenza surveillance data. To extrapolate estimates to countries without data, we divided countries into three analytic divisions for three age groups (<65 years, 65–74 years, and ≥75 years) using WHO Global Health Estimate (GHE) respiratory infection mortality rates. We calculated mortality rate ratios (MRR) to account for differences in risk of influenza death across countries by comparing GHE respiratory infection mortality rates from countries without EMR estimates with those with estimates. To calculate death estimates for individual countries within each age-specific analytic division, we multiplied randomly selected mean annual EMRs by the country's MRR and population. Global 95% credible interval (CrI) estimates were obtained from the posterior distribution of the sum of country-specific estimates to represent the range of possible influenza-associated deaths in a season or year. We calculated influenza-associated deaths for children younger than 5 years for 92 countries with high rates of mortality due to respiratory infection using the same methods.

Findings—EMR-contributing countries represented 57% of the global population. The estimated mean annual influenza-associated respiratory EMR ranged from 0·1 to 6·4 per 100 000 individuals for people younger than 65 years, 2·9 to 44·0 per 100 000 individuals for people aged between 65 and 74 years, and 17·9 to 223·5 per 100 000 for people older than 75 years. We estimated that 291 243–645 832 seasonal influenza-associated respiratory deaths (4·0–8·8 per 100 000 individuals) occur annually. The highest mortality rates were estimated in sub-Saharan Africa (2·8–16·5 per

100 000 individuals), southeast Asia (3·5–9·2 per 100 000 individuals), and among people aged 75 years or older (51·3–99·4 per 100 000 individuals). For 92 countries, we estimated that among children younger than 5 years, 9243–105 690 influenza-associated respiratory deaths occur annually.

Interpretation—These global influenza-associated respiratory mortality estimates are higher than previously reported, suggesting that previous estimates might have underestimated disease burden. The contribution of non-respiratory causes of death to global influenza-associated mortality should be investigated.

Introduction

Annual influenza epidemics result in substantial mortality, especially among adults aged 65 years and older. Previous estimates attributed to WHO¹ indicated that 250 000–500 000 influenza-associated deaths occur annually, corresponding to estimates of 3·8–7·7 deaths per 100 000 individuals calculated using 2005 UN Department of Economic and Social Affairs World Population Prospects.² The methods used to calculate this WHO estimate have not been published and might not have accounted for annual variability in the incidence of influenza virus infection, the age and health status of populations, or risk of influenza death across countries. A 2013 study,³ which used data from 2005 to 2009, suggested that 148 000–249 000 annual influenza respiratory deaths might occur each year.³ Current, reliable global and country-specific influenza-associated mortality estimates are needed to inform decisions about the value of influenza prevention and control and to inform global public health priorities.

Estimating the burden of annual influenza epidemics is challenging for many countries because of the requirement for high-quality systematic vital records and local viral surveillance data. As a result, most influenza-associated mortality estimates have been obtained from high-income countries with a temperate climate.^{4–26} Many developing or recently industrialised countries have leveraged improvements in influenza surveillance data²⁷ to develop country-specific influenza-associated mortality estimates, which are generally higher (4·3–31·6 per 100 000 individuals) than WHO-attributed estimates,^{28–31} implying that the current global influenza death estimates might underestimate the global mortality burden of influenza. The wide variation in influenza-associated excess mortality estimates between countries and between seasons and years highlights the effect of specific circulating influenza viruses on mortality and the need to include more country-specific estimates in global mortality estimation to better quantify global disease burden. Furthermore, global and country-specific estimates should be updated periodically to account for changes in population demographics, improvements in health care, and viral evolution.

Improved methods to estimate baseline and influenza-associated mortality have been developed.^{32–37} However, influenza virus infections are rarely confirmed systematically by laboratory diagnosis, and thus influenza deaths might be attributed to other comorbid conditions or secondary infections. Ecological models are commonly used to estimate influenza-associated mortality. Vital records death data, which have varying levels of quality,

completeness, and population coverage, are systematically coded for cause of death using the International Classification of Diseases (ICD),^{38,39} and categories of death commonly associated with influenza, including respiratory or circulatory causes,⁴⁰ are modelled with virological data to identify periods of influenza virus circulation and to estimate influenza-associated excess deaths. The inclusion of virological data is important for the quantification of influenza-associated deaths because the circulating strains of the virus subtypes vary from year to year, which can affect annual mortality.^{40,41} The application of these methods is challenging in many low-income and middle-income countries because they often have year-round or multiple peaks in influenza virus circulation, vital records data that are not of sufficient quality, or they have too few years of reliable surveillance data for robust estimates despite recent efforts to improve and expand surveillance.^{27,35,42,43}

We aimed to estimate the number of country-specific influenza-associated respiratory deaths and to update global and regional influenza-associated respiratory death estimates among individuals younger than 65 years, 65–74 years, and 75 years and older, using excess death estimates from contributing countries extrapolated to countries without such data.

Methods

Study design and data sources

We developed a statistical modelling approach to generate country-specific estimates of influenza-associated death for countries with no available estimates accounting for uncertainty in estimated risk of influenza death and variability between countries (figure 1). This analysis complied with the WHO Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER),^{44,45} and a GATHER checklist for this study is included in the appendix.

In this study, the terms country or countries referred to WHO member states, Hong Kong, Taiwan, or regions within a country. We contacted potential collaborators in 62 countries who were identified from literature published in the past 20 years or through the solicitation of data from surveillance or research contacts. Of the 62 countries, 47 contributed data: 33 countries provided model estimates of age-specific influenza-associated respiratory excess mortality rates (EMRs), 13 countries contributed age-specific annual respiratory deaths, and one country contributed annual estimates of influenza-associated respiratory death using a multiplicative model (table 1). Of the 15 remaining countries contacted, eight did not respond to collaboration requests, five were unable to share data by September, 2017, and two had vital records data of insufficient quality.

The 33 countries with annual influenza-associated excess mortality estimates are referred to as EMR-contributing countries. For these countries, we requested at least 4 years of weekly or monthly vital records mortality data collected between 1999 and 2015 for three age groups (<65 years, 65–74 years, and ≥75 years) for all respiratory causes of death (ICD ninth revision⁴⁸ codes 460–519; ICD tenth revision⁴⁹ codes, J00–J99). We also requested viral surveillance data, including the total number of specimens tested for influenza and the number of positive specimens for each influenza type and subtype, for the same time period. For EMR-contributing countries with these data that were not able to share with external

partners, we requested influenza-associated excess respiratory mortality estimates for the three age groups for at least four separate seasons or years (appendix).

13 countries provided the annual number of all ICD-coded respiratory deaths for the three age groups, which were used to validate the extrapolated estimates. One country provided estimates of influenza-associated acute respiratory infection deaths obtained using a multiplicative model with verbal autopsy and viral surveillance data, which were used as a comparison for our extrapolated estimates. The type and quality of data obtained from these 14 validation countries is described in the appendix.

WHO Global Health Estimates

We used 2015 WHO Global Health Estimates (GHE) respiratory infection mortality rates,^{47,50} including both lower respiratory infection (ICD tenth revision⁴⁹ codes J09–J22, P23, and U04) and upper respiratory infection (ICD codes⁴⁹ J00–J06) mortality estimates to assign countries to age-specific analytic divisions. We also used the 2015 GHE mortality rates to calculate respiratory infection mortality rate ratios (MRRs) to account for differences in risk of influenza-associated or respiratory death between EMR-contributing countries and countries without excess mortality estimates. GHE respiratory infection mortality rate estimates were obtained for three age groups (<65 years, 65–74 years, and ≥75 years). Hong Kong and Taiwan were not included in 2015 GHE mortality estimates and thus respiratory infection mortality rates were obtained from their 2015 ICD-coded vital records. Estimation methods for GHE differed by country depending on quality and availability of cause-specific death information (appendix).⁵⁰

Population estimates

2015 population estimates were obtained from the UN Department of Economic and Social Affairs World Population Prospects² for 184 countries and the US Census Bureau⁴⁶ mid-year population estimates for one country.

Calculation of mortality estimates

We used a step-wise approach to extrapolate influenza-associated excess mortality rates from countries with estimates to countries without estimates (figure 1). First, we used the 2015 GHE respiratory infection mortality rates⁴⁷ to group countries into analytic divisions, based on the assumption that variability in these rates reflected variability in circulation of influenza viral strains or case fatality ratio between countries. To establish analytic divisions for each age group, we categorised countries into quartiles according to GHE respiratory infection mortality rate (figure 1A). Because respiratory infection mortality rates varied widely by age, countries were sometimes categorised into different quartiles according to age group. Few EMR-contributing countries were grouped into the fourth quartile, therefore the third and fourth quartiles were combined resulting in three analytic divisions for each age group (nine analytic divisions in total; appendix). For each age-specific analytic division, the number of EMR-contributing countries ranged between six and 18 (table 2). We estimated global influenza-associated respiratory deaths for 185 countries. For this global analysis, the world was defined as WHO member states, Hong Kong, and Taiwan. 11 member states (Andorra, Cook Islands, Dominica, Saint Kitts and Nevis, Monaco, Marshall

Islands, Niue, Nauru, Palau, San Marino, and Tuvalu) were excluded, which comprised 0.006% of the global population. Influenza-associated death estimates were not calculated for these 11 member states because 2015 GHE estimates for respiratory infection mortality rates for these countries were not available.

We estimated country-specific influenza-associated respiratory EMRs per 100 000 population for the 33 EMR-contributing countries using time series log-linear regression models. Different models were selected for each country on the basis of data availability and quality of information (appendix). 26 countries included data on influenza-like illness consultations or the percentage of people who tested positive for each influenza virus type or subtype, and five countries accounted for respiratory syncytial virus circulation by including the percentage of people who tested positive for respiratory syncytial virus. Seven countries did not have sufficient viral surveillance data for modelling. For these countries, linear regression with a Serfling³³ approach was used in addition to either pneumonia and influenza mortality data, influenza-like illness activity, or viral surveillance information to define the influenza virus circulation season for each of the countries.²⁹ To account for temporal correlation in the residuals, we used bootstrapping to calculate individual year or season standard errors around these estimates.³²

To account for variability between countries and annual variability in excess mortality estimates within each analytic division, we used a Bayesian hierarchical model incorporating individual season or year estimates and standard errors to calculate age-specific and country-specific mean annual EMRs per 100 000 population to represent the collection of annual estimates available from each EMR-contributing country (figure 1B).

Posterior inference was done using the Markov chain Monte Carlo method (appendix). We applied a constraint to ensure that the estimated mean annual EMRs were not less than 0 (table 2). We excluded estimates from the 2009 influenza A(H1N1)pdm09 period, specifically estimates for the 2009–10 season for temperate countries in the northern hemisphere and 2009 annual estimates for countries with a tropical climate and temperate countries in the southern hemisphere, because the effect of the influenza A(H1N1)pdm09 virus on mortality was different from that of typical seasonal epidemics.^{3,51}

To account for differences in the risk of influenza death between countries, we calculated MRRs using two formulas (figure 1C) on the basis of the quality of GHE source information and cause-of-death estimates (appendix).⁵⁰ The MRRs for countries with higher quality GHE cause-of-death estimates⁵⁰ were calculated by dividing that country's GHE respiratory infection mortality rate by the GHE respiratory infection mortality rate for a randomly selected reference EMR-country for each extrapolation simulation. The MRRs for countries with lower quality GHE cause-of-death estimates⁵⁰ were calculated by replacing the individual country's GHE respiratory infection mortality rate with a randomly selected GHE respiratory infection mortality rate from the distribution of GHE respiratory infection mortality rates from all countries within that age-specific analytic division and dividing by the GHE respiratory infection mortality rate for the randomly selected reference EMR-country. We used this approach to account for unknown error in GHE respiratory infection mortality rates for countries with poor quality or no vital records data. To verify our MRR

approach, we plotted GHE respiratory infection mortality rates by mean annual EMR rates from the 33 countries stratified by age group.

We estimated the number of influenza-associated respiratory deaths within each age-specific analytic division for each country by extrapolating randomly selected mean annual influenza-associated EMRs from the 33 EMR-contributing countries (figure 1D). For each posterior sample within an analytic division, we multiplied a randomly selected mean annual EMR from a contributing country, or reference EMR, by the age-specific and country-specific MRR and population to generate a distribution of possible influenza-associated respiratory death estimates for each country. This process was repeated for each posterior sample (n=5000) by randomly selecting a different reference EMR and associated MRR to account for variability caused by the choice of reference countries. To obtain individual country estimates, we used interval estimates corresponding to the 95% credible interval (95% CrI) of the Bayesian posterior distributions to represent the range of possible influenza-associated respiratory deaths in a specific year or season (appendix).

Individual country posterior distributions were summed within each age-specific analytic division to calculate regional and global estimates (figure 1E). We used the 95% CrI of the posterior distribution to represent the range of possible global annual influenza-associated deaths in a specific season or year because of expected annual variability in circulating virus strains. We also summed estimates by WHO region and World Bank classification.⁵² After evaluating and validating our extrapolation approach, we replaced extrapolated estimates for each EMR-contributing country with the mean annual influenza-associated respiratory EMR and death estimate from the Bayesian hierarchical model, with the exception of Brazil and Kenya because their provided estimates were not nationally representative. The proportion of the median influenza-associated respiratory death estimates that were derived from either EMR-contributing country estimates or from our extrapolation model was calculated to compare the proportion of the total estimate that was derived from countries with EMR data with the proportion that were extrapolated.

For countries with high respiratory infection mortality in children, we also obtained estimates of influenza-associated excess mortality for children younger than 5 years for a subanalysis. Of the 185 countries that we had estimated global influenza-associated respiratory deaths for, two (1%; Hong Kong and Taiwan) did not have GHE respiratory infection mortality estimates for children younger than 5 years and therefore could not be categorised into an analytic division. Once grouped into analytic divisions, only countries in analytic division 3 (n=92) were selected for subanalysis. We used the same analytic and extrapolation approach as previously described to estimate respiratory influenza-associated deaths for the 92 countries with the highest child respiratory infection mortality, which were primarily located in sub-Saharan Africa, southeast Asia, and the Eastern Mediterranean region. The number of deaths in children younger than 5 years for these 92 countries represents 95% of all respiratory infection deaths globally in this age group (appendix).^{47,50} Influenza-associated respiratory EMRs from 1999 to 2015 for Kenya, India, Romania, and South Africa were used as reference EMRs. These EMR-contributing countries had sufficient vital records death data for children younger than 5 years for modelling. EMR estimates were not available for this age group in countries with lower overall respiratory

infection mortality rates or countries in analytic divisions 1 or 2 because too few deaths were recorded each week in these countries to estimate excess mortality using time series log-linear models.

Evaluation of extrapolation approach

To evaluate each country's effect on the global estimate, we did the extrapolation by removing one EMR-contributing country from the model at a time. We also compared each EMR-contributing country's mean annual influenza-associated respiratory death 95% CrIs to the extrapolated respiratory death estimate calculated when that specific country was removed from the analysis and with the extrapolated annual death interval estimate for that country using all EMRs within the analytic division. To assess differences between our extrapolation and the country-specific EMR, we considered non-noticeable differences to be if the 95% CrIs overlapped or if the difference in medians was 10% or more when all countries were included in the extrapolation.

For another validation comparison, we calculated the proportion of all respiratory deaths that were influenza-associated for 32 of the 33 EMR-contributing countries that provided the total age-specific number of respiratory deaths by year or season. Within each age-specific analytic division, we calculated the range of the proportion of influenza-associated deaths of all respiratory deaths across all annual estimates for each EMR-contributing country. We applied the range within each analytic division to the annual age-specific ICD-coded respiratory deaths provided by 13 validation countries. We evaluated our extrapolation estimates by comparing the range of influenza-associated respiratory deaths estimated using the proportion of influenza-associated respiratory deaths out of all respiratory deaths with the 95% CrI estimates from the posterior distribution for the 13 validation countries. We considered our extrapolation model to have reasonably estimated influenza-associated deaths for these countries if the intervals overlapped. For the other validation country—Bangladesh—which provided annual estimates of influenza-associated mortality calculated using a multiplier approach, we compared our extrapolated estimate with the mean annual estimate for that country. We considered non-noticeable differences to be if the 95% CrIs overlapped. We considered that an overlap in these ranges implied that our extrapolation model reasonably estimated influenza-associated deaths for these countries compared with alternative methods of estimating influenza-associated deaths using a proportion.

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There was no funding source for this study. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

The 33 EMR-contributing countries accounted for 57% of the global population (4 153 487 759 of 7 335 457 097 individuals; appendix). Of these 33 countries, two (6%) were in sub-Saharan Africa, 13 (39%) were in Europe, eight (24%) were in the Americas (three [9%] in North America and five [15%] in central or South America), two (6%) in southeast Asia, and eight (24%) in the western Pacific. EMR-contributing countries provided between four and

16 annual influenza-associated respiratory EMR estimates calculated between 1999 and 2015 for the three age groups (>65 years, 65–74 years, and ≥75 years).

The estimated mean annual influenza-associated respiratory EMR ranged from 0·1 to 6·4 per 100 000 individuals for people younger than 65 years, 2·9 to 44·0 per 100 000 individuals for people aged between 65 and 74 years, and 17·9 to 223·5 per 100 000 for people older than 75 years (table 2; appendix).

We found a positive correlation ($r^2=0\cdot29$ in the ≥75 years age group to $r^2=0\cdot74$ in the <65 years age group; appendix) between GHE respiratory infection mortality rates and the mean annual influenza-associated excess mortality rates for the EMR-contributing countries (appendix). MRRs were calculated using 2015 GHE respiratory infection mortality estimates. For example, the country-specific and age-specific MRR for analytic division 2 among people aged 65–74 years was calculated as follows: for countries with higher quality GHE cause-of-death estimates, the numerator was their country-specific respiratory infection mortality rate estimate (44·2–93·5 per 100 000 individuals) and the denominator was the GHE respiratory infection rate for the randomly selected reference EMR-contributing country within that analytic division (45·9–87·6 per 100 000 individuals; table 3). For countries with lower quality GHE cause-of-death estimates, the MRR numerator represented the distribution of estimates for all countries within the analytic divisions. The range of country-specific and age-specific MRRs are shown in the appendix.

Using data from 1999–2015, we estimated that between 291 243 and 645 832 influenza-associated respiratory deaths (4·0–8·8 per 100 000 individuals) occur annually (table 4). The median estimated number of global influenza-associated respiratory deaths (409 111) represent 13% of all GHE respiratory infection deaths (3 200 874 [appendix]). Country-specific influenza-associated respiratory death estimates are shown in the appendix. The annual number of influenza-associated respiratory deaths was highest among people younger than 65 years (175 303 deaths, 95% CrI 67 255–342 576)—accounting for 42% of all global influenza-associated respiratory deaths—and people older than 75 years (172 420, 122 876–237 933)—accounting for 41% of all global influenza-associated respiratory deaths (appendix). The highest rates of influenza-associated respiratory deaths were among people older than 75 years (51·3–99·4 per 100 000 individuals; table 4, figure 2). Across all age groups, the widest range of deaths was in sub-Saharan Africa (27 813–163 074; 17%) and the highest proportion of deaths occurred in southeast Asia (68 258–178 049; 25% of total deaths) and the western Pacific (67 728–141 436; 25%; table 4; appendix). The widest range of influenza-associated respiratory death rates occurred in countries in sub-Saharan Africa, the Eastern Mediterranean, and southeast Asia (appendix). Lower-middle-income and low-income countries had a wider range of influenza-associated deaths (112881–420841 annual deaths) compared with high-income and upper middle-income countries (table 4). The highest number of annual influenza-associated respiratory deaths and mortality rates were in countries with the highest respiratory infection mortality (ie, analytic division 3) for all age groups (appendix). For our global estimates of median influenza-associated respiratory deaths, 73% (128 749) of estimates were derived from the extrapolation model for people younger than 65 years, 39% (27 456) for individuals aged 65–74 years, and 32% (53 911) for people aged 75 years and older (appendix).

We estimated 9243–105 690 annual influenza-associated respiratory deaths occur among children younger than 5 years for 92 countries (appendix). The overall rate of influenza-associated respiratory deaths among children younger than 5 years ranged from 2·1 to 23·8 per 100 000 population (appendix). Of the 47 countries in sub-Saharan Africa, we categorised 45 (96%) into analytic division 3 and estimated that between 721 and 46 336 (0·5–29·0 per 100 000) influenza-associated deaths occur annually among children younger than 5 years in this region (appendix). For southeast Asia, we extrapolated deaths for eight (73%) of 11 countries and estimated that 5565–42 536 (3·2–24·5 per 100 000) influenza-associated deaths occur annually among children younger than 5 years in the region. For children younger than 5 years, 71% (31 622) of median influenza-associated respiratory death estimates were derived from the extrapolation model (appendix).

When we compared global seasonal influenza-associated death estimates using all EMR-contributing countries with estimates when one EMR-contributing country was removed, we observed few differences by age group, analytic division, or WHO region (appendix). In the youngest age group (<65 years), when Argentina was removed, the upper 95% CrI of the death estimates decreased from 552 727 to 410 635 deaths and when Romania was removed the width of the interval estimates increased by 22 468 deaths (appendix). Additionally, when Thailand was removed from the extrapolation, the median influenza-associated respiratory deaths in the youngest age group (<65 years) increased by 24 528 deaths. In the 65–74 year age group, removing any EMR-contributing country had little effect on the overall estimates. In the oldest age group (≥ 75 years), when Australia was removed, the width of the interval estimates increased by 120 801 deaths; however, when Argentina was removed the width of the interval estimate decreased by 67 832 deaths (appendix). When we compared our extrapolated estimates across analytic divisions and WHO region, we found that removing Argentina from estimates for the youngest age group (<65 years) decreased the death interval by 140 164 deaths, but had a smaller effect on analytic divisions and regional comparisons for the older age groups compared with the youngest age group (appendix). We did not observe any other noticeable differences in the analytic division death intervals for the older age groups (65–74 and ≥ 75 years) when other EMR-contributing countries were removed. We observed no noticeable differences in WHO regional interval estimates in the older age groups (65–74 and ≥ 75 years) when we removed an EMR-contributing country (appendix). We also compared interval estimates for each EMR-contributing country using only their mean annual influenza-associated respiratory death estimates with those estimated from the full extrapolation model and an extrapolation model in which the EMR-contributing country was removed (appendix). All EMR-contributing countries had intervals that overlapped considerably with those derived from extrapolations, including the comparison between the mortality estimate derived using the multiplier approach (for Bangladesh) and the extrapolated estimates. All interval influenza-associated respiratory death estimates from our extrapolation model were more likely to have wider interval widths than those countries where the interval of influenza-associated respiratory death estimates were replaced with their own mean annual estimates of influenza-associated excess mortality. Additionally, we applied the proportion of influenza-associated respiratory deaths out of the total number of respiratory deaths (appendix) to the annual number of respiratory deaths from the 13 validation countries and found that the

extrapolated 95% CrIs and the range of proportions overlapped for all validation countries (appendix).

Discussion

We estimated that more influenza-associated respiratory deaths occur annually worldwide than reported in the WHO-attributed estimate, which included both respiratory and circulatory deaths. Among the six WHO regions, the highest burden of annual influenza-associated deaths was in sub-Saharan Africa, the western Pacific, and southeast Asia. The widest range of influenza-associated mortality rates was observed among people aged 75 years and older or in countries in the Eastern Mediterranean, sub-Saharan Africa, and southeast Asia. These results suggest considerable temporal variability in influenza-associated deaths that are likely to be due to differences in circulation of virus strains and their severity from year to year. Furthermore, our results underscore the effect influenza viral infections have on population health and provide burden estimates to inform local decision making and global policies for influenza prevention and control measures.

Our estimates of influenza-associated respiratory mortality (291 243–645 832 deaths annually; 4.0–8.8 per 100 000 individuals) are higher than previously published estimates,³ which estimated 148 000–249 000 annual influenza-associated respiratory deaths, and the WHO-attributed estimate¹ of 250 000–500 000 respiratory and circulatory deaths (3.8–7.7 per 100 000 individuals). One explanation for the difference is that our extrapolation uses an adjustment factor that accounts for differences in influenza death risk between countries and possible differences in underlying health status and access to care, whereas Simonsen and colleagues³ imputed estimates for countries without influenza EMRs using selected non-influenza health indicators to predict influenza mortality. Previous estimates might not have accounted for global variability in influenza mortality risk. Furthermore, our estimates included rates from a higher quantity of resource-limited countries with higher observed influenza-associated EMRs. However, it was not possible to fully evaluate the discrepancies between the attributed estimate¹ and our estimate because the methods used for the WHO-attributed estimate were not available.

Another model⁵³ from the Institute of Health Metrics and Evaluation (IHME) estimated that 2 500 300–2 860 800 global lower respiratory infection deaths and 55 700–122 100 global influenza-attributed lower respiratory infection deaths occurred in 2015. IHME attributed approximately 3% of lower respiratory infection deaths to influenza as the primary cause of death, compared with 13% in our model. IHME estimates attribute deaths to influenza by calculating an aetiological fraction of influenza virus detections, and their estimates assume that these influenza-attributed deaths were the primary cause of death. Our estimates might be higher because we did not require influenza virus detection recognising that many people with an influenza virus infection who subsequently die are more likely to have another cause of death listed on their death certificate. Estimating the number of deaths directly attributable to influenza is difficult because influenza virus infections are rarely confirmed virologically or specified as the cause of death on death certificates.^{40,54,55} Additionally, many influenza-associated deaths occur as a result of secondary complications when influenza viruses are no longer detectable.^{40,54,55} We recognised the scarcity of high-quality

mortality data in lower-income countries and accounted for this by including uncertainty in the extrapolation, which might also explain differences between IHME and our estimates. Additional comparisons between these three methods are described in the appendix.

Our estimated range of 9243–105 690 annual influenza-associated deaths among children younger than 5 years in countries with high child respiratory infection mortality estimated using EMRs from four countries was similar to the influenza-associated acute lower respiratory infection death estimate by Nair and colleagues⁵⁶ (28 000–111 500 annual deaths), which used severe acute lower respiratory infection case fatality proportions from 17 countries. We chose to only estimate deaths for countries with a higher burden of GHE respiratory infection mortality because EMRs for countries with a lower burden of respiratory infection mortality were not available since few deaths occur each week among children younger than 5 years.⁵⁷ Furthermore, we were concerned about overestimating burden by extrapolating estimates from countries with higher burden of influenza-associated respiratory deaths to countries with a lower burden. However, we do not believe that excluding these countries from our estimation substantially affected our estimates since the countries included in our extrapolation represent 95% of all GHE respiratory infection deaths in this age group. Future studies could explore the availability of influenza-associated EMRs or alternative methods to estimate influenza-associated deaths in children younger than 5 years from countries with lower respiratory infection mortality burden for children younger than 5 years to inform a model that could estimate deaths for this age group for all countries.

Our approach to estimate global seasonal influenza-associated mortality used a multistep approach to generate estimates. The use of analytic divisions allowed us to group countries with similar respiratory infection mortality rates and extrapolate estimates of influenza-associated mortality from countries with similar mortality risk. We evaluated different approaches for categorising countries into analytic divisions^{52,58–60} to account for variability in the influenza attack rate or case fatality ratio between countries. Nevertheless, quantifying differences in seasonal influenza attack rate between countries was challenging because such information is scarce. Thus, we assumed a constant attack rate between countries and explored various sources to account for differences in the case fatality ratio such as poverty levels, health indicators, health-seeking behaviours, or respiratory infection rates. We assumed that the GHE respiratory infection estimates address differences in case fatality ratio, and categorised countries into analytic divisions using GHE respiratory infection mortality rates.

GHE respiratory infection mortality rates show that risk of respiratory infection mortality varies by country and these differences might be influenced by multiple factors such as quality and access to health care and differences in the underlying health status of the population. Because some of these influencing factors are known and others are not, we developed MRRs from the GHE respiratory infection estimates as a proxy for overall differences in mortality risk between countries and used these ratios to extrapolate influenza-associated EMRs from countries with available estimates to those without. Furthermore, to address the annual variability in influenza-associated deaths related to changes in circulating virus strains from year to year, we included all annual EMRs from contributing countries

and presented a possible range of estimated annual influenza-associated deaths for country, region, and global estimates.

Our methods and estimates did have limitations. Our estimates are limited by the availability of vital records and viral surveillance data, especially in sub-Saharan Africa, the Eastern Mediterranean, southeast Asia, other low-income countries, and countries with a tropical climate. Specifically, estimates derived for countries in analytic division 3 might have less precision because this division contained only a small number of EMR-contributing countries to inform the extrapolation and lower-quality GHE respiratory infection mortality rates to adjust for differences in risk. This limitation was observed for the youngest age group in analytic division 3, which contained only a small number of EMR-contributing countries, whereby the inclusion of a mean annual EMR in conjunction with a lower GHE respiratory infection rate for Argentina led to higher MMRs when Argentina served as the reference country, resulting in wider death intervals. Additionally, the highest rates of influenza-associated mortality were observed in sub-Saharan Africa, the Eastern Mediterranean, and southeast Asia where vital records data are scarce. This highlights the need for more low-income countries and countries with high respiratory mortality to establish or maintain vital records systems and contribute to global estimates. Nevertheless, our model used EMR estimates from 33 countries (21 high-income countries), which represented 57% of the global population.

Additionally, available vital records data might be limited by poor reliability of cause-of-death coding despite an internationally standardised coding system, and differences might exist in death coding practices both within and between countries, which might bias national level coding efforts. Furthermore, the regression models used to estimate excess mortality have inherent uncertainty and error, which could affect the accuracy of death estimates, and model-fit information might not provide reliable guidance for interpretation or certainty of EMR estimates. Although we used Bayesian inference to generate probabilistic distributions for mortality estimates and accounted for various sources of uncertainty, the modelling framework relies on assumptions that might affect the accuracy and precision of the estimates. For example, the Bayesian approach for combining estimates from different countries incorporates uncertainties including standard errors, but does not account for systematic bias without additional information (eg, the degree of overestimation using a Serfling model because of the scarcity of available viral data). Additionally, we assumed that any of the EMR-contributing country estimates were equally likely to serve as a reference and a more informative choice of reference country might result in smaller interval widths. Extrapolation simulations were done using mean annual EMRs and represent the collection of estimates provided by countries and thus do not represent any specific year. Because of the paucity of data, our hierarchical model also assumed the EMRs to be independent between countries and seasons; however, if spatial and temporal dependence were present, that might have resulted in narrower interval estimates. Also, the GHE respiratory infection mortality estimates used to develop the MRR for our analysis were limited by variability in source information quality and availability between countries. Furthermore, 2015 GHE respiratory infection mortality rates for 11 countries (representing 0.006% of the world population) were not available. Since respiratory infection rates are used throughout the extrapolation, we could not estimate influenza-associated deaths for these countries. The

exclusion of these countries is unlikely to have affected overall influenza-associated death estimates. Finally, in the MRR calculation, we assumed a constant influenza attack rate between countries, which might not be true and could result in overestimation or underestimation of the number of deaths. We were not able to account for differences in influenza-virus circulation between countries in our extrapolation, indicating a need for additional studies to evaluate how seasonal influenza attack rates might vary by geographical region.

Our estimates reflect only influenza-associated respiratory mortality, which is likely to underestimate the true burden of influenza on deaths. Influenza virus infection is also associated with hospital admission for circulatory problems and deaths, especially among older adults.^{40,61–66} Some national studies^{14,22} that estimated both respiratory and non-respiratory (eg, circulatory) deaths found that non-respiratory deaths accounted for more than half of all influenza-associated deaths. Other studies^{7,18,30} found that non-respiratory deaths contributed equally or accounted for fewer than half of all influenza-associated deaths. These studies suggest that the effect of influenza on non-respiratory causes of death might be more variable between countries and our estimates therefore only represent a portion of all annual influenza-associated deaths globally. Additional efforts to quantify the burden of both respiratory and non-respiratory causes of death are needed to provide a more comprehensive estimate of the global influenza-associated mortality burden.

Our 95% CrI estimates are intended to represent influenza-associated respiratory deaths between 1999 and 2015 and might reflect the variability in circulating influenza virus strains between seasons. Although our methods to estimate influenza-associated excess mortality included influenza virus type and subtype when possible, future studies should consider quantifying the effect of influenza virus type and subtypes on global deaths. Although regression models to estimate influenza-associated EMRs adjusted for respiratory syncytial virus when possible, few data were available to account for respiratory syncytial virus or other respiratory pathogens in the extrapolation. Additional studies to estimate global burden should also attempt to quantify the burden of respiratory syncytial virus and other respiratory pathogens and develop methods to account for other infectious respiratory pathogens. Estimates should be revisited periodically as new country data become available, to improve methods of estimation for both excess mortality and extrapolation, and to improve methods to account for differences in risk of influenza-associated death between countries.

This study shows that influenza contributes to a substantial annual burden of deaths globally, with the greatest effect among low-income countries in sub-Saharan Africa and southeast Asia. These estimates imply a greater burden of influenza deaths than previously recognised. Country and global policy makers should consider these data to inform influenza prevention and control programmes, especially the possible introduction or expansion of vaccination programmes. Although countries with influenza vaccination programmes have estimated reductions in severe disease and deaths,⁶⁷ relatively few countries have robust seasonal influenza vaccination programmes despite WHO recommendations⁶⁸ for use in key target groups. The considerable annual burden of influenza presented here could inform the efforts of global partners, such as Gavi, the Vaccine Alliance, and the Partnership for Influenza

Vaccine Introduction, to increase accessibility to influenza vaccines in low-income and middle-income countries. Further work to refine the estimates by including non-respiratory causes of death are ongoing as part of a multilateral consortium of scientists and public health officials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

Previous estimates commonly attributed to WHO indicate that 250 000–500 000 deaths occur annually worldwide due to seasonal influenza viruses. However, no information has been published about the methods or data sources used to calculate these global estimates. These estimates began to be cited in publications and on WHO's website around 2004, suggesting that the estimates might have been generated using data from the 1990s. Since the 1990s, improvements in influenza virus surveillance and vital records systems in many countries have led to more estimates of influenza-associated mortality for countries across the world, including some estimates from middle-income and low-income countries. Global estimates of pandemic influenza deaths are available; however, these estimates might not meet the requirements for global seasonal influenza estimates because deaths during pandemic periods are likely to differ from seasonal epidemics. We searched PubMed for articles that estimated influenza-associated excess deaths or excess mortality published between Jan 1, 1960 and Dec 31, 2012, using the search terms “influenza”, “death”, “mortality”, “excess death”, “excess mortality”, “Serfling”, “negative binomial”, “time series”, “respiratory”, “circulatory”, “pneumonia”, and “influenza” with no language restrictions. Previously published data were not suitable for our extrapolation model to estimate global influenza deaths because of heterogeneity between the age groups studied and death outcomes (eg, pneumonia and influenza, respiratory, all-cause, or circulatory) investigated. Thus, we initiated an effort to directly collect data from partners around the world using common age groups and death outcomes to update and improve global seasonal influenza-associated mortality estimates.

Added value of this study

Previous global influenza mortality estimates were calculated more than 10 years ago and detailed information about the methods used are not available. Since these estimates were made available by WHO the number of countries with capacity to calculate national estimates for seasonal influenza-associated excess mortality has increased. We initiated a project to use this additional information to update and improve global estimates of influenza-associated respiratory mortality. We worked with collaborators from 47 countries to develop an innovative statistical model to calculate global estimates of influenza-associated mortality using vital records and viral surveillance data, including estimates for 1999–2015 from countries with data, which were extrapolated to countries without such data. Our study presents a comprehensive analysis of influenza-associated mortality, in which we provide extensive details about methods used and account for differences between countries. In this study, we calculated country-specific estimates for influenza-associated respiratory deaths in three age groups (<65 years, 65–74 years, and ≥75 years) and did a subanalysis for children younger than 5 years, which might help country-level policy makers to understand the impact of influenza virus infection on their populations. Additionally, our analysis complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations.

Implications of all the available evidence

Our estimates of influenza-associated respiratory mortality are higher than previous estimates. The results of this study help to improve understanding about the burden of influenza viral infections and emphasise the need for continued support to detect, prevent, and control influenza viruses. Furthermore, this study provides age-specific and country-specific influenza-associated respiratory death estimates that could be used by countries to inform prevention and control measures for influenza virus infection in their population. This study improves on earlier estimates by including primary data from 47 countries to estimate global influenza-associated deaths and by validating our extrapolation models.

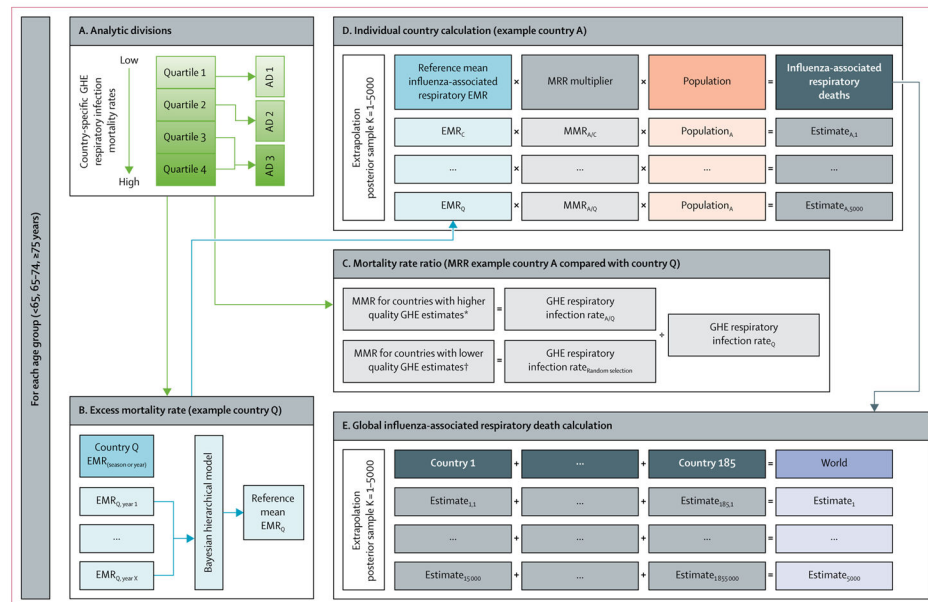


Figure 1. Extrapolation model approach for individual country and global estimates of influenza-associated respiratory deaths

Country refers to WHO member states, Hong Kong, Taiwan, or regions within a country. WHO GHE were used to categorise countries into ADs and in the extrapolation model. Usability was defined using the following equation: usability (%) = completeness of death registration data (%) $\times$ (1 – proportion of ill-defined death registration data). AD = analytic division. EMR = excess mortality rate. MMR = mortality rate ratio. GHE = Global Health Estimates. *Countries with at least 5 years of death registration data available (starting from 2005) with a mean usability of all available years (from 2000 onwards) of 60% or more if International Classification of Diseases-coded registration data for specific causes of death were reported, or with a mean usability of 80% or more if only summarised causes of death data were reported. †Countries with no annual death registration data available or countries with less than 5 years of death registration available (starting from 2005) with a mean usability of all available years (from 2000 forward) of less than 60% if International Classification of Diseases-coded registration data for specific causes of death were reported, or a mean usability of 80% or less if only summarised causes of death data were reported.

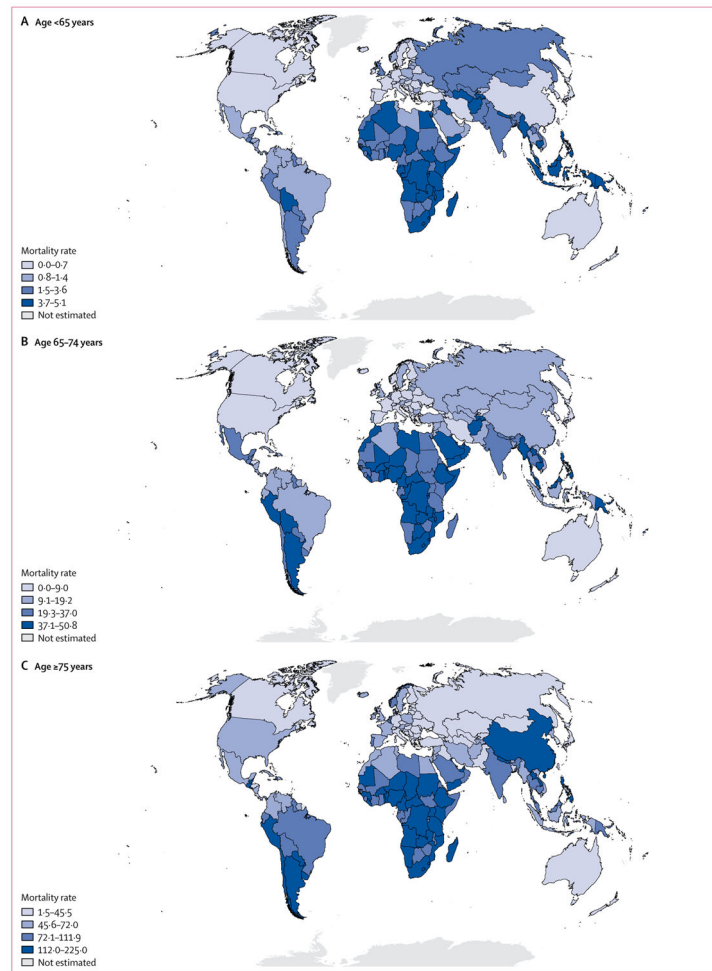


Figure 2. Estimated country-specific and age-specific influenza-associated respiratory mortality rates

Median influenza-associated respiratory mortality rates (per 100 000 individuals) in people aged (A) 65 years or younger, (B) 65–74 years, and (C) 75 years and older.

EMR-contributing countries with modelled influenza-associated excess respiratory mortality or annual estimates of respiratory mortality by age group for validation

	Income level*	Global population (%)†	Seasons or years with estimates available	Time series	Type of influenza virus data used in statistical model	Analytic division		
						Age<65 years	Age65–74 years	Age≥75 years
Countries or territories with modelled influenza-associated respiratory EMRs (EMR-contributing countries)								
Sub-Saharan Africa								
Kenya	Low	0.63%	2007–13	Monthly	Influenza virus	3	3	3
South Africa	Upper middle	0.74%	1999–2013	Monthly (1999–2008) and weekly (2009–13)	Influenza virus	3	3	3
Europe								
Austria	High	0.12%	1999/2000–2009/10	Weekly	Influenza virus	1	1	1
Czech Republic	High	0.14%	1999/2000–2010/11	Weekly	Virus type	1	2	2
Denmark	High	0.08%	2002/03–2013/14	Weekly	Virus subtype	1	1	2
Germany	High	1.10%	2001/02–2013/14	Weekly	NA	1	1	1
Israel	High	0.11%	2004/05–2013/14	Weekly	Virus subtype	1	2	2
Netherlands	High	0.23%	1999/2000–2010/11	Weekly	Virus type	1	1	2
Norway	High	0.07%	1999/2000–2014/15	Weekly	Virus type	1	1	2
Portugal	High	0.14%	1999/2000–2013/14	Weekly	NA	2	2	3
Romania	Upper middle	0.27%	2000/01–2014/15	Monthly	Virus subtype	3	2	1
Serbia	Upper middle	0.12%	2000/01–2010/11	Weekly	NA	1	1	1
Spain	High	0.63%	2000/01–2012/13	Weekly	Virus subtype	1	1	1
Switzerland	High	0.11%	1999/2000–2013/14	Weekly	Virus subtype	1	1	1
UK‡	High	0.88%	2006/07–2011/12	Weekly	Virus type	1	1	2
The Americas								
Argentina	Upper middle	0.59%	2002–09	Monthly	NA	3	3	3
Southern Brazil	Upper middle	2.83%	2002–09	Monthly	NA	2	3	3
Canada	High	0.49%	1999/2000–2007/08	Weekly	Virus type	1	1	1
Chile	High	0.24%	2002–09	Weekly	NA	1	1	2
Mexico	Upper middle	1.73%	2002/03–2009/10	Weekly	NA	2	2	2
Paraguay	Lower middle	0.09%	2002–09	Weekly	NA	2	2	2

	Income level*	Global population (%)†	Seasons or years with estimates available	Time series	Type of influenza virus data used in statistical model	Analytic division		
						Age<65 years	Age65–74 years	Age≥75 years
USA	High	4·39%	1999/2000–2014/15	Weekly	Virus subtype	2	2	1
Uruguay	High	0·05%	2004, 2007–2009	Weekly	NA	2	2	2
Southeast Asia								
India	Lower middle	17·87%	2010–13	Weekly	Virus subtype	3	3	3
Thailand	Upper middle	0·93%	2006–11	Weekly	Virus subtype	3	3	3
Western Pacific								
Australia	High	0·33%	2003–09	Weekly	Virus subtype	1	1	1
China	Upper middle	18·76%	2004/05–2009/10	Weekly	Virus subtype	1	2	1
Hong Kong§	High	0·10%	2000–13	Weekly	Virus subtype	2	3	3
Japan	High	1·73%	1999/2000–2010/11	Weekly	Virus subtype	1	2	3
New Zealand	High	0·06%	2002–13	Weekly	Virus subtype	1	1	1
Singapore	High	0·08%	2004–11	Weekly	Influenza virus	2	3	3
South Korea	High	0·69%	2003/04–2013/14	Weekly	Virus type	1	2	2
Taiwan§	High	0·32%	2000/01–2013/14	Weekly	Virus subtype	2	2	3
Countries with annual estimates of respiratory deaths by age group (validation countries)								
Eastern Mediterranean								
Kuwait	High	0·05%	2000–11	..	..	1	3	3
Morocco	Lower middle	0·47%	2010–13	..	..	3	3	2
The Americas								
Colombia	Upper middle	0·66%	2002–08	..	..	2	2	2
Costa Rica	Upper middle	0·07%	2002–09	..	..	1	1	1
Cuba	Upper middle	0·16%	2005, 2007, and 2009	..	..	2	3	3
Ecuador	Upper middle	0·22%	2002–09	..	..	3	2	3
El Salvador	Lower middle	0·08%	2002–09	..	..	3	3	3
Guatemala	Lower middle	0·22%	2005–09	..	..	3	3	3
Panama	Upper middle	0·05%	2004, 2006–09	..	..	2	2	2
Peru	Upper middle	0·43%	2005–07	..	..	3	3	3
Venezuela	Upper middle	0·42%	2002, 2006–07	..	..	2	2	2
Southeast Asia								
Indonesia	Lower middle	3·51%	2014	..	..	3	2	2

	Income level*	Global population (%)†	Seasons or years with estimates available	Time series	Type of influenza virus data used in statistical model	Analytic division		
						Age<65 years	Age65–74 years	Age≥75 years
Western Pacific								
Mongolia	Lower middle	0.04%	2002–10	..	..	3	1	1
Countries with estimates of influenza-associated excess respiratory mortality obtained using multiplier approach								
Bangladesh	Low	2.19%	2010/11–2011/12	..	..	3	2	1

EMR=excess mortality rate. NA=not available.

* Income level categorisation based on World Bank classification.⁴⁶

† Obtained from UN Census Estimates and the US Census Bureau Estimates for 2015.^{2,47}

‡ Influenza-associated EMR estimates for England and Wales only.

§ Analytic divisions for Hong Kong and Taiwan were based on vital records data from the Census and Statistics Department of the Hong Kong Government and the Ministry of Health and Welfare in Taiwan, because WHO Global Health Estimates did not include Hong Kong or Taiwan.

Table 2
Mean annual influenza-associated EMR per 100 000 population by age group for EMR-contributing countries

	Age <65 years			Age 65–74 years			Age ≥75 years		
	Mean annual EMR* (SE)	Analytic division†		Mean annual EMR* (SE)	Analytic division†		Mean annual EMR* (SE)	Analytic division†	
Argentina	3·0 (0·6)	3		44·0 (7·8)	3		223·5 (44·4)	3	
Australia	0·5 (0·2)	1		3·5 (1·7)	1		20·8 (9·8)	1	
Austria	1·0 (0·4)	1		11·9 (3·9)	1		63·8 (9·5)	1	
Southern Brazil	1·0 (0·2)	2		19·8 (5·6)	3		111·1 (40·5)	3	
Canada	0·4 (0·1)	1		6·1 (2·2)	1		44·5 (12·5)	1	
Chile	1·4 (0·2)	1		30·4 (6·3)	1		187·4 (39·9)	2	
China	0·7 (0·3)	1		19·1 (7·0)	2		112·7 (34·3)	1	
Czech Republic	0·5 (0·1)	1		5·5 (0·9)	2		20·4 (3·5)	2	
Denmark	0·6 (0·2)	1		4·2 (1·6)	1		51·0 (14·3)	2	
Germany	0·4 (0·1)	1		2·9 (1·3)	1		21·0 (7·6)	1	
Hong Kong‡	0·4 (0·05)	2		12·0 (1·3)	3		84·6 (9·3)	3	
India	2·2 (1·2)	3		35·5 (12·3)	3		88·1 (30·4)	3	
Israel	0·2 (0·05)	1		3·2 (0·8)	2		29·3 (4·9)	2	
Japan	0·2 (0·03)	1		3·5 (0·4)	2		27·5 (2·9)	3	
Kenya§	6·4 (2·5)	3		..	3		..	3	
Mexico	1·4 (0·3)	2		19·3 (4·5)	2		68·9 (22·1)	2	
Netherlands	0·4 (0·1)	1		12·6 (2·5)	1		91·1 (19·9)	2	
New Zealand	0·3 (0·1)	1		4·8 (1·2)	1		36·7 (7·7)	1	

	Age <65 years		Age 65–74 years		Age ≥75 years	
	Mean annual EMR* (SE)	Analytic division†	Mean annual EMR* (SE)	Analytic division†	Mean annual EMR* (SE)	Analytic division†
Norway	0·9 (0·2)	1	9·2 (2·2)	1	75·1 (8·1)	2
Portugal	2·2 (0·7)	2	25·3 (7·2)	2	118·1 (41·2)	3
Paraguay	0·6 (0·1)	2	10·3 (3·2)	2	92·0 (22·2)	2
Romania	0·6 (0·1)	3	6·7 (1·1)	2	20·2 (3·6)	1
Serbia	0·7 (0·2)	1	6·6 (2·2)	1	17·9 (5·6)	1
Singapore	1·5 (0·2)	2	39·5 (4·2)	3	187·9 (16·1)	3
South Africa	5·2 (0·4)	3	37·4 (4·0)	3	123·3 (7·5)	3
South Korea	0·1 (0·03)	1	3·8 (1·0)	2	24·9 (6·6)	2
Spain	0·3 (0·1)	1	6·8 (1·6)	1	54·7 (15·0)	1
Switzerland	0·3 (0·03)	1	4·8 (0·6)	1	33·4 (6·2)	1
Taiwan‡	0·2 (0·05)	2	3·4 (1·0)	2	33·4 (6·7)	3
Thailand	1·4 (0·9)	3	25·0 (16·0)	3	118·9 (76·0)	3
UK¶	2·4 (1·9)	1	17·3 (13·2)	1	66·6 (39·9)	2
Uruguay	2·4 (3·0)	2	40·6 (42·6)	2	199·5 (148·2)	2
USA	0·6 (0·1)	2	8·6 (1·0)	2	49·4 (6·2)	1

EMR=excess mortality rate.

* Mean annual respiratory EMRs per 100 000 population for EMR-contributing countries were calculated using an age-specific and country-specific Bayesian hierarchical model for seasonal or annual estimates and their standard errors.

† Analytic divisions were calculated using WHO Global Health Estimates of respiratory infection mortality.

‡ The analytic divisions for Hong Kong and Taiwan were based on vital records data from the Census and Statistics Department of the Hong Kong Government and the Ministry of Health and Welfare in Taiwan because WHO Global Health Estimates did not generate estimates for Hong Kong or Taiwan.

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§ Influenza-associated respiratory EMR estimates were only available for the youngest age group (<65 years).

¶ Influenza-associated respiratory EMR estimates include deaths in England and Wales only.

Table 3

WHO Global Health Estimates of respiratory infection mortality rate (per 100 000 individuals) by age group and analytic division

	Analytic division 1(n=46)	Analytic division 2(n=46)	Analytic division 3(n=93)
Number of EMR-contributing countries			
Age group			
<65 years	18	9	6
65–74 years	13	12	7
≥75 years	11	11	10
WHO Global Health Estimates of respiratory infection mortality rate (per 100 000)			
All countries			
<65 years	0·8–5·3	5·3–12·8	13·0–181·6
65–74 years	5·4–43·0	44·2–93·5	96·2–897·1
≥75 years	9·3–277·7	279·1–553·8	571·6–2996·2
EMR-contributing countries			
<65 years	0·9–5·2	5·3–12·8	13·1–42·8
65–74 years	8·5–41·7	45·9–87·6	108·5–301·5
≥75 years	94·6–275·8	302·7–545·7	677·2–1650·3

Data are n, or range. Analytic divisions were calculated using WHO Global Health Estimates of respiratory infection mortality. EMR=excess mortality rate.

Table 4

Estimated annual influenza-associated respiratory deaths and mortality rate per 100 000 population by age group, WHO region, and World Bank income classification

	Age <65 years			Age 65–74 years			Age ≥75 years			All ages		
	Median annual influenza-associated respiratory mortality* (95% CrI)	Annual influenza-associated respiratory mortality per 100 000 individuals*	Proportion of total influenza-associated respiratory deaths†	Median annual influenza-associated respiratory mortality* (95% CrI)	Annual influenza-associated respiratory mortality per 100 000 individuals*	Proportion of total influenza-associated respiratory deaths†	Median annual influenza-associated respiratory mortality* (95% CrI)	Annual influenza-associated respiratory mortality per 100 000 individuals*	Proportion of total influenza-associated respiratory deaths†	Median annual influenza-associated respiratory mortality* (95% CrI)	Annual influenza-associated respiratory mortality per 100 000 individuals*	Proportion of total influenza-associated respiratory deaths†
Worldwide	175 303 (67 255–342 576)	1·0–5·1	42%	72 720 (48 810–102 187)	13·3–27·8	17%	172 420 (122 876–237 933)	51·3–99·4	41%	409 111 (291 243–645 832)	4·0–8·8	..
WHO Regions												
Sub-Saharan Africa	51 767 (9607–127 569)	1·0–13·3	29%	8841 (2648–17 744)	12·0–80·4	13%	11 874 (3477–27 502)	36·3–286·9	7%	69 359 (27 813–163 074)	2·8–16·5	17%
The Americas	12 778 (7027–20 203)	0·8–2·3	8%	9160 (6236–12 776)	10·5–21·5	13%	29 908 (21 624–43 777)	52·2–105·7	17%	51 674 (41 007–71 710)	4·2–7·3	12%
Europe	10 476 (4179–19 518)	0·5–2·5	6%	6566 (3732–12 753)	5·0–17·2	9%	27 509 (15 679–47 438)	23·4–70·7	16%	44 774 (28 457–72 627)	3·1–8·0	11%
Eastern Mediterranean	23 648 (4468–71 208)	0·7–11·6	13%	4753 (1349–9905)	7·4–54·1	7%	5777 (2035–12 114)	21·8–129·9	3%	33 528 (13 350–86 490)	2·1–13·4	8%
Southeast Asia	51 412 (21 044–119 561)	1·2–6·6	32%	21 782 (10 499–35 014)	14·2–47·5	30%	30 936 (16 602–48 618)	44·6–130·5	18%	105 167 (68 258–178 049)	3·5–9·2	25%
Western Pacific	16 951 (7197–28 946)	0·4–1·7	10%	20 425 (8903–33 078)	7·4–27·7	28%	66 529 (33 858–99 617)	45·3–133·2	38%	103 728 (67 728–141 436)	3·6–7·5	25%
World Bank income classifications												
High income	9531 (5312–16 208)	0·5–1·5	6%	9639 (7161–14 078)	6·1–12·0	13%	45 372 (34 309–59 355)	33·9–58·6	26%	64 680 (51 083–83 623)	3·9–6·4	16%
Upper middle income	30 848 (17 221–48 991)	0·8–2·2	18%	26 328 (14 242–39 974)	10·6–29·8	36%	78 997 (44 854–113 418)	56·8–143·7	45%	136 017 (97 776–181 157)	4·0–7·3	32%
Lower middle income	83 604 (30 191–184 009)	1·2–7·3	49%	28 442 (15 467–43 723)	16·7–47·3	39%	38 418 (21 438–64 775)	44·3–133·9	23%	148 105 (90 738–270 831)	3·4–10·2	36%
Low income	45 848	0·8–13·9	26%	7793	8·9–67·0	11%	10 099	27·5–209·4	6%	60 979	2·5–16·7	15%

Age <65 years			Age 65–74 years			Age ≥75 years			All ages		
Median annual influenza-associated respiratory* mortality (95% CrI)	Annual influenza-associated respiratory mortality 95% CrI per 100 000 individuals*	Proportion of total influenza-associated respiratory deaths†	Median annual influenza-associated respiratory* mortality (95% CrI)	Annual influenza-associated respiratory mortality 95% CrI per 100 000 individuals*	Proportion of total influenza-associated respiratory deaths†	Median annual influenza-associated respiratory* mortality (95% CrI)	Annual influenza-associated respiratory mortality 95% CrI per 100 000 individuals*	Proportion of total influenza-associated respiratory deaths†	Median annual influenza-associated respiratory* mortality (95% CrI)	Annual influenza-associated respiratory mortality 95% CrI per 100 000 individuals*	Proportion of total influenza-associated respiratory deaths†
(6731–119 752)			(2047–15 378)			(2980–22 685)			(22 143–150 010)		

CrI=credible interval.

* After applying our extrapolation approach to all countries, excess mortality rate (EMR)-contributing country extrapolated estimates were replaced with mean annual influenza-associated respiratory EMRs and death estimates, with the exception of Brazil and Kenya.

† Estimates do not add up across all age groups because age-specific models were run separately and were not additive. Estimated proportions were calculated for each of 5000 extrapolation simulations and the median proportion from the 5000 simulations is presented.



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[Intervention Review]

Neuraminidase inhibitors for preventing and treating influenza in adults and children

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ABSTRACT

Background

Neuraminidase inhibitors (NIs) are stockpiled and recommended by public health agencies for treating and preventing seasonal and pandemic influenza. They are used clinically worldwide.

Objectives

To describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all clinical study reports of published and unpublished randomised, placebo-controlled trials and regulatory comments.

Search methods

We searched trial registries, electronic databases (to 22 July 2013) and regulatory archives, and corresponded with manufacturers to identify all trials. We also requested clinical study reports. We focused on the primary data sources of manufacturers but we checked that there were no published randomised controlled trials (RCTs) from non-manufacturer sources by running electronic searches in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE (Ovid), EMBASE, Embase.com, PubMed (not MEDLINE), the Database of Reviews of Effects, the NHS Economic Evaluation Database and the Health Economic Evaluations Database.

Selection criteria

Randomised, placebo-controlled trials on adults and children with confirmed or suspected exposure to naturally occurring influenza.

Data collection and analysis

We extracted clinical study reports and assessed risk of bias using purpose-built instruments. We analysed the effects of zanamivir and oseltamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalisations and adverse events in the intention-to-treat (ITT) population. All trials were sponsored by the manufacturers.

Main results

We obtained 107 clinical study reports from the European Medicines Agency (EMA), GlaxoSmithKline and Roche. We accessed comments by the US Food and Drug Administration (FDA), EMA and Japanese regulator. We included 53 trials in Stage 1 (a judgement of appropriate study design) and 46 in Stage 2 (formal analysis), including 20 oseltamivir (9623 participants) and 26 zanamivir trials (14,628 participants). Inadequate reporting put most of the zanamivir studies and half of the oseltamivir studies at a high risk of selection bias. There were inadequate measures in place to protect 11 studies of oseltamivir from performance bias due to non-identical presentation of placebo. Attrition bias was high across the oseltamivir studies and there was also evidence of selective reporting for both the zanamivir and oseltamivir studies. The placebo interventions in both sets of trials may have contained active substances.

Time to first symptom alleviation. For the treatment of adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% confidence interval (CI) 8.4 to 25.1 hours, $P < 0.0001$). This represents a reduction in the time to first alleviation of symptoms from 7 to 6.3 days. There was no effect in asthmatic children, but in otherwise healthy children there was (reduction by a mean difference of 29 hours, 95% CI 12 to 47 hours, $P = 0.001$). Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days, $P < 0.00001$), equating to a reduction in the mean duration of symptoms from 6.6 to 6.0 days. The effect in children was not significant. In subgroup analysis we found no evidence of a difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups ($P = 0.53$).

Hospitalisations. Treatment of adults with oseltamivir had no significant effect on hospitalisations: risk difference (RD) 0.15% (95% CI -0.78 to 0.91). There was also no significant effect in children or in prophylaxis. Zanamivir hospitalisation data were unreported.

Serious influenza complications or those leading to study withdrawal. In adult treatment trials, oseltamivir did not significantly reduce those complications classified as serious or those which led to study withdrawal (RD 0.07%, 95% CI -0.78 to 0.44), nor in child treatment trials; neither did zanamivir in the treatment of adults or in prophylaxis. There were insufficient events to compare this outcome for oseltamivir in prophylaxis or zanamivir in the treatment of children.

Pneumonia. Oseltamivir significantly reduced self reported, investigator-mediated, unverified pneumonia (RD 1.00%, 95% CI 0.22 to 1.49); number needed to treat to benefit (NNTB) = 100 (95% CI 67 to 451) in the treated population. The effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. There were no definitions of pneumonia (or other complications) in any trial. No oseltamivir treatment studies reported effects on radiologically confirmed pneumonia. There was no significant effect on unverified pneumonia in children. There was no significant effect of zanamivir on either self reported or radiologically confirmed pneumonia. In prophylaxis, zanamivir significantly reduced the risk of self reported, investigator-mediated, unverified pneumonia in adults (RD 0.32%, 95% CI 0.09 to 0.41); NNTB = 311 (95% CI 244 to 1086), but not oseltamivir.

Bronchitis, sinusitis and otitis media. Zanamivir significantly reduced the risk of bronchitis in adult treatment trials (RD 1.80%, 95% CI 0.65 to 2.80); NNTB = 56 (36 to 155), but not oseltamivir. Neither NI significantly reduced the risk of otitis media and sinusitis in both adults and children.

Harms of treatment. Oseltamivir in the treatment of adults increased the risk of nausea (RD 3.66%, 95% CI 0.90 to 7.39); number needed to treat to harm (NNTH) = 28 (95% CI 14 to 112) and vomiting (RD 4.56%, 95% CI 2.39 to 7.58); NNTH = 22 (14 to 42). The proportion of participants with four-fold increases in antibody titre was significantly lower in the treated group compared to the control group (RR 0.92, 95% CI 0.86 to 0.97, I^2 statistic = 0%) (5% absolute difference between arms). Oseltamivir significantly decreased the risk of diarrhoea (RD 2.33%, 95% CI 0.14 to 3.81); NNTB = 43 (95% CI 27 to 709) and cardiac events (RD 0.68%, 95% CI 0.04 to 1.0); NNTB = 148 (101 to 2509) compared to placebo during the on-treatment period. There was a dose-response effect on psychiatric events in the two oseltamivir "pivotal" treatment trials, WV15670 and WV15671, at 150 mg (standard dose) and 300 mg daily (high dose) ($P = 0.038$). In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75 to 10.29); NNTH = 19 (95% CI 10 to 57). There was a significantly lower proportion of children on oseltamivir with a four-fold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00, $I^2 = 0\%$).

Prophylaxis. In prophylaxis trials, oseltamivir and zanamivir reduced the risk of symptomatic influenza in individuals (oseltamivir: RD 3.05% (95% CI 1.83 to 3.88); NNTB = 33 (26 to 55); zanamivir: RD 1.98% (95% CI 0.98 to 2.54); NNTB = 51 (40 to 103)) and in households (oseltamivir: RD 13.6% (95% CI 9.52 to 15.47); NNTB = 7 (6 to 11); zanamivir: RD 14.84% (95% CI 12.18 to 16.55); NNTB = 7 (7 to 9)). There was no significant effect on asymptomatic influenza (oseltamivir: RR 1.14 (95% CI 0.39 to 3.33); zanamivir: RR 0.97 (95% CI 0.76 to 1.24)). Non-influenza, influenza-like illness could not be assessed due to data not being fully reported. In oseltamivir prophylaxis studies, psychiatric adverse events were increased in the combined on- and off-treatment periods (RD 1.06%, 95% CI 0.07 to 2.76); NNTH = 94 (95% CI 36 to 1538) in the study treatment population. Oseltamivir increased the risk of headaches whilst on treatment (RD 3.15%, 95% CI 0.88 to 5.78); NNTH = 32 (95% CI 18 to 115), renal events whilst on treatment (RD 0.67%, 95% CI -2.93 to 0.01); NNTH = 150 (NNTH 35 to NNTB > 1000) and nausea whilst on treatment (RD 4.15%, 95% CI 0.86 to 9.51); NNTH = 25 (95% CI 11 to 116).

Authors' conclusions

Oseltamivir and zanamivir have small, non-specific effects on reducing the time to alleviation of influenza symptoms in adults, but not in asthmatic children. Using either drug as prophylaxis reduces the risk of developing symptomatic influenza. Treatment trials with oseltamivir or zanamivir do not settle the question of whether the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions. The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, psychiatric effects

and renal events in adults and vomiting in children. The lower bioavailability may explain the lower toxicity of zanamivir compared to oseltamivir. The balance between benefits and harms should be considered when making decisions about use of both NIs for either the prophylaxis or treatment of influenza. The influenza virus-specific mechanism of action proposed by the producers does not fit the clinical evidence.

PLAIN LANGUAGE SUMMARY

Regulatory information on trials of oseltamivir (Tamiflu) and zanamivir (Relenza) for influenza in adults and children

Oseltamivir and zanamivir have been stockpiled in many countries to treat and prevent seasonal and pandemic influenza, before an influenza vaccine matched to the circulating virus becomes available. Oseltamivir is classified by the World Health Organization as an essential medicine.

How this review has been approached

We have updated and combined our reviews on the antiviral drugs zanamivir and oseltamivir for influenza in adults and children on the basis of the manufacturers' reports to regulators (clinical study reports) and the regulators' comments. We have called these comments and reports 'regulatory information'. Clinical study reports are unpublished, extensive documents with great detail on the trials that formed the basis for market approval. They include the protocols, methods and results. Clinical study reports have until now been confidential, seen only by the manufacturers and regulators.

Why we have taken this approach

In previous versions of this review we identified unresolved discrepancies in the data presented in published trial reports and substantial publication bias. As a consequence, we elected not to use data from journal articles but included the documents generated during licensing processes. We have accessed such data from the UK, USA, European Medicines Agency (EMA), Japanese regulators and clinical study reports from the manufacturers (after a protracted media campaign). This has enabled us to verify information from the randomised, placebo-controlled trials on adults and children with confirmed or suspected exposure to naturally occurring influenza.

Based on our assessments of the regulatory documents (in excess of 160,000 pages), we came to the conclusion that there were substantial problems with the design, conduct, reporting and availability of information from many of the trials.

What we have found

We have used data from 46 trials (20 oseltamivir and 26 zanamivir studies) in this review. We identified problems in the design of many of the studies that we included, which affects our confidence in their results. We found that both drugs shorten the duration of symptoms of influenza-like illness (unconfirmed influenza or 'the flu') by less than a day. Oseltamivir did not affect the number of hospitalisations, based on the data from all the people enrolled in treatment trials of oseltamivir. Zanamivir trials did not record this outcome. The effects on pneumonia and other complications of influenza, such as bronchitis, middle ear infection (otitis media) and sinusitis, were unreliably reported, as shown by the case report form in the trial documents. Some forms showed limitations in the diagnostic criteria for pneumonia. Regulatory comments noted problems with missing follow-up diary cards from participants. In children with asthma there was no clear effect on the time to first alleviation of symptoms.

Prophylaxis trials showed that oseltamivir and zanamivir reduced the risk of symptomatic influenza in individuals and households. There was no evidence of an effect on asymptomatic influenza or on non-influenza, influenza-like illness, but trial conduct problems prevent any definitive conclusion.

Oseltamivir use was associated with nausea, vomiting, headaches, renal and psychiatric events; these last three were when it was used to prevent influenza (prophylaxis). Its effect on the heart is unclear: it may reduce cardiac symptoms, but may induce serious heart rhythm problems. In adult treatment trials of zanamivir there was no increased risk of reported adverse events. The evidence on the possible harms associated with the treatment of children with zanamivir was sparse.

Agreement with other findings

The lack of good evidence demonstrating an effect on complications agrees with the conservative conclusions on both drugs drawn by the US Food and Drug Administration (FDA). The FDA only allowed claims of effectiveness of both drugs for the prevention and treatment of symptoms of influenza and not for other effects (including the interruption of person-to-person spread of the influenza virus or prevention of pneumonia). The FDA described the overall performance of both drugs as 'modest'.

Mechanism of action for beneficial effects

These findings all suggest that the low immune response with low levels of pro-inflammatory cytokines, which is induced by the action of oseltamivir carboxylate, may reduce the symptoms of influenza unrelated to an inhibition of influenza virus replication. The potential hypothermic or antipyretic effect of oseltamivir as a central nervous system depressant may also contribute to the apparent reduction of

host symptoms. Statements made on the capacity of oseltamivir to interrupt viral transmission and reduce complications are not supported by any data we have been able to access.

The mechanism of action proposed by the producers (influenza virus-specific) does not fit the clinical evidence which suggests a multi-system and central action.

BACKGROUND

This review (known as A159) reports our efforts to get to the bottom of the issue of the effects of NIs by appraising evidence from unpublished clinical study reports (see Glossary, [Appendix 1](#)) and regulatory documents containing comments and reviews. We have called the body of clinical studies and regulatory comments 'regulatory information'. For the history and evolution of the review see [Appendix 2](#).

Description of the condition

Influenza is mostly a mild, self limiting infection of the upper airways with local symptoms, including sniffles, nasal discharge, dry cough and sore throat, and systemic symptoms such as fever, headache, aches and pains, malaise and tiredness.

Occasionally patients with influenza develop complications such as pneumonia, otitis media and dehydration or encephalopathy with or without liver failure, which may be due to the effects of the influenza virus itself or associated secondary bacterial infections and/or adverse effects of drugs such as antipyretics (including salicylates and other non-steroidal anti-inflammatory drugs) ([Hama 2008](#)).

Influenza is not clinically distinguishable from influenza-like illness (ILI) ([Call 2005](#)). Epidemic influenza in humans is caused by influenza A and B viruses. Currently, influenza A/H1N1, influenza A/H3N2 and influenza B cause most influenza infections worldwide ([CDC 2013](#)).

Description of the intervention

Neuraminidase inhibitors (NIs) comprise inhaled zanamivir (Relenza, GlaxoSmithKline), oral oseltamivir (Tamiflu, Gilead Sciences and F. Hoffman-La Roche), parenteral peramivir (BioCryst Ltd), inhaled laninamivir (Daiichi Sankyo Co. Ltd) ([Sugaya 2010](#)) and others still under development ([Hayden 2009](#)). The use of NIs has increased dramatically since the outbreak of A/H1N1 in April 2009, partly because of the rise in amantadine/rimantadine resistance and, in the early stages of the outbreak, the lack of a vaccine, which meant that NIs became a widespread public health intervention. The World Health Organization (WHO) had previously encouraged member states to stockpile and gain experience of using NIs ([WHO 2002a](#); [WHO 2002b](#); [WHO 2004](#)).

How the intervention might work

Although NIs may reduce the ability of the virus to penetrate the mucus in the very early stage of infection ([Bhatia 2007](#); [Matrosovich 2004](#); [Moscona 2005](#); [Ohuchi 2006](#)), their main mechanism of action is thought to lie in their ability to inhibit influenza viruses from exiting host cells ([Liu 1995](#); [Moscona 2005](#)). The manufacturers state that oseltamivir does not prevent infection, nor affect antibody production ([Smith 2006](#)), but it reduces symptom duration probably by reducing viral load, spread and release of cytokines ([Hayden 1999](#); [WV15670](#)), diminishing the chance of complications and interrupting person-to-person viral spread.

Oseltamivir phosphate (Tamiflu) is the pro-drug of oseltamivir carboxylate, the effective form. Oseltamivir phosphate dissociates in the gastrointestinal tract to form oseltamivir, which is absorbed and metabolised into oseltamivir carboxylate by hepatic carboxylesterase (h-CE). Oseltamivir may have a central depressant

action ([Hama 2008](#)) and may also inhibit human sialidase ([Li 2007](#)), causing abnormal behaviour.

Inhaled zanamivir reaches a far lower plasma concentration compared to its intravenous administration ([Cass 1999](#)).

Any treatment that reduces the complications of influenza (for example, pneumonia) and the excretion of the virus from infected people might be a useful public health measure to contain an epidemic by limiting the impact and spread of the virus. In addition to symptomatic treatment, prophylactic use for interrupting the spread of disease has informed pandemic planning over the past decade.

Why it is important to do this review

There are three major reasons for conducting this review, in addition to questions of efficacy associated with the clinical use of NIs for influenza:

1. Influenza antivirals are a commonly used and stockpiled drug against past and future pandemics on the basis of international and national recommendations. These recommendations are based on the claimed and assumed ability of the drug to reduce complications and transmission ([HHS 2005](#); [WHO 2007](#)). In theory, containing the spread of influenza allows time for an organised response with longer-term interventions (such as vaccines), which take time to produce ([WHO 2007](#)).
2. There are legitimate reasons to doubt these claims and the results of previous Cochrane reviews of NIs in adults ([Jefferson 2006](#); [Jefferson 2009a](#)) and children ([Shun-Shin 2009](#)), due to the risk of reporting bias, including the certainty of publication bias ([Doshi 2012a](#); [Doshi 2012b](#)).
3. Oseltamivir is now on the list of WHO essential drugs ([WHO 2013a](#); [WHO 2013b](#)).

Process

A159 is an amalgamation of two long-standing Cochrane reviews on the effects of NIs for influenza in healthy adults ([Jefferson 2010a](#), also published as [Jefferson 2009a](#)) and children ([Matheson 2007](#)), and it is based on the assessment of trials through their clinical study reports and other regulatory information: a decision we made after finding substantial reporting bias in the journal publications of the relevant trials.

For the rationale for this process see [Appendix 2](#).

Examples of discrepancies and reporting bias

We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled, phase III treatment trials of oseltamivir have never been published. This includes [M76001](#), the biggest treatment trial ever undertaken on oseltamivir (with just over 1400 people of all ages). Exclusion of unpublished data changed our previous findings regarding the ability of oseltamivir to reduce the complications of influenza ([Doshi 2009](#); [Jefferson 2009a](#)). In some cases, mistakes in the attribution of adverse events were only discovered through matching summary tables with individual participant listings ([Gravenstein 2013](#); [Peters 2001](#); [WV15825](#)).

A modified approach

We have modified the routine Cochrane processes to improve our previous methods, which we now consider inadequate. To resolve inconsistencies and under-reporting, we changed our approach by no longer including trial data as reported in papers published in biomedical journals. Instead, we treated clinical study reports as our basic unit of analysis. Clinical study reports are often sent to national drug regulators such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (formerly EMEA), which require far more stringent standards for completeness and accuracy of reporting than biomedical journals. Journal articles can be regarded as a very succinct synthesis of a clinical study report. In addition to seeking clinical study reports, we decided to read and review regulatory documentation. The FDA in particular (and the EMA to a far lesser extent) make many of its scientific reviews available on its website. Unlike Cochrane review authors, regulators can have access to the whole data set and their comments can provide useful insight, helping to achieve a better understanding of trial programmes.

Clinical study reports generally remain hidden from public view and are not readily available for wider scientific scrutiny, despite the wealth of information they contain for those willing and able to spend the time reading them and despite calls to make all relevant trial data public (Doshi 2013; Godlee 2009), as well as the known problems with reporting biases (McGauran 2010; Wieseler 2013).

Implications

This modified approach to a Cochrane review aims to provide patients, clinicians and policy-makers with the most transparent and independent information possible about NIs for influenza. In addition, it should contribute to improving a European regulatory and pharmacovigilance legal framework, which commentators consider weak (Cohen 2009; Godlee 2009). We believe that as NIs have become public health drugs, recommended and stockpiled globally, independent scrutiny of all the evidence relating to harms and effects on complications is necessary to provide patients, policy-makers and physicians with a complete and unbiased view of their risks and benefits.

Implication for A/H1N1 (2009) influenza

In response to our 2010 review (Jefferson 2009a; Jefferson 2010a), some have argued that its findings cannot be applied to the 2009 A/H1N1, suggesting that it is a new virus and thus we need new evidence (JAID 2010; Maugh 2009; Nebahay 2009; NHS 2009; NHS 2010). Novel A/H1N1 is a new strain of a subtype that has been circulating since 1977, but it also resembles the A/H1N1 strain that has been circulating since before 1957 (CDC 2009) or before the 1918 pandemic (Itoh 2009). Influenza subtype A/H1N1 was indeed circulating in the clinical trials we have included in our previous reviews. In addition, oseltamivir and zanamivir were approved by regulators worldwide for the treatment and prevention of influenza types A and B, not specific subtypes or strains of influenza A and B. The expectation of regulatory approval is thus that the effects of these drugs demonstrated in clinical trials will apply to future strains of influenza A and B. Use of these drugs during the pandemic was not off-label. It was approved use because of the assumption that the clinical trial evidence underpinning regulatory approval applied to novel A/H1N1. We reviewed the clinical trial evidence with the expectation that our results, similar to regulators, will apply to all influenza viruses.

Wider implications

The modified approach in this Cochrane review grew out of a realisation that prior methods employed to review NIs were inadequate. There seems to be no compelling reason to think that the lessons learned are limited to these particular drugs (Godlee 2009; Rodgers 2013; Vedula 2009; Vedula 2013; Wieseler 2013). For this reason, our independent scrutiny, using all possible trial information, may inform both the wider debate on the adequacy of existing regulatory frameworks in the adoption of new drugs and the question of whether other systematic reviews should move to this new, more rigorous, approach, which focuses on trial programmes rather than single trials (Eyding 2010; Ioannidis 2010) (see Glossary, Appendix 1). Although there is substantial evidence for the effects of reporting bias in estimates of effectiveness, less is known of its impact on the evidence of harms (Chou 2005). We decided to quantify the additional resources required to follow our modified methodological approach to assess the feasibility of other systematic reviews proceeding in a similar fashion.

See the [Differences between protocol and review](#) section for the previous version of the objectives of this review.

OBJECTIVES

To describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all clinical study reports of published and unpublished randomised, placebo-controlled trials and regulatory comments.

METHODS

Criteria for considering studies for this review

Types of studies

We included evidence from randomised controlled trials (RCTs) testing the effects of NIs for prophylaxis, post-exposure prophylaxis (PEP) and treatment of influenza. Prophylaxis is the mode of use of NIs when there is expectation of possible near-future exposure to influenza. PEP is the use of NIs following probable exposure to influenza but before symptoms develop. Treatment is the use of NIs in persons showing probable signs of influenza.

Due to discrepancies between published and unpublished reports of the same trials, we decided to include only those trials for which we had unabridged clinical study reports (for example, with consecutively numbered pages), even though they may be parts of clinical study reports (i.e. Module 1 only) and information on reports of trials that were considered "pivotal" (i.e. first or second-line evidence to regulators in support of the registration application).

Types of participants

We included previously healthy people (children and adults). 'Previously healthy' includes people with chronic illness (such as asthma, diabetes, hypertension), but excludes people with illnesses with more significant effects on the immune system (such as malignancy or HIV infection). We included only trials on people exposed to naturally occurring influenza with or without symptoms. We targeted the intention-to-treat (ITT) and safety populations as our prior review discovered compelling evidence that the intention-to-treat-influenza-infected (ITTI), the sub-population deemed to be influenza-infected, were not

balanced between treatment groups in the Roche oseltamivir trials. In addition, estimates from the ITT population will be more generalisable to clinical practice, where routine testing for influenza is not common in many countries (and even where used, remains of variable accuracy).

Types of interventions

NIs administered by any route compared with placebo during the period in which medication was assumed and during the follow-up (on- and off-treatment: on-t and off-t) periods.

Types of outcome measures

Primary outcomes

Primary outcome measures for treatment studies

1. Symptom relief
2. Hospitalisation and complications
3. Harms

Primary outcome measures for prophylaxis studies

1. Influenza (symptomatic and asymptomatic, always with laboratory confirmation) and influenza-like illness (ILI)
2. Hospitalisation and complications
3. Interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts)
4. Harms

Secondary outcomes

Secondary outcome measures for treatment studies

1. Symptom relapse after finishing treatment
2. Drug resistance
3. Viral excretion
4. Mortality

Secondary outcome measures for prophylaxis studies

1. Drug resistance
2. Viral excretion
3. Mortality

Whilst overall symptom reduction is well documented, our interest was particularly focused on complications and adverse events, as this is where evidence is currently scarce or inconclusive (Jefferson 2009a; Shun-Shin 2009). Our preliminary examination of some regulatory documents and some published versions of the studies had identified that some symptoms and sequelae of influenza (such as pneumonia) had been classified as either a 'complication of influenza' or as an 'adverse event of the treatment', or both. This is somewhat confusing and we intended to analyse 'compliharms' (see Glossary, [Appendix 1](#)) irrespective of the classification as a 'complication of influenza' or as an 'adverse event of the treatment' ([Appendix 3](#)) in oseltamivir trials. Complications of particular interest included pneumonia, bronchitis, otitis media and sinusitis as these were the secondary illnesses often collected in the Roche oseltamivir trials and we agreed that these events are clinically important. Initially we constructed a table to illustrate the design methodology used for each complication by study ([Table 1](#)). The table included

the following variables: definition of which events are termed complications; where complications are first defined in the clinical study report; diagnosis method; and availability of data. We then stratified our analysis by method of diagnosis with three possible criteria: (1) laboratory-confirmed diagnosis (e.g. based on radiologically or microbiologically confirmed evidence of infection); (2) clinical diagnosis without laboratory confirmation (diagnosed by a doctor after a clinical examination); (3) other type of diagnosis such as self reported by patient. We conducted analysis of any complication (pneumonia, bronchitis, otitis media and sinusitis) that was classified as serious or led to study withdrawal.

In all cases of influenza complications reporting (pneumonia, bronchitis, sinusitis, otitis media) there is a variable degree of participant self reporting, of investigator mediation (for example, in writing down the details in the case report form) and lack of verification with investigations such as culture or imaging. The 'self reported, investigator-mediated, unverified' title is relevant to all complications but for brevity we use it as sparingly as possible.

For harms we were limited by the frequency of occurrence of the adverse events collected in the trials. Consequently we meta-analysed (1) all serious adverse events; (2) all adverse events leading to study withdrawal; (3) all withdrawals; (4) all adverse events within a clinical study report's defined body system; as well as (5) a small group of common adverse events as defined in the FDA drug label for oseltamivir. There were too few events to meta-analyse (1) deaths; (2) serious adverse events by body system; and (3) any events that had an overall incidence of less than 0.5%. We did not meta-analyse outcomes with fewer than 10 events in total. We conducted analyses separately for on-treatment and off-treatment periods. However, in two cases where (on-treatment) treatment effects were borderline statistically significant (prophylaxis with oseltamivir: renal body system on-treatment and psychiatric body system on-treatment), we conducted additional analysis combining on- and off-treatment periods to maximise statistical power. We conducted dose-response harms analysis for two treatment trials ([WV15670](#) and [WV15671](#)) combined and one prophylaxis study ([WV15673/WV15697](#)), as these trials investigated the active agent at multiple doses. These studies included standard-dose and high-dose oseltamivir arms. For these analyses we used logistic regression, adjusting for study effects if appropriate (i.e. for the two treatment trials) and testing for trend using a likelihood ratio test. We tested the hypothesis that increased dose of drug leads to increased incidence of adverse effects.

Search methods for identification of studies

To identify trials in the manufacturer-funded clinical trial programmes for NIs, as well as non-manufacturer-funded clinical trials of NIs, we used a variety of methods applied to a variety of sources from the literature, manufacturers and from regulatory bodies. These methods, as well as our methodology for identifying and obtaining relevant clinical study reports, are detailed in [Appendix 4](#), [Appendix 5](#) and [Appendix 6](#).

Electronic searches

We used electronic searches to identify trials not identified by the methods outlined in [Appendix 4](#), particularly for non-manufacturer-funded clinical trials. See [Appendix 5](#) for details. For the 2012 review, we updated our searches of the electronic

databases of published studies that were previously carried out for the Cochrane reviews on NIs in children (Matheson 2007) and healthy adults (Jefferson 2010a), and then updated the searches again on 22 July 2013.

Searching other resources

For the description of our searches for regulatory information (FDA, EMA, Roche, GlaxoSmithKline (GSK), Japanese Pharmaceuticals and Medical Devices Agency (PMDA)), see Appendix 6.

Data collection and analysis

Collection and inventory of the evidence base was facilitated by the tools specifically developed for the review (Appendix 7). The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

'Other bias' includes potentially active placebos.

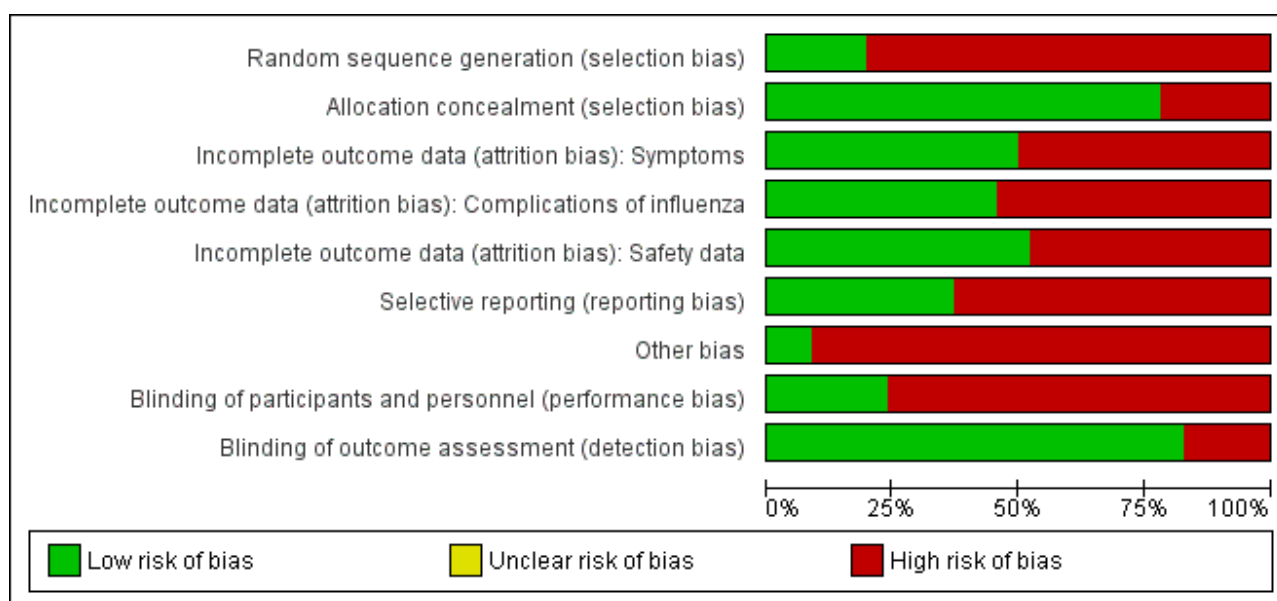


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

'Other bias' includes potentially active placebos.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias): Symptoms	Incomplete outcome data (attrition bias): Complications of influenza	Incomplete outcome data (attrition bias): Safety data	Selective reporting (reporting bias)	Other bias	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
167-101	+	+	+	+	+	+	+	+	+
JNAI-01	+	+	+	+	+	+	+	+	+
JNAI-04	+	+	+	+	+	+	+	+	+
JNAI-07	+	+	+	+	+	+	+	+	+
JV15823	+	+	+	+	+	+	+	+	+
JV15824	+	+	+	+	+	+	+	+	+
M76001	+	+	+	+	+	+	+	+	+
ML16369	+	+	+	+	+	+	+	+	+
NAI30008	+	+	+	+	+	+	+	+	+
NAI30009	+	+	+	+	+	+	+	+	+
NAI30010	+	+	+	+	+	+	+	+	+
NAI30011	+	+	+	+	+	+	+	+	+
NAI30012	+	+	+	+	+	+	+	+	+
NAI30015	+	+	+	+	+	+	+	+	+
NAI30020	+	+	+	+	+	+	+	+	+
NAI30028	+	+	+	+	+	+	+	+	+
NAI30031	+	+	+	+	+	+	+	+	+
NAI30034	+	+	+	+	+	+	+	+	+

Figure 2. (Continued)

NAI30034	-	+	+	+	+	+	-	-	+
NAIA/B2008	-	+	+	+	+	-	-	-	+
NAIA/B2009	-	+	+	+	+	+	-	-	+
NAIA2005	-	+	+	+	+	+	-	-	+
NAIA2006	-	+	+	+	+	+	-	-	+
NAIA3002	-	+	+	+	+	+	+	-	+
NAIA3003	-	+	+	+	+	+	-	-	+
NAIA3004	-	+	+	+	+	+	-	-	+
NAIA3005	-	+	+	+	+	+	-	-	+
NAIB2005	-	+	+	+	+	+	-	-	+
NAIB2006	-	+	-	-	-	+	-	-	+
NAIB2007	-	+	+	+	+	-	-	-	+
NAIB3001	-	+	+	+	+	+	-	-	+
NAIB3002	-	+	+	+	+	+	-	-	+
NV16871	+	+	-	-	-	-	-	-	+
PE-01	-	-	-	-	-	-	-	-	-
WV15670	-	+	-	-	+	-	-	+	+
WV15671	+	-	-	-	-	-	-	+	+
WV15673/WV15697	-	-	-	-	-	-	-	-	+
WV15707	+	+	-	-	-	-	-	+	+
WV15708	-	-	-	-	-	-	-	-	+
WV15730	-	+	-	-	-	-	-	+	+
WV15758	-	+	-	-	-	-	-	+	+
WV15759/WV15871	-	+	-	-	-	-	-	+	+
WV15799	+	+	-	-	+	-	-	+	+
WV15812/WV15872	+	+	-	-	-	-	-	-	+
WV15819/WV15876/WV15978	+	+	-	-	-	-	-	+	+
WV15825	-	-	-	-	-	-	-	-	+
WV16277	+	-	+	-	+	-	-	-	-

Selection of studies

For this 2013 review, two authors (PD, TJ) reapplied the inclusion criteria for the oseltamivir clinical study reports and resolved disagreements by discussion. Two review authors (ES, IO) applied

the criteria for the zanamivir clinical study reports while one review author (CH) arbitrated.

For the procedures followed in the 2012 review, see [Appendix 8](#) and [Appendix 9](#).

Data extraction and management

The sizeable quantity of available data led us to subdivide the extraction, appraisal and analysis of the data into a two-stage exercise. In Stage 1 we assessed the reliability and completeness of the identified trial data. We decided to include in Stage 2 of the review (full analysis following standard Cochrane methods) only data that satisfied the following three criteria.

1. Completeness. Clinical study reports/unpublished reports include both identifiable CONSORT statement-specified methods to enable replication of the study. Identifiable CONSORT statement-specified results (primary outcomes, tables, appendices) must be available.
2. Internal consistency. All parts (for example, denominators) of the same clinical study reports/unpublished report are broadly consistent.
3. External consistency. Consistency of data as reported in regulatory documents, other versions of the same clinical study reports/unpublished reports and other references, to be established by cross-checking.

This was a different approach to that used in the previous version of the current review (Jefferson 2012), since we only had incomplete information at that time and only applied the second and third criteria.

Stage 1

For details of the use of the CONSORT-based extraction template and the assessment for Stage 1 inclusion in the A159 (Jefferson 2012) review, see Appendix 7. In this review assessment for inclusion in Stage 1 was part of the inclusion procedure.

Stage 2

In Stage 2, one review author extracted data and a second review author checked it. We extracted data onto standard forms, checked and recorded it.

Use of regulatory information

We used regulatory information to assess the possible correlation between citation frequency of oseltamivir treatment trials in the FDA regulatory documents and trial size.

Post-protocol analyses

After publication of the A159 protocol in December 2010, but before validation of our CONSORT-based extractions in the Northern Hemisphere spring of 2011, we decided to carry out analyses (which we called post-protocol analyses) to test five null hypotheses that we had formulated while reading, summarising and reconstructing the clinical study reports. The hypotheses originated from our observations of discrepancies and other unexpected observations in the clinical study reports' data and were informed by reading regulatory information. Appendix 10 reports the rationale, methods to formulate and test, and the results of the hypotheses.

The hypotheses reflect the uncertainty prevailing in the evidence base at a time when full clinical study reports were not available for all studies.

Assessment of risk of bias in included studies

Previous studies comparing regulatory with published or internal company sources of evidence have reported a variety of different biases that affect medical knowledge (Chou 2005; MacLean 2003; McGauran 2010; Wieseler 2013). We will report in detail elsewhere our comments on using the Cochrane 'Risk of bias' tool (Higgins 2011) to appraise clinical study reports and for trial programmes, and our efforts to construct an instrument for assessing risk of bias in complete clinical study reports. A full description of the methods used to quantify biases will be published in another paper.

Measures of treatment effect

To estimate treatment effects we first calculated the risk ratios (RRs) and used the average (mean) control event rate and the pooled RRs reported in the figures to calculate the risk differences (RD). For consistency we adopted this method for both the 'Summary of findings' tables and for the RDs reported in the text. For the analysis we chose to report the RRs as they are more consistent across the studies, and we have reported the heterogeneity for the pooled RR. We reinterpreted the results using the RD as this result is applicable to clinical decision-making. We calculated mean differences (MDs) for time to first alleviation of symptoms. For time to first alleviation of symptoms we also estimated the treatment effect as the percentage reduction in the average time to first alleviation of symptoms in the placebo group. Most zanamivir clinical study reports only reported treatment effects in terms of medians in each treatment group as well as P values from a hypothesis test comparing the time-to-event distributions. These data are insufficient for conducting meta-analysis. However, often sufficient time-to-event data were reported to allow us to estimate restricted means and standard deviations. Restricted means are based on the maximum time reported where alleviation occurred. There were some patients where alleviation was censored at the maximum follow-up time, therefore restricted means are underestimates of the true means. However, the proportion of patients censored was generally low and similar in both treatment arms, hence this limitation is unlikely to have led to bias. The length of follow-up varied across trials and this has led to high variation in the estimated means and standard deviations (SDs) across trials.

A post hoc analysis was undertaken after we discovered seven zanamivir trials provided data on time to first alleviation of symptoms with and without relief medication. Each patient in the studies may or may not have taken relief medication during the trial. Alleviation of symptoms may have occurred while the patient was taking relief medication and the "standard" comparison was made using this scenario. However, an additional analysis used a stricter definition where alleviation of symptoms could only be achieved without the use of relief medication. For example, a patient may have achieved alleviation using relief medication after five days but took seven days to achieve alleviation without the use of relief medication. The comparison we reported is for all patients where we used the stricter definition for the zanamivir group (alleviation without relief medication) and the less strict definition for the placebo group (alleviation with relief medication).

We planned to use the tri-dimensional dose-relatedness, timing and patient susceptibility (DoTS) methodology to assess the likelihood of harms causality (Aronson 2003), but the quality of the data available did not allow for this.

Unit of analysis issues

Problems with unit of analysis are described in the 'Risk of bias' and 'Post-protocol hypotheses' sections.

Dealing with missing data

We developed a comprehensive strategy for dealing with data that we know are missing at the trial level, i.e. unpublished trials (see [Search methods for identification of studies](#) section and [Appendix 4](#), [Appendix 5](#) and [Appendix 6](#)) and unreliable published records, which are a very concentrated summary of clinical study reports. For example, in the oseltamivir trial programme, some trials' clinical study reports (e.g. [WP16263](#)) consist of 8545 pages. This has a 1000-fold greater length compared to its published version ([Dutkowski 2010](#)), which consists of seven pages. The purpose of this review is to provide as complete a picture as possible of trial programmes, without reliance on the published literature. [Appendix 11](#) reports an example of the content of a typical Roche clinical study report.

Assessment of heterogeneity

We used Tau² (inverse variance method) and the I² statistic to estimate between-study variance as measures of the level of statistical heterogeneity and the Chi² test to test for heterogeneity.

Assessment of reporting biases

We carried out assessment of reporting biases (comparing clinical study report with the relevant publication) only in the first publication of A159. For this version, as we had complete clinical study reports for the trial programmes of the two drugs, we expected to find all relevant information in these documents and adopted a binary assessment (high risk, low risk or unclear bias).

Data synthesis

We used the random-effects approach of DerSimonian and Laird based on MDs for analysis of time to first alleviation of symptoms. For all other outcomes we used the random-effects approach for binary data of DerSimonian and Laird, where Tau² was estimated using the inverse variance method.

Whilst overall symptom reduction is well documented, our interest was particularly focused on complications and adverse events, as this is where evidence is currently scarce or inconclusive ([Jefferson 2009a](#); [Matheson 2007](#); [Shun-Shin 2009](#)). Our preliminary examination of clinical study reports identified that some symptoms and sequelae of influenza (such as "pneumonia") had been classified as either a 'complication of influenza' or as an 'adverse event of the treatment' or both. We called this somewhat confusing classification 'compli-harms'. We decided to deal with compli-harms as follows. We identified complications of particular clinical interest as "pneumonia", bronchitis, otitis media and sinusitis. We tabulated the type of data capture used for each complication ("secondary illness") by study including the following variables: definition of what events are termed complications, which part of the clinical study report captured data on complications, who reported and captured the data, which diagnostic method was used, whether and where the diagnostic pathway was (usually a form) and whether prescription for treatment were captured. We then aimed to stratify our analysis by method of diagnosis with three possible criteria: (1) laboratory-confirmed diagnosis (e.g. based on radiological-

or microbiologically-confirmed evidence of infection); (2) clinical diagnosis without laboratory-confirmation (diagnosed by a doctor/investigator after a clinical examination); (3) other type of diagnosis such as self-reported by patient. We also conducted analysis of any complication (such as "pneumonia", bronchitis, otitis media and sinusitis) that was classified as serious or led to study withdrawal.

We tested the effects of oseltamivir in prophylaxis of influenza and influenza-like illness. However the clinical study reports of prophylaxis trials do not define influenza-like illness but report eight different definitions for influenza with laboratory-confirmation (see web extra influenza definitions).

This is a complex and confusing set of definitions where, for example, the definition for Upper Respiratory Tract Infection (URTI) with systemic disturbance is the same as one of the definitions for asymptomatic influenza. After discovering the absence of a definition for influenza-like illness and the complex and confusing definitions for laboratory-confirmed influenza, we classified influenza-like illness as two or more symptoms from the following: nasal congestion, headache, chills/sweats, sore throat, cough, fatigue, myalgia and fever. These were the symptoms reported in the efficacy listing of individual patients in Module 3 of the prophylaxis trials clinical study reports.

In two oseltamivir treatment trials ([WV15670](#); [WV15671](#)) and one prophylaxis study ([WV15673/WV15697](#)) there were three treatment arms comparing placebo, standard dose and high dose. For time to first alleviation of symptoms we restricted comparison to placebo versus standard dose (as this is how it was reported in the original report). However, for all other outcomes we combined the standard and high-dose treatment arms. There was little apparent difference in the incidence of outcomes between the standard and high-dose arms and combining the arms did not appear to cause heterogeneity. However, in two cases there was some evidence of a dose-response effect. These cases are described more fully in the [Results](#) section under 'Analysis of harms'.

The majority of zanamivir trials compared placebo with inhaled zanamivir. However, some trials also included an intranasal zanamivir treatment arm and a combined arm of inhaled and intranasal treatment. The multiple zanamivir arms were generally combined for meta-analysis as effects appeared similar and did not appear to cause heterogeneity.

Subgroup analysis and investigation of heterogeneity

We investigated the robustness of complications outcomes using subgroup analysis by method of diagnosis. We investigated high estimates of heterogeneity, where possible, using subgroup analysis. For example, we conducted subgroup analysis of time to first alleviation of symptoms in studies of oseltamivir treatment in children by partitioning studies into those of otherwise healthy children and those of children with chronic illness (asthma). Based on a referee's comment, we conducted a subgroup analysis on time to first alleviation of symptoms by infection status for zanamivir. We could not do a similar analysis for oseltamivir because we did not have data on the non-influenza-infected patients and we could not correctly identify the patients with influenza infection due to the effect of oseltamivir on antibodies.

In the trial programmes for both oseltamivir and zanamivir there was large variation in treatment effects for pneumonia across

the populations studied (i.e. adults and children as well as treatment and prophylaxis), hence we conducted meta-regression to investigate this heterogeneity. We included all studies that reported pneumonia (32 studies in total) and investigated the four binary factors: age group (adults versus children); drug (oseltamivir versus zanamivir); indication (treatment versus prophylaxis) and method of diagnosis. For oseltamivir studies, the method of diagnosis was either based on data collected on non-specific adverse events or secondary/intercurrent illness forms or data collected on specific "diagnosis of secondary illness" forms that included objective criteria such as X-ray confirmation. For zanamivir, two trials included X-ray confirmation of pneumonia. We conducted meta-regression in Stata/SE, version 13 for Windows using the *metareg* command. There were some studies where one treatment group had zero events, therefore we added 0.5 events to all treatment groups for all studies prior to analysis. The dependent variable in the regression was log relative risk. A further post hoc analysis was undertaken after we discovered seven trials provided data on time to first alleviation of symptoms with and without relief medication. Each patient in the studies may or may not have taken relief medication during the trial. Alleviation of symptoms may have occurred while the patient was taking relief medication and the "standard" comparison was made using this scenario. However, an additional analysis used a stricter definition where alleviation of symptoms could only be achieved without the use of relief medication. For example, a patient may have achieved alleviation using relief medication after five days but took seven days to achieve alleviation without the use of relief medication. The comparison we reported is for all patients where we used the stricter definition for the zanamivir group (alleviation without relief medication) and the less strict definition for the placebo group (alleviation with relief medication).

Sensitivity analysis

Sensitivity analyses applicable to our post-protocol analyses have been covered earlier in the Methods section of this review. We used the fixed-effect method of Mantel and Haenszel as a sensitivity analysis to supplement our primary analyses using the random-effects method of DerSimonian and Laird. Random-effects meta-analysis is known to be overly conservative with sparse data. Hence we conducted sensitivity analysis using Peto's method on two occasions where we had sparse data and borderline statistically significant results (prophylaxis with oseltamivir: renal body system on-treatment and psychiatric body system on-treatment).

RESULTS

Description of studies

We searched trial registries, electronic databases and regulatory archives, corresponded with manufacturers to identify all trials and requested clinical study reports. Although this review focuses on the primary data sources of manufacturers, we checked that there were no published randomised controlled trials (RCTs) from non-manufacturer sources by running electronic searches in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 6), limited to year published 2010 to 2013 (20 search results); MEDLINE (January 2011 to July week 2, 2013) (56 search results) and MEDLINE (Ovid) from 1 January 2011 to July week 2, 2013 (56 search results); EMBASE (January 2011 to July 2013) (90 search results) and Embase.com from 1 January 2011 to July 2013 (90 search results); and PubMed (not MEDLINE)

with no date limit (21 records). We searched PubMed to identify publisher-submitted records that will never be indexed in MEDLINE and the most recently added records not yet indexed in MEDLINE. To identify reviews that may possibly have referenced further trials we searched: the Database of Reviews of Effects (DARE) (2013, Issue 2 of 4 April) (four search results); the NHS Economic Evaluation Database (NHSEED) (Issue 2 of 4 April 2013) (two search results), both resources part of *The Cochrane Library* (accessed 22 July 2013), and the Health Economic Evaluations Database (HEED) (searched 22 July 2013) (three search results).

Results of the search

Use of regulatory information

We were able to download 2673 pages from the FDA website. The table of contents is in [Table 2](#), [Table 3](#), [Table 4](#) and [Table 5](#). We used these pages to identify all trials that had been conducted within a drug's trial programme. There was no correlation between citation frequency of oseltamivir treatment trials in the FDA regulatory documents and trial size. The biggest treatment trial ([M76001](#)) is cited only four times in three documents, while other contemporary treatment trials are cited far more ([WV15670](#); [WV15671](#); [WV15730](#); [WV15812](#)/[WV15872](#); [WV15707](#)). [WV15670](#), for example, is cited 46 times in the FDA documents. However, the combined enrolled denominator of the four treatment trials completed at the time ([WV15670](#); [WV15671](#); [WV15707](#); [WV15730](#)) was 1442, smaller than [M76001](#) (1459). This suggested that the FDA's regulatory evaluation of Roche's New Drug Application was based predominantly on what Roche had offered them as "pivotal" or trials that best demonstrated the properties of oseltamivir, not the complete evidence base of all oseltamivir trials. One possible alternative explanation for this observation could have been the interval between trial completion, generation of the report and New Drug Applications (NDA) submission. This explanation is supported by the relatively brief interval between completion of the [M76001](#) trial (19 February 1999) and submission (on 30 April 1999) of NDA 021087 to the FDA. However, the core part of the submission (the clinical development programme) contains data from two (at the time) ongoing trials ([WV15819](#)/[WV15876](#)/[WV15978](#); [WV15812](#)/[WV15872](#)).

The basis of the selection of trials to regulators is therefore unclear but appears to be dictated by criteria other than availability and size. The importance of trials (to manufacturers and possibly to regulators) may not be based on the same criteria that systematic reviewers would use (i.e. the capability of the trial to answer questions).

Due to the vast size of FDA documents, sometimes hundreds of pages long, it was difficult to determine important emerging themes solely by reading. To identify items of interest in the FDA comments we used word clouds ([Feinberg 2009](#)). Word clouds give greater prominence to words that appear more frequently in the source document. The resulting graphic representation showed words such as 'diary' and 'baseline' to be heavily mentioned in the relevant (abridged) text from the FDA's Medical Officer Review ([FDA 1999c](#), PDF page 19). Examining the 'diary' entry in more detail, we found the following FDA comment:

"The majority of subjects participating in the treatment trials had only used the first diary card. The second diary card was issued in 15% to 20% of participants. In response to FDA's request, the applicant provided a summary of diary card dispensing in the 8/6/99 submission. It became apparent that instructions on

when to start a second diary card were not uniformly followed in [WV15670](#), [WV15671](#), and [WV15730](#) trials. There were examples of patients who had alleviated symptoms yet also received a second diary card. Conversely, there were also examples of patients who did not alleviate all symptoms but did not receive a second diary card. Thus the second diary card was used inconsistently which is viewed as a flaw of these trials. The lack of consistency in collecting symptom information after alleviation precluded a complete documentation of symptom fluctuation. Also missing second diary cards in subjects who had not alleviated symptoms were responsible for the majority of censored data which may have potentially influenced the results of efficacy analysis. In order to address the impact of censoring, the applicant performed several sensitivity analyses which will be summarized in the Integrated Summary of Efficacy".

This comment highlights problems with the follow-up procedure of treatments trials, which may have impaired the regulator's ability to draw conclusions on the duration of effect of oseltamivir. It also provides a good example of how graphic methods can help identify crucial comments in vast regulatory files.

Several other experiments with text from the same FDA document showed that the choice of text to be represented as a Word cloud heavily influenced cloud construction, visibility of words and hence our ability to detect important comments. It is for this reason that we decided to adopt a mixed approach: mapping citations while reading FDA comments and integrating such comments in our appraisal of the evidence. Regulatory comments were all the more important, because at the time we developed this method we had few clinical study reports and comments helped to identify the gaps in our knowledge of the trial programmes.

Once the table of contents had been constructed, we postulated that given the huge work involved in reviewing lots of regulatory

files, our new instrument could also help us by indicating which parts were more important than others, thus focusing our efforts. We experimented with a variety of methods reported in the [Data collection and analysis](#) section.

Clinical study reports

After prolonged correspondence and media pressure ([Appendix 2](#)), we were able to access the trial programmes for both oseltamivir and zanamivir without clauses restricting their accessibility to third parties.

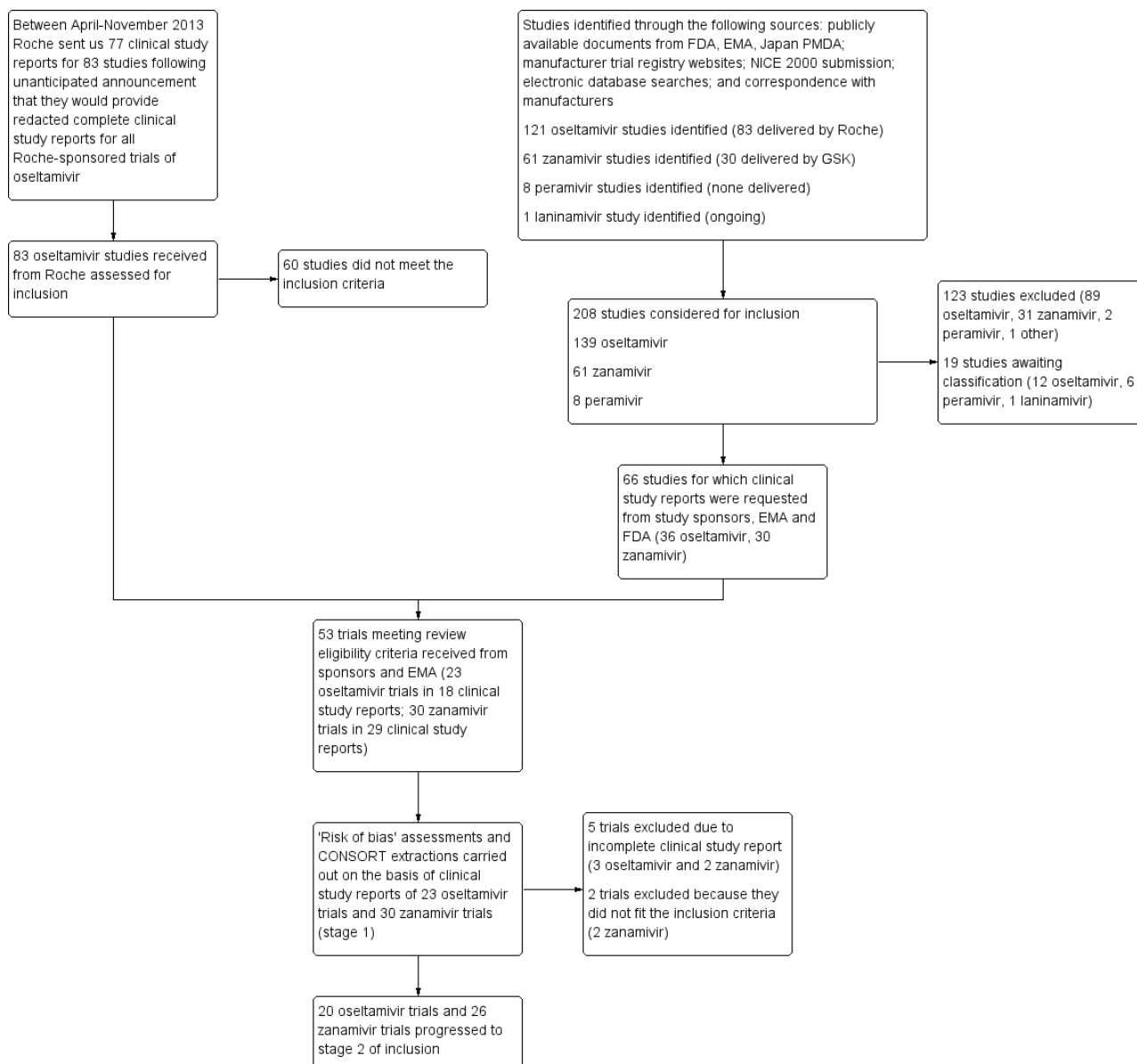
Electronic searches

Two review authors (CDM, MT) independently scanned the titles and abstracts of the electronic searches. Three identified studies ([NCT00980109](#); [NCT01032837](#); [JPRN-JapicCTI-111647](#)) were published versions of trials possibly unknown to us. We wrote to the first trial author to ask for clinical study reports or equivalent on 12 November 2013 who confirmed that the trials had not been completed.

Included studies

The absence of documentation of trial programmes for both drugs, listing all sponsored trials completed or underway, meant we had to rely on a variety of sources for the reconstruction of the trial programmes and identification of relevant clinical study reports. This complexity is reflected in the flowchart presented in [Figure 3](#), illustrating the study selection process for this review. The two main pathways were the spontaneous release of 77 full clinical study reports by Roche (long after our request for 36 of them) and the requests to regulatory authorities and GSK for all the relevant reports.

Figure 3. Flow diagram describing the number of studies identified, inclusion, exclusion and progression from identification to stage 1 to stage 2 of the review. NB Because of the absence of trial programmes for both drugs listing all sponsored trials completed or underway, we had to rely on a variety of sources for the reconstruction of the trial programmes and retrieval of relevant clinical study reports. This complexity is reflected in the flowchart, illustrating the study selection process for this review. The two main pathways were the spontaneous release of 77 clinical full clinical study reports by Roche and the requests to regulatory authorities and GSK for all the relevant reports. There was overlap in trial reports retrieved following the different pathways



We carried out the inclusion into Stage 1 using the clinical study reports, titles, abstracts and any other relevant information. Through this process we identified 208 potentially relevant studies (139 oseltamivir trials, 61 zanamivir trials and eight peramivir trials). We excluded 123 studies (listed in the [Characteristics of excluded studies](#) table) as clearly ineligible. A further 19 studies are awaiting classification (see [Characteristics of studies awaiting classification](#)). We requested 66 trials from study sponsors, the EMA and the FDA. From these different methods the total number of trials available for assessment for inclusion in our review at Stage 1 was 53.

Twenty three studies of oseltamivir (JV15823; JV15824; M76001; ML16369; NV16871; WV15670; WV15671; WV15673/ WV15697; WV15707; WV15708; WV15730; WV15758; WV15759/ WV15871; WV15799; WV15812/WV15872; WV15819/WV15876/ WV15978; WV15825; WV16277) and 28 of zanamivir (167-101; JNAI-01; JNAI-04; JNAI-07; NAI30008; NAI30009; NAI30010; NAI30011; NAI30012; NAI30015; NAI30020; NAI30028; NAI30031; NAI30034; NAIA/B2008; NAIA/B2009; NAIA2005; NAIA2006; NAIA3002; NAIA3003; NAIA3004; NAIA3005; NAIB2005; NAIB2006; NAIB2007; NAIB3001; NAIB3002; PE-01) were included in Stage 1. It was not uncommon for more than one trial to be reported

in the same clinical study reports. This was either due to the amalgamation of two or more trials because of low influenza virus circulation and difficulties in recruitment (for example, [WV15812/WV15872](#)), or because the trials bore different ID numbers when in reality they followed the same protocol, albeit in two different hemispheres (for example, [WV15759/WV15871](#)).

We also identified six completed or ongoing studies of peramivir in dose-response or placebo-controlled studies ([NCT00419263](#); [NCT00453999](#); [NCT00486980](#); [NCT00610935](#); [NCT00705406](#); [NCT00958776](#)).

The included trials were predominantly conducted in adults during influenza seasons in both hemispheres. A small number of studies were conducted in older people residing in care homes and in people with underlying respiratory diseases. All trials were sponsored by the manufacturers.

Oseltamivir

Of the 23 oseltamivir trials in Stage 1, 15 were multicentre trials conducted in both the Northern and Southern Hemispheres, while eight were done in only one country (USA five, Japan two and China one). In total 9623 participants were included (6574 in treatment trials and 3049 in prophylaxis trials). The age of the participants ranged from 1 to 82 years and the duration of follow-up varied from 6 to 42 days.

Two of the trials were conducted within nursing homes; 20 were within free-living populations; one was performed in in- and out-patient departments. Three trials were conducted in children, while participants in 20 trials were adults. In some trials the eligible population included participants at increased risk of influenza complications, or with diagnoses of asthma or chronic obstructive pulmonary disease, but the majority included only otherwise healthy adults. In one trial ([WV15730](#)), participants were stratified by smoking status, while those in another trial were stratified by the presence or absence of otitis media ([WV15758](#)).

All trials compared orally administered oseltamivir (either as capsules or reconstituted powder) with placebo.

Of the 23 trials, we included 20 RCTs for the analysis examining the use of oseltamivir compared with placebo. Two were excluded from the meta-analysis because they were only synopsis reports ([JV15823](#); [JV15824](#)) and another because it was not a full clinical study report ([ML16369](#)).

We finally included 20 oseltamivir trials into Stage 2: 11 on treatment in adults ([M76001](#); [WV15670](#); [WV15671](#); [WV15707](#); [WV15730](#); [WV15812/WV15872](#); [WV15819/WV15876/WV15978/WV16277](#)), four in children ([NV16871](#); [WV15758](#); [WV15759/WV15871](#)), and five on prophylaxis: two in adults ([WV15673/WV15697](#)), two in the elderly ([WV15708](#); [WV15825](#)) and one in households ([WV15799](#)). Of the 15 included treatment trials of oseltamivir only three ([M76001](#); [WV15670](#); [WV15758](#)) were successful in recruiting the a priori planned sample size.

Zanamivir

Of the 28 included zanamivir trials, 18 were multicentre trials done in both the Northern and Southern Hemisphere and 10 were done in only one country (Japan five, USA three, Finland and Germany one each). In total 14,628 participants were included (7678 in treatment

trials and 6950 in prophylaxis trials). Participants' age ranged from 5 to 12 years to over 65 and duration of follow-up varied from 5 to 35 days.

Two of the trials were performed within nursing homes; several were within free-living populations; one was performed within a university student population. In some trials the eligible population included participants at increased risk of influenza complications, or with diagnoses of asthma or chronic obstructive pulmonary disease, but the majority included only adults who were otherwise healthy.

Zanamivir was administered as an intranasal spray, an inhalation or a combination of both and placebos were designed to match. Administration was by the participant in the majority of trials and by nursing staff in the trials within nursing homes. Twenty-two trials compared inhaled zanamivir with placebo and six trials compared inhaled zanamivir, or intranasal zanamivir, with placebo or usual care.

Of the 28 trials we included 26 RCTs for the analysis examining the use of zanamivir compared with placebo. Two were excluded from the meta-analysis because one was only a synopsis ([NAI30020](#)) and one compared zanamivir to usual care and not placebo ([NAIA3003](#)).

We finally included 26 zanamivir trials: 14 on treatment in adults ([JNAI-01](#); [JNAI-04](#); [JNAI-07](#); [NAI30008](#); [NAI30011](#); [NAI30012](#); [NAI30015](#); [NAIA/B2008](#); [NAIA2005](#); [NAIA3002](#); [NAIB2005](#); [NAIB2007](#); [NAIB3001](#); [NAIB3002](#)), two in children ([NAI30009](#); [NAI30028](#)) and 10 trials in prophylaxis ([167-101](#); [NAI30034](#); [NAIA/B2009](#); [NAIA2006](#); [NAIA3004](#); [NAIA3005](#); [NAIB2006](#); [PE-01](#); [NAI30010](#); [NAI30031](#)).

Our attempt at collecting sufficient information from regulatory files to reconstruct missing clinical study reports also failed because the information appeared insufficient for a reliable reconstruction.

Excluded studies

We excluded 123 studies from entering Stage 1 for various reasons. Some were pharmacokinetic studies, or had an active comparator, or compared higher- versus lower-dose schedules, or were ongoing trials. A further 19 trials are awaiting assessment ([Characteristics of studies awaiting classification](#)).

Risk of bias in included studies

Study level assessments are reported in the 'Risk of bias' tables. To address the problem of reporting bias, we ignored published trial reports and directed our attention to clinical study reports and regulatory information. Our problems in reviewing the copious material at our disposal were how to identify and analyse important details in the midst of thousands of pages of information and how to construct a coherent appraisal of large and complex trial programmes.

In addition, since we gained unrestricted access to the full clinical study reports (apart from personal de-identifying redactions) we took the view that all information needed to judge risk of bias should be present. Therefore when this information was not available, we judged the corresponding risk of bias element as at 'high' risk of bias. For example, when details of the random sequence generation are missing from journal publications of clinical trials, it is customary to record this as "unknown" risk of bias. This judgment usually carries the assumption that the random

sequence generation details are available in more detailed reports. But when these details were still missing in even full clinical study reports, we chose to rate this risk of bias element at "high" risk of bias.

In the following paragraphs we report some of the salient findings using the current Cochrane format but applying the logic of reviewing regulatory data.

Allocation

In 10 of the 20 oseltamivir studies included in Stage 2 the description of random sequence generation is missing. The reporting of all zanamivir trials but one ([NAI30028](#)) was biased by the absence of description of random sequence generation.

Blinding

The placebo and active drug capsule cap were not identical in 11 of the 20 trials of oseltamivir. This may have compromised blinding of participants. For all but one of the zanamivir trials we did not have the certificates of analysis to enable us to reconstruct the appearance, taste and texture of the two principles.

Incomplete outcome data

In addition to the missing diary cards in three treatment trials (see [Results of the search](#) section), we were unable to identify all data for all outcomes in all oseltamivir trials and in eight of the zanamivir trials. For example, hospitalisations were not reported in zanamivir trials and inconsistently reported in oseltamivir trials. The relevant data in this review come from a table of hospitalisations sent to us by Roche in late 2013. In addition, in some trials we were unable to track individual participants through tables, narratives and individual listings. The issue of compliharms impeded the ascertainment of harms in oseltamivir treatment trials ([Appendix 1](#)). We had difficulty in following the logic of compliharms, even with access to full clinical study reports. The definition of adverse events in the RCTs of oseltamivir and zanamivir is different from the ordinary definition of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2D guideline, which is as follows: "An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product". (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf accessed 27 December 2013).

As an example, the definition of adverse events in the [WV15671](#) study is as follows (PDF page 35): "following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event, however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness) and therefore do not appear as adverse events" and [WV15670](#): "**any adverse change from the subject's baseline (pre-treatment) condition**, which occurred during the course of the study after treatment had started, whether considered related to treatment or not". Treatment included **all** investigational agents (including

placebo and comparative agents) administered during the course of the study)" (our emphasis). As a consequence, adverse events that are similar to the symptoms of influenza (such as headache and mild gastrointestinal adverse events) tend to be excluded from the treatment trials.

We identified a report of a site inspection for the adult prophylaxis trial [WV15673/WV15697](#). The FDA carried out the inspection in September 2000 at various trial sites in the US including the West Virginia site (which was responsible for enrolling many hundreds of participants). An FDA official letter reported several violations including failure to report serious harms to the sponsor (Roche) as the protocol required and in addition stated: "... we view the statement in the payment section of the consent form used in the study that subjects '...will receive \$300.00 for participating in and completing the study. No payment will be made to you if you withdraw from the study for personal reasons...' to be an improper procedure. When subjects are to be paid for participating in a study, the payment should be prorated for the subject's actual participation in the study in order to avoid the possibility of coercion" ([FDA 2000e](#), PDF page 177). However, the FDA allowed the data (which had been published a year earlier in a prime journal) to stand in support of Roche's application for the prophylaxis indication. We do not know whether the participant contract was standard (i.e. whether the observation of possible improper procedures could be generalised to other sites and other trials), but the document cited by the FDA inspector is the subject of one of our (as yet unfulfilled) Freedom of Information (FOI) requests. The possibility of financial pressure, if confirmed, could seriously confound drop-out rates because of harms or any other causes in prophylaxis trials.

The significantly higher incidence of diarrhoea in placebo recipients of treatment trial [WV15671](#) was identified by the FDA reviewers who remarked "Diarrhea was reported more frequently among subjects receiving placebo than among subjects receiving Ro 64-0796 [oseltamivir]. Diarrhoea, although not specified as an inclusion criterion, has been documented to be a clinical manifestation of influenza infection. The reduction in the incidence of diarrhoea for the treatment groups compared with the placebo group could be considered as a possible treatment effect of Ro 64-0796" ([FDA 1999c](#)). However, according to the Japanese Summary Basis for Approval (JSBA) of oseltamivir capsules for prophylaxis, diarrhoea was reported more frequently in the oseltamivir arm (49/986) than in the placebo group (38/973) in the summarised table of adverse events from three trials ([WV15673/WV15697](#); [WV15708](#); [WV15825](#)). Our findings are inconsistent with the explanation by the FDA.

Selective reporting

All oseltamivir trials and almost half of the zanamivir trials had selected reporting. The oseltamivir trials showed a consistent trend of missing original protocols (except for [M76001](#)), changing outcome definitions while the trial was running, protocol amendments even after the trial had been completed, inconsistent approaches to outcome data collection, missing statistical analysis plans, missing date of unblinding and the use of self reported outcomes such as pneumonia ([M76001](#); [WV15670](#); [WV15671](#); [WV15707](#); [WV15730](#); [WV16277](#)). This represent 55% of pneumonia event data. As an example, in trial [WV15670](#), secondary illnesses were patient reported. The body of the clinical study report states that complications requiring antibiotic treatment were specified a

priori but even in the final version of the protocol, for which we have the full text, there is no predefined list of secondary illnesses (i.e. no mention of pneumonia, bronchitis, sinusitis or otitis in the protocol), nor did complications have anything to do with antibiotic treatment according to the protocol, nor does the Case Report Form mention specific secondary illnesses by name. Zanamivir trials reported outcomes not specified in the protocol provided.

We found evidence of possible selective reporting bias when we analysed the JSBA data on prophylaxis. The regulatory data reports tables for individual trials as well as 10 pages of summarised tables for three trials of prophylaxis ([WV15673/WV15697](#); [WV15708](#); [WV15825](#)). Tables for individual trials include data for high-dose arms but report few psychiatric adverse events overall. However, the summarised tables list a variety of psychiatric adverse events including psychotic and suicidal adverse events, but not adverse events from the high-dose group. As a preliminary exploratory analysis, we combined the following suspected serious adverse events collectively: hallucination and delusion that are classified grade 3 (serious) by the National Cancer Institute–Common Toxicity Criteria Version 2.0 (NCI-CTC V2.0), psychosis (hallucination and delusion are the two major symptoms of this disease), suicidal attempt that is classified grade 3 (serious) by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (CTCAE V4.0) and hostility that includes aggression, hostility, violence, murder and commonly considered as serious events though not listed in the NCI-CTC V2.0 or CTCAE V4.0. Numbers of suspected serious psychotic/suicidal adverse events (including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide) were five in the oseltamivir group and zero in the placebo group during the on-treatment period. When the off-treatment period data are added the total was eight versus one. The prophylaxis programme is crucial in understanding the harms profile of the drug as the potential for harms witnessed to be confounded by the apparently numerous symptoms and signs of influenza infection is far less, as many participants do not become infected with influenza. This makes a causality assessment more straightforward.

Other potential sources of bias

All but three of the oseltamivir treatment trials were under-recruited. Several of the zanamivir trials were also under-recruited. We noted the use of different relief medication across different centres within the same trial and in one zanamivir trial ([NAI30031](#)), according to the protocol participants receiving antibiotics for bacterial respiratory tract infection should have been excluded but in the trial this did not happen. In the zanamivir trial [NAI30034](#), the definition of "confirmed influenza" was amended after protocol closure.

We also noted several other items that were not included in all full clinical study reports:

- Study protocols dated prior to participant enrolment (missing for many oseltamivir trials).
- Certificates of analysis for the intervention/placebo preparations.

- Patient enrolment dates explicitly reported (only trial inception and cessation dates are given; in zanamivir trials these are partially redacted).
- Explicitly reported date of trial unblinding. We frequently noted the statement "the database was authorized on xxxx" to identify the unblinding date but an explicit date is important to report. In some cases, the date of unblinding was reported but the actual date within the month was redacted. This practice also applied to zanamivir protocol amendments.
- Authorship and accountability for the writing of the clinical study reports.
- Statistical analysis plans in some cases.
- Patient consent forms (missing from most zanamivir trials).
- Patient information form (missing from most zanamivir trials).
- List of randomisation codes (variably included).
- Case report form templates in zanamivir trials do not allow for determining who completes the form (patient or clinician).
- Core data sheet.

Other important documents that we did not have included:

- Study manual of procedures.
- Minutes of safety data monitoring committee meetings.

The placebo interventions in both sets of trials may have contained active substances. The placebo for zanamivir trials contained lactose powder, which can potentially cause bronchospasm, while the placebo for oseltamivir trials contained dehydrocholic acid and dibasic calcium phosphate dehydrate, which can cause gastrointestinal symptoms.

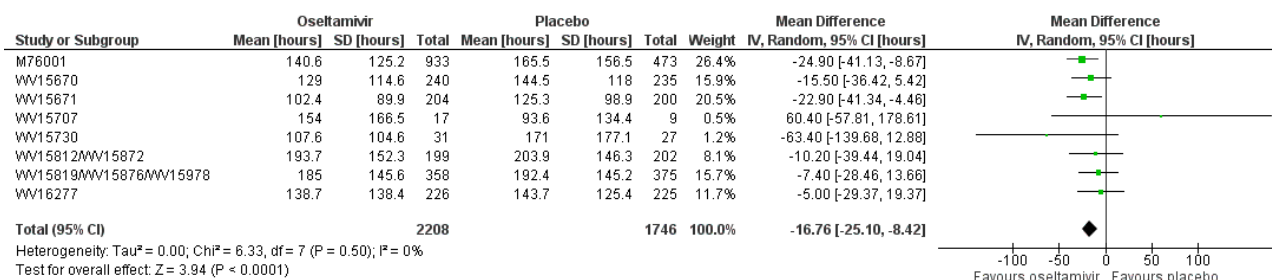
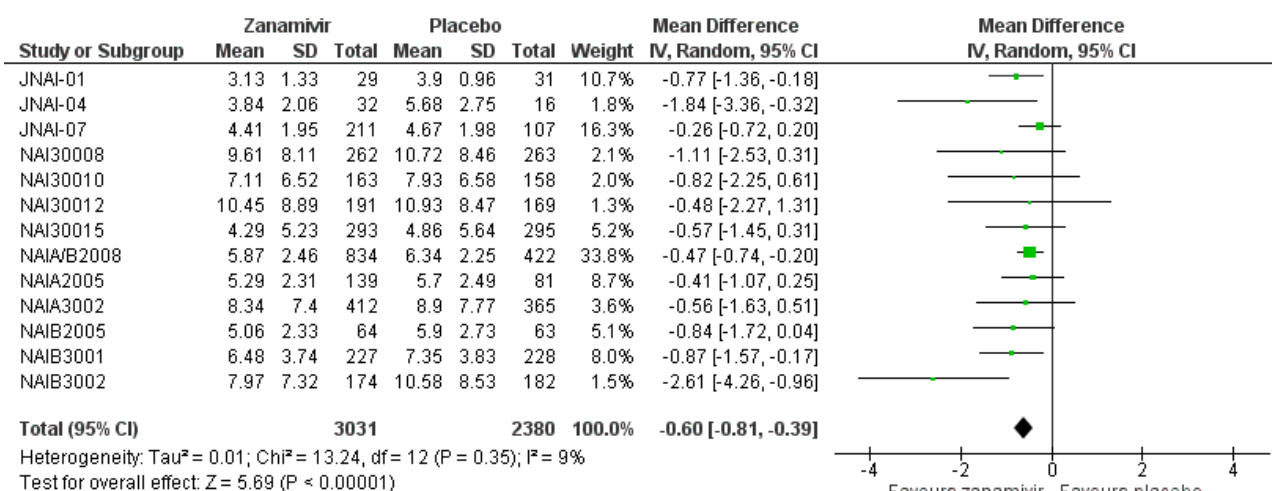
Data on participants by influenza-infected status (in treatment trials) and for participants with influenza-like illness (in prophylaxis trials) were not reported in the oseltamivir clinical study reports.

Finally, data on the effects of rescue or relief medication (mainly paracetamol/acetaminophen) were incomplete in clinical study reports of oseltamivir trials and not reported separately in all zanamivir trials.

Effects of interventions

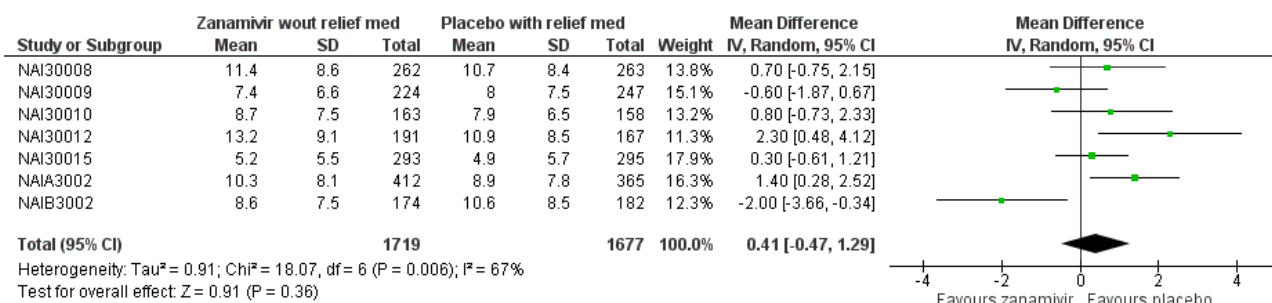
Analysis of time to first symptom alleviation

In adult treatment, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% confidence interval (CI) 8.4 to 25.1 hours, I^2 statistic = 0%), representing a 10% reduction from 7 days to 6.3 days ([Analysis 1.1](#); [Figure 4](#)). There was no significant effect in asthmatic children: increased by 5.2 hours (95% CI 11.1 hours lower to 21.4 hours higher, I^2 statistic = 0%). But there was an effect in otherwise healthy children, based on one trial: 29 hours, 95% CI: 12 to 47 hours, P = 0.001). ([Analysis 1.46](#)). Zanamivir reduced time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days, I^2 statistic = 9%), which equates to a 14.4 hours (10%) reduction in symptoms from 6.6 days to 6.0 days ([Analysis 3.1](#); [Figure 5](#)). There was no significant effect in children: time to first alleviation of symptoms was 1.08 days lower in the zanamivir group (95% CI 2.32 lower to 0.15 days higher, I^2 statistic = 72%) ([Analysis 3.14](#)).

Figure 4. Forest plot of comparison: 1 Oseltamivir versus placebo for treatment, outcome: 1.1 Time to first alleviation of symptoms in adult treatment (ITT population) [hours].**Figure 5. Forest plot of comparison: 3 Zanamivir versus placebo for treatment, outcome: 3.1 Time to first alleviation of symptoms in adult treatment (days).**

In eight zanamivir trials that reported on use of relief medication, in all participants the median days to alleviation in both the placebo and the treatment arms was less when compared to those who did not use relief medications (Table 6). In seven zanamivir trials, time to first alleviation of symptoms was also reported with and without rescue medication. Using these data we were able to compare zanamivir without rescue medication with placebo with rescue

medication. Overall there was a non-significant 0.41 day decrease (95% CI 0.47 days lower to 1.29 days higher, I^2 statistic = 67%) in time to first alleviation of symptoms in the placebo with rescue medication group, suggesting that zanamivir itself is no better than rescue medication and possibly even less effective, although the varying levels of use of rescue medication in the seven trials did give rise to large heterogeneity (Analysis 3.68; Figure 6).

Figure 6. Forest plot of comparison: 3 Zanamivir versus placebo for treatment, outcome: 3.68 Time to first alleviation of symptoms in adults with/without relief medication [days].

In subgroup analysis of time to first alleviation of symptoms in adults by infection status, we found no evidence of a difference in

treatment effect for zanamivir on the influenza-infected subgroup compared to the non-influenza-infected subgroup ($P = 0.53$). The

treatment effect was 0.67 days (95% CI 0.35 to 0.99 days, I^2 statistic = 17%) for influenza-infected patients and 0.52 days (95% CI 0.18 to 0.86 days, I^2 statistic = 0%) for non-influenza-infected patients (Analysis 3.69).

Analysis of hospitalisations

In oseltamivir treatment of adults, there was no significant difference in hospitalisation rate between treatment groups (risk ratio (RR) 0.92, 95% CI 0.57 to 1.50, I^2 statistic = 0%) (Analysis 1.2), or in treatment of children (RR 1.92, 95% CI 0.70 to 5.23, I^2 statistic = 0%) (Analysis 1.47), with wide CIs; or in prophylaxis (RR 1.14, 95% CI 0.66 to 1.94, I^2 statistic = 0%) (Analysis 2.7). Data on hospitalisations for the zanamivir studies were not reported.

Analysis of influenza complications

Pneumonia

In adult treatment trials, oseltamivir significantly reduced self reported, investigator-mediated, unverified pneumonia (RR 0.55, 95% CI 0.33 to 0.90, I^2 statistic = 0%; risk difference (RD) 1.00%, 95% CI 0.22 to 1.49; number needed to treat to benefit (NNTB) = 100, 95% CI 67 to 451) in the treated population. The effect was significant in the six trials that collected data on non-specific adverse events

or secondary/intercurrent illness forms (RR 0.44, 95% CI 0.22 to 0.88, I^2 statistic = 0%; RD 0.99%, 95% CI 0.21 to 1.38; NNTB = 101, 95% CI 73 to 470). However, it was not significant in the five trials (two clinical study reports) that used more detailed diagnostic data collection forms, and in no studies that reported on radiological confirmation of pneumonia (Figure 7; Analysis 1.17). There was no significant effect on pneumonia in children (RR 1.06, 95% CI 0.62 to 1.83, I^2 statistic = 0%) (Analysis 1.52). In two zanamivir adult trials (NAI30012; NAI30015), pneumonia reporting was based on a stricter definition of X-ray confirmation and there was also no significant treatment effect (RR 1.02, 95% CI 0.35 to 3.02, I^2 = 39%) (Analysis 3.3). In nine zanamivir trials (NAI30008; NAI30010; NAI30011; NAIA/B2008; NAIA2005; NAIA3002; NAIB2007; NAIB3001; NAIB3002), pneumonia was a self reported, investigator-mediated, unverified outcome (Figure 8; Figure 9). Overall, there was no significant effect of zanamivir on mixed verified and unverified pneumonia in adult treatment (RR 0.90, 95% CI 0.58 to 1.40, I^2 statistic = 0%) (Analysis 3.2). Analysis 4.5 shows that in prophylaxis trials, zanamivir reduced the risk of self reported, investigator-mediated, unverified pneumonia in adults (RR 0.30, 95% CI 0.11 to 0.80, I^2 statistic = 0%; RD 0.32%, 95% CI 0.09 to 0.41; NNTB = 311, 95% CI 244 to 1086).

Figure 7. Forest plot of comparison: 1 Oseltamivir versus placebo for treatment, outcome: 1.17 Complications: pneumonia in adult treatment.

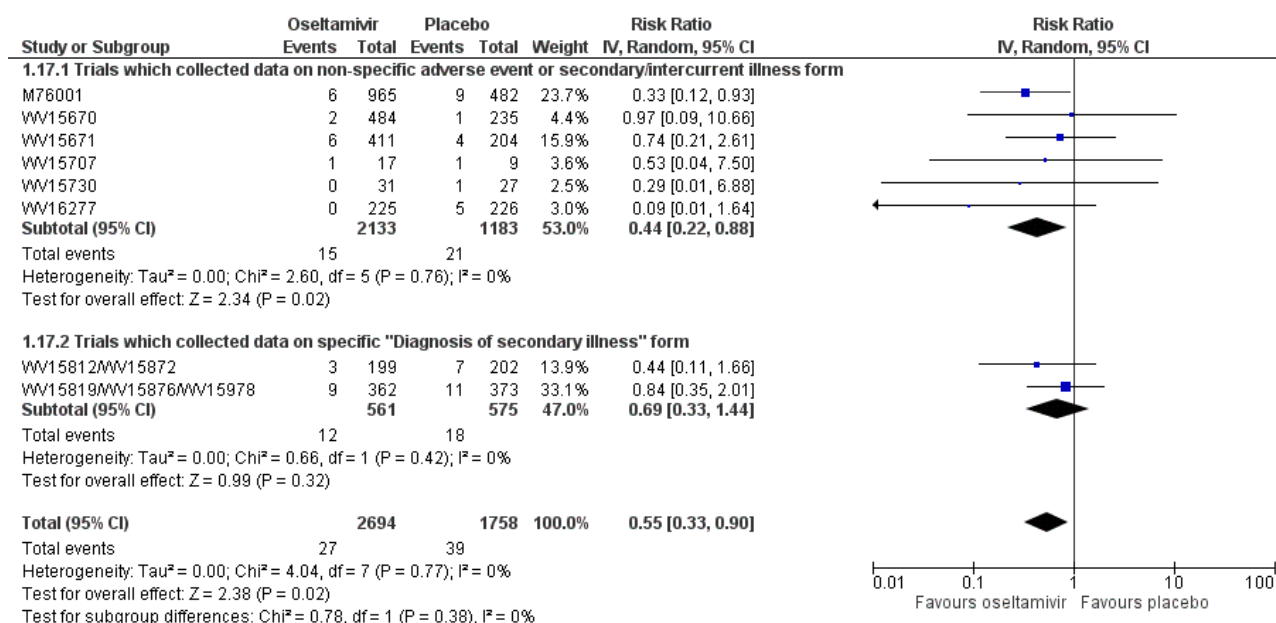


Figure 8. Example Diary card from case-report form for Zanamivir trial

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Protocol code: NAIB3002 Session number: [] Subject initials: [] Subject number: []

DAY 6
Post-Treatment Visit

Date of assessment: [] [] [] [] VSDT (D7) [R]

Diary Card [REDACTED] 9:56 AM A1

Was the subject's Diary Card (Days 1-5) reviewed for accuracy and completeness? Yes ☐ No ☐
Please resolve any discrepancies in the Diary Card with the subject. OCCURS (A1) [R] [V-YES/NO]

Global Assessment of Symptoms SEVERE (A1) [R]

How would you rate the subject's overall influenza-like symptoms? [V-SEVERE]

None ☐ Mild ☐ Moderate ☐ Severe ☐

Influenza Complications FULL CP (A1) [R] [SYNALL]

Has the subject experienced any complications, since the last visit, as a result of their influenza-like illness? Yes ☐ No ☐
If YES, please ✓ ALL complications below: CPTX (A2) [R] [CPTX]

Pulmonary Pneumonia ☐ Exacerbation of COPD* ☐ Exacerbation of asthma ☐ Bronchitis ☐ Respiratory failure ☐ Other ☐ Specify: CPTX (A6b) [R]

Cardiovascular Congestive heart failure ☐ Angina ☐ Myocardial infarction ☐ Arrhythmia ☐ Other ☐ Specify: CPTX (A6b) [R]

*COPD = Chronic Obstructive Pulmonary Disease

Ear/Nose/Throat Infections Sinusitis ☐ Otitis ☐ Pharyngitis ☐ Other ☐ Specify: CPTX (A6b) [R]

Other Complications Other ☐ Specify: CPTX (A6b) [R]

Record ALL complications of influenza on the NON-SERIOUS ADVERSE EVENT page or SERIOUS ADVERSE EVENT page.
Any medication used to treat an Influenza Complication should be recorded on the Concurrent Medications page.

8

Figure 9. Example Diary card from case-report form for Zanamivir trial (cont)

GlaxoWellcome		Confidential	
Product code NAIB3002	Session number [] [] [] [] [] [] [] []	Subject initials [] [] [] [] [] [] [] []	Subject number [] [] [] [] [] [] [] []
DAY 28 Follow-up Visit			
Date of assessment		YES? P. 8.	
[] [] day	[] [] month	[] [] year	VSPT (A1) [R]
Diary Card			
Was the subject's Diary Card for Days 6-14 and 15-28 (if applicable), reviewed for accuracy and completeness? Yes ☐ No ☐			
Please resolve any discrepancies in the Diary Card with the subject.			
Influenza Complications			
Has the subject experienced any new complications, since the last visit, as a result of their influenza-like illness? Yes ☐ No ☐			
If YES, please ✓ ALL complications below: CPTX (A3) [R] VCAPCTY			
Pulmonary		Cardiovascular	
Pneumonia ☐		Congestive heart failure ☐	
Exacerbation of COPD* ☐		Angina ☐	
Exacerbation of asthma ☐		Myocardial infarction ☐	
Bronchitis ☐		Arrhythmia ☐	
Respiratory failure ☐		Other ☐ Specify: CPTX (A66)	
Other ☐ Specify: CPTX (A66) [R]			
*COPD = Chronic Obstructive Pulmonary Disease			
Ear/Nose/Throat Infections		Other Complications	
Sinusitis ☐		Other ☐ Specify: CPTX (A66)	
Otitis ☐			
Pharyngitis ☐			
Other ☐ Specify: CPTX (A66) [R]			
Record all complications of influenza on the NON-SERIOUS ADVERSE EVENT page or SERIOUS ADVERSE EVENT page. Any medication used to treat an Influenza Complication should be recorded on the Concurrent Medications page.			

In meta-regression of 'pneumonia' based on 32 studies, treatment effects were not statistically different by age group ($P = 0.22$), drug ($P = 0.89$) or indication ($P = 0.14$). However, treatment effects were statistically different by method of diagnosis ($P = 0.025$). For unclear objective diagnosis of pneumonia, the treatment effect was RR 0.51 (95% CI 0.35 to 0.75, I^2 statistic = 0%), whereas for objective diagnosis data collection of pneumonia, the treatment effect was 1.01 (95% CI 0.69 to 1.47, I^2 statistic = 0%). A subgroup analysis of pneumonia for all 32 studies by method of diagnosis is shown in [Analysis 5.1](#). Please note that estimates in the subgroup analysis are slightly different to those obtained in meta-regression due to the different methodologies.

Serious complications and study withdrawals

In oseltamivir trials, treatment did not significantly affect complications classified as serious or those that led to withdrawal from the trial in adults (RR 0.91, 95% CI 0.40 to 2.06, I^2 statistic = 0%) (Analysis 1.20) or in children (RR 1.98, 95% CI 0.58 to 6.72, I^2 statistic = 0%) (Analysis 1.55). This outcome could not be assessed in oseltamivir prophylaxis due to an insufficient number of events. There was no significant effect of zanamivir, in adult treatment, in reducing the risk of any complication classified as serious or which led to study withdrawal (RR 1.10, 95% CI 0.46 to 2.63, I^2 statistic = 0%) (Analysis 3.7) or in prophylaxis (RR 1.09, 95% CI 0.36 to 3.26, I^2

statistic = 0%) ([Analysis 4.8](#)). This outcome could not be assessed in children due to an insufficient number of events.

Bronchitis, sinusitis and otitis media

Neither zanamivir ([Analysis 4.6](#); [Analysis 4.7](#)) nor oseltamivir ([Analysis 2.8](#); [Analysis 2.9](#)) significantly reduced the risk of bronchitis or sinusitis in prophylaxis trials. In adults, treatment with oseltamivir did not significantly reduce the risk of bronchitis (RR 0.75, 95% CI 0.56 to 1.01, I^2 statistic = 36%) ([Analysis 1.16](#)), sinusitis (RR 1.03, 95% CI 0.76 to 1.40, I^2 statistic = 0%) ([Analysis 1.18](#)) or otitis media (RR 1.11, 95% CI 0.57 to 2.15, I^2 statistic = 0%) ([Analysis 1.19](#)). The result for bronchitis was sensitive to the methods used, as a fixed-effect analysis showed a significant effect ($P = 0.02$). Oseltamivir did not significantly affect complications in treatment of children ([Analysis 1.52](#); [Analysis 1.50](#); [Analysis 1.53](#)), including otitis media (RR 0.80, 95% CI 0.62 to 1.02, I^2 statistic = 0%) ([Analysis 1.51](#)).

Treatment with zanamivir significantly reduced the risk of bronchitis in adults (RR 0.75, 95% CI 0.61 to 0.91, I^2 statistic = 0%; RD 1.80%, 95% CI 0.65 to 2.80; NNTB = 56, 95% CI 36 to 155) (Analysis 3.4), but did not reduce the risk of sinusitis (Analysis 3.5) or otitis media (Analysis 3.6). In children, zanamivir treatment did not significantly reduce the risk of sinusitis (RR 0.87, 95% CI 0.12 to

6.45, I^2 statistic = 40%) (Analysis 3.17) or otitis media (RR 1.00, 95% CI 0.59 to 1.72, I^2 statistic = 0%) (Analysis 3.18).

See Table 1 for a summary of the methodology used for collecting and assessing complications in oseltamivir treatment trials. See Table 7 for the overall results for oseltamivir in adults and Table 8 for children. See Table 9 for the overall results for zanamivir in adults and Table 10 for children.

Analysis of influenza outcomes in prophylaxis studies

Symptomatic influenza was lower in the oseltamivir arms compared to placebo in studies of prophylaxis (RR 0.45, 95% CI 0.30 to 0.67, I^2 statistic = 0%; RD 3.05%, 95% CI 1.83 to 3.88; NNTB = 33, 95% CI 26 to 55) (Analysis 2.1); but there were no differences for all other influenza outcomes including overall influenza-like-illness reported as an adverse event on-treatment. In household prophylaxis, one small study with missing outcome data and selective reporting, including 405 participants, showed a significant reduction of symptomatic influenza in the oseltamivir arm compared to placebo (RR 0.20, 95% CI 0.09 to 0.44; RD 13.6%, 95% CI 9.52 to 15.47) (Analysis 2.3), but in the same study there was no significant reduction in asymptomatic influenza (RR 1.14, 95% CI 0.39 to 3.33) (Analysis 2.4). Asymptomatic influenza was not significantly reduced and there was no non-influenza, influenza-like illness reported throughout the study period.

In prophylaxis trials we could not analyse effects on influenza-like illness because of a lack of definition in the clinical study reports. However, using our definition (see methods), oseltamivir did not reduce influenza-like illness in participants (RR 0.95, 95% CI 0.86 to 1.06).

The Roche trial programme assessing the effects of oseltamivir in post-exposure prophylaxis (PEP) submitted to the FDA on 22 May 2000 consisted of two trials: WV15799 and WV16139. We included only trial WV15799 because WV16139 was not placebo-controlled. WV15799 was a double-blind, cluster-randomised trial in which contact clusters of index cases were randomised to oseltamivir 75 mg a day or placebo for seven days. The manufacturer concluded that the trial proved that oseltamivir could prevent influenza in contacts by interrupting transmission from index cases. Interruption of transmission has two components: reduction of viral spread from index cases (measured by nasal shedding of influenza viruses) and prevention of onset of influenza in contacts measured with a mixture of symptoms and signs and 'laboratory confirmation' (i.e. viral culture from the upper airways and/or at least a four-fold rise in antibody titres measured between baseline and two to three weeks later). The design of the WV15799 is weak. All index cases were left untreated except for a paracetamol rescue pack, making it impossible to assess the effect of oseltamivir on nasal avoidance of index cases. Nasal viral avoidance was measured only in symptomatic participants thereby missing out on potential asymptomatic infected people.

Zanamivir similarly significantly reduced the risk of symptomatic influenza for individuals (RR 0.39, 95% CI 0.22 to 0.70, I^2 statistic = 45%; RD = 1.98%, 95% CI: 0.98 to 2.54; NNTB = 51, 95% CI 40 to 103) (Analysis 4.1), as well as households (RR 0.33, 95% CI 0.18 to 0.58, I^2 statistic = 40%; RD = 14.84%, 95% CI 12.18 to 16.55, NNTB = 7, 95% CI 6 to 9) (Analysis 4.3). However, it did not reduce the risk of asymptomatic influenza in the prophylaxis of individuals (RR 0.97, 0.76 to 1.24, I^2 statistic = 0%) (Analysis 4.2) or asymptomatic

individuals in post-exposure prophylaxis of households (RR 0.88, 95% CI 0.65 to 1.20, I^2 statistic = 0%) (Analysis 4.4). See Table 11 for the overall results for oseltamivir in adults and Table 9 for children. See Table 12 and Table 13 for the overall results for zanamivir in adults and Table 14 for children.

Analysis of harms

Oseltamivir treatment

Nausea, vomiting and diarrhoea

Oseltamivir in the treatment of adults is associated with increased risk of nausea (RR 1.57, 95% CI 1.14 to 2.15, I^2 statistic = 43%; RD 3.66%, 95% CI 0.90 to 7.39; number needed to treat to harm (NNTH) = 28, 95% CI 14 to 112) (Analysis 1.5) and vomiting (RR 2.43, 95% CI 1.75 to 3.38, I^2 statistic = 12%; RD 4.56%, 95% CI 2.39 to 7.58; NNTH = 22, 95% CI 14 to 42) (Analysis 1.6). It is associated with a decreased risk of diarrhoea (RR 0.67, 95% CI 0.46 to 0.98, I^2 statistic = 44%; RD 2.33%, 95% CI 0.14 to 3.81; NNTB = 43, 95% CI 27 to 709) (Analysis 1.7) when compared to placebo during on-treatment periods. Both nausea and vomiting were associated with significant heterogeneity where treatment effects appeared larger in otherwise healthy adults compared to the elderly and the chronically ill. However, one trial of otherwise healthy adults also showed smaller effects (WV16277). Vomiting was more common in those children on oseltamivir treatment compared to those on placebo (RR 1.70, 95% CI 1.23 to 2.35, I^2 statistic = 0%; RD 5.34%, 95% CI 1.75 to 10.29; NNTH = 19, 95% CI 10 to 57) (Analysis 1.63).

Cardiac effects

The cardiac effects of oseltamivir are unclear. Exposure to oseltamivir may reduce cardiac general events compared to placebo (RR 0.49, 95% CI 0.25 to 0.97, I^2 statistic = 0%; RD 0.68%, 95% CI 0.04 to 1.00; NNTB = 148, 95% CI 101 to 2509), excluding WV16277 in which ECG was included in the safety parameters (Analysis 1.27). However, exposure to oseltamivir may increase QTc prolongation (including borderline) as reported in trial WV16277 (RD 4.0%, 95% CI 0.71 to 7.30; NNTH = 25, 95% CI 14 to 140) compared to placebo during on-treatment periods.

Psychiatric effects

In treatment trials, there was no significant increase in risk between oseltamivir and on-treatment psychiatric adverse events overall (Analysis 1.32). However, there was a dose-response effect in the two "pivotal" treatment trials. In the identically designed trials WV15670 and WV15671 there were two active treatment groups: 150 mg (standard dose) and 300 mg (high dose) oseltamivir per day. In the dose-response analysis there was an increased risk of psychiatric body system adverse events over the entire follow-up period ($P = 0.038$ based on likelihood ratio test). In trial WV15670, the event rates were: 1/204, 1/206 and 4/205 in the placebo, 75 mg and 150 mg arms respectively, whereas trial WV15671 had rates of 2/235, 0/242 and 5/242, respectively.

Effect on antibodies (post-protocol hypotheses)

The proportion of patients being diagnosed as influenza-infected in oseltamivir treatment of adults was significantly lower in the treated compared to the control group (RR 0.95, 95% CI 0.91 to 0.99, I^2 statistic = 0%) (Analysis 1.3). The proportion of patients with four-fold increases in antibody titre was significantly lower in the treated group compared to the control group (RR 0.92, 95% CI 0.86 to 0.97, I^2

statistic = 0%) (Analysis 1.4). This represents an absolute difference of 5% between treatment groups. There was a lower proportion of children on oseltamivir with a four-fold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00, I^2 statistic = 0%) (Analysis 1.49).

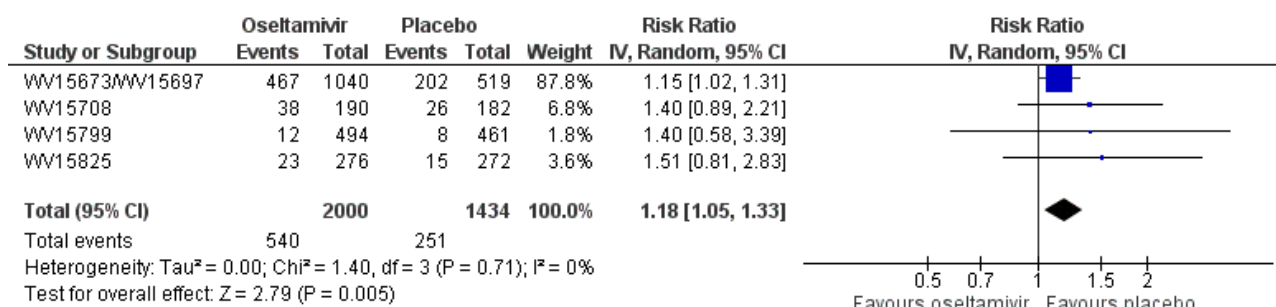
Oseltamivir prophylaxis

Headaches and nausea

In oseltamivir prophylaxis, there was an increased risk of headaches on-treatment (RR 1.18, 95% CI 1.05 to 1.33, I^2 statistic =

0%; RD 3.15%, 95% CI 0.88 to 5.78; NNTH = 32, (95% CI 18 to 115) (Analysis 2.19; Figure 10) and nausea on-treatment (RR 1.96, 95% CI 1.20 to 3.20, I^2 statistic = 49%; RD 4.15%, 95% CI 0.86 to 9.51; NNTH = 25, 95% CI 11 to 116) (Analysis 2.20). There was also a dose-response effect for headaches in study WV15673/WV15697 ($P = 0.013$ based on likelihood ratio test), where on-treatment rates were: 202/519, 225/520 and 242/520 in the placebo, standard-dose and high-dose arms, respectively.

Figure 10. Forest plot of comparison: 2 Oseltamivir versus placebo for prophylaxis, outcome: 2.19 Adverse events: headache in adult prophylaxis (on-treatment).



Psychiatric effects

Figure 11 (Analysis 2.54) shows that in prophylaxis trials of oseltamivir there was a significant increase in patients with psychiatric adverse events over the on- and off-treatment periods (RR 1.80, 95% CI 1.05 to 3.08, I^2 statistic = 0%; RD 1.06%, 95%

CI 0.07 to 2.76; NNTH = 94, 95% CI 36 to 1538). Initial analysis of patients with psychiatric adverse events in the on-treatment period showed a borderline statistically significant result ($P = 0.06$), hence we conducted sensitivity analysis using Peto's method ($P = 0.05$) as well as the analysis reported in Figure 11.

Figure 11. Forest plot of comparison: 2 Oseltamivir versus placebo for prophylaxis, outcome: 2.54 Adverse events: psychiatric body system in adult prophylaxis (on- and off-treatment).

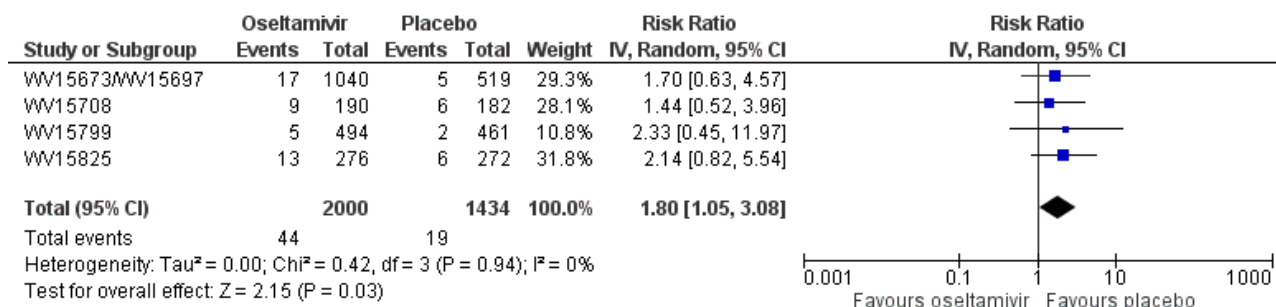


Table 15 shows a summary of all psychiatric adverse events in oseltamivir prophylaxis trials. Of particular note was an oseltamivir patient in study WV15825 who had severe confusion on day 27 and was hospitalised. On day 28 the patient was taken off medication and the event resolved. On day 29 the patient was discharged from hospital and subsequently resumed medication. However, confusion reappeared on day 32. The initial event was misclassified in the clinical study report as "mental impairment" but has since been corrected in an erratum published in the same journal that published the original trial manuscript (Gravenstein 2013; Peters 2001).

Renal effects

There was a non-significant increase in renal events on-treatment (RR 3.17, 95% CI 0.96 to 10.49, I^2 statistic = 0; RD 0.67%, 95% CI -2.93 to 0.01; NNTH = 150, 95% CI NNTH 35 to ∞ to NNTB > 1000) (Analysis 2.38). However, in sensitivity analysis using Peto's method the result for renal events was statistically significant ($P = 0.02$).

Zanamivir

Serious adverse events

There was no significant effect on serious adverse events in adult treatment trials (RR 0.86, 95% CI 0.49 to 1.50, I^2 statistic = 0%) (Analysis 3.11).

Nausea, vomiting and diarrhoea

In treatment trials, there was no significant effect on diarrhoea in adults (RR 0.87, 95% CI 0.66 to 1.14, I^2 statistic = 5%) (Analysis 3.33) or headache (RR 0.84, 95% CI 0.60 to 1.18, I^2 statistic = 0) (Analysis 3.35). However, during the on-treatment phase, nausea and vomiting were significantly less frequent in the zanamivir arm (RR 0.60, 95% CI 0.39 to 0.94, I^2 statistic = 0%; RD 1.63%, 95% CI 0.24 to 2.48%; NNTB = 62, 95% CI 41 to 411) (Analysis 3.32).

Renal, psychiatric and other harms

There was no significant effect observed on the renal system (RR 0.84, 95% CI 0.41 to 1.72, I^2 statistic = 0%) (Analysis 3.45), or the psychiatric system (RR 1.16, 95% CI 0.57 to 2.38, I^2 statistic = 0%) (Analysis 3.48). In adult treatment trials of zanamivir, there was no significantly increased risk of any other reported adverse events and there was no significant increase in adverse effects observed in prophylaxis trials, including psychiatric (Analysis 4.29) and renal effects (Analysis 4.30) on-treatment. There was no significant increase in harms associated with zanamivir treatment of children but data were sparse.

Effect on antibodies

There was no significant effect of zanamivir treatment on influenza diagnosis (Analysis 3.8) or probability of a four-fold increase in antibody titre (Analysis 3.9; Analysis 3.10).

Deaths

In oseltamivir treatment trials, there was one death overall. This event occurred due to acute respiratory syndrome in a placebo patient without influenza in study WV15812/WV15872. In prophylaxis trials, there were four deaths in total, all in elderly patients, with two in the placebo group and two in the oseltamivir group. Causes of death were reported as two cancers, one myocardial infarction and one intestinal perforation. However, for both deaths in the oseltamivir arms the participants experienced acute renal failure on-treatment prior to death.

There were eight deaths in total in the zanamivir trials. Six of the deaths were caused by neoplasias or cardiovascular events in elderly patients with multiple pathologies. However, two deaths were reported as due to influenza A pneumonia. One participant was on inhaled rimantadine plus placebo and the other on zanamivir.

The results of post-protocol hypotheses are in Appendix 10.

DISCUSSION

Oseltamivir and zanamivir have small, non-specific effects on reducing time to alleviation of influenza-like illness symptoms in adults, but not in asthmatic children. Using either drug as prophylaxis reduces the risk of developing symptomatic influenza. Treatment trials with oseltamivir or zanamivir do not settle the question of whether complications of influenza such as pneumonia are reduced, because of a lack of diagnostic definitions. Use of oseltamivir increases the risk of adverse effects such as nausea, vomiting, psychiatric effects and renal events in adults and the risk of vomiting in children. The lower bioavailability may explain the lower toxicity of zanamivir compared to oseltamivir. The influenza virus-specific mechanism of action proposed by the producers does not fit the clinical evidence.

Reconstructing trial lists and indexing regulatory comments

Calls for incorporating unpublished data to supplement published trial data in systematic reviews and meta-analyses highlight deficiencies in the current methods for obtaining the most complete understanding of a drug's effects (Godlee 2010). Our methodological approach entailed comprehensive searching of unpublished sources, with a particular emphasis on obtaining unpublished and internal reports from drug manufacturers intended for regulatory submission and comments from national regulatory bodies. Our decision not to use published evidence as a basis for trial appraisal and data extraction meant that we had to reconcile and synthesise information from multiple unpublished sources. We had to devise a new method of searching, indexing, retrieving and reviewing trial data and to combine this understanding with regulatory comments to produce an informative review. The first step in this process entailed the need to develop our own reconstruction of the trial programme without initial help from outside sources. The reconstructed list of trials and then programmes took a whole-time-equivalent (WTE) researcher 20 days to compile. Due to the complexity of the task we suggest that in the future some of the essential phases, such as trial ID checking, be conducted in pairs.

One of the comments received on our protocol suggested that discrepancies between published and unpublished versions of the same data set could be due to mistakes in the non-peer reviewed, unedited clinical study reports (which may be corrected by the time of publication). Our experience, especially with the non-reporting of serious adverse events, points to the opposite being the case (Jefferson 2011b). Considering the fact that unintentional errors can occur, we believe the response should not be a resort to published papers as 'most accurate' and best unit of analysis, but rather that clinical study reports - as by far the most comprehensive record of a trial - remain the key unit of analysis, with the expectation that they be amended and kept as accurate as possible over time, with complete documentation of reasons for any amendments. We believed that the results of our review would be undermined without accessing a more complete body of evidence that we knew to be outside the public domain.

In theory, trial registers would be expected to provide a comprehensive picture of a drug's trial programme. However, registers were not our primary instruments to reconstruct zanamivir and oseltamivir trial programmes. Both drugs' programmes were mainly run in the late 1990s, before trial registration became the norm. In addition, registers may suffer from some of the problems that we were trying to address. Bourgeois 2011 audited entries for 546 trials of five major classes of drugs on ClinicalTrials.gov, the biggest prospective register of clinical trials, and found evidence of risk of reporting bias and delay in reporting of results. Another review of 152 trials found that the description of 123 (or 81%) of the trials in the sample had been changed in at least one key element in the time between registration and publication. The most frequent changes regarded outcomes (Huic 2011). Despite the current limits of registers, both specifically to this review and in the way they are run and updated, we believe that registers are an obvious first choice to start reconstruction of trials programmes. Searching for unpublished material has not yet become standard practice in conducting Cochrane reviews (Van Driel 2009), and is currently variably reported (Gherzi 2010).

The indexing and review of regulatory files was also a very laborious task. It took a WTE researcher three days to review the US Food and Drug Administration (FDA) regulator's comments and gain a basic understanding of the content. Four additional days were needed to read and annotate the FDA zanamivir files and 28 days for reading and annotating the oseltamivir files and building the Table of Contents-Evidence (TOCE). The exercise had to be repeated several times to cross-check content and expand annotations. Construction of the Table of Contents (TOC) was laborious. A first attempt at electronic mapping the TOC content took 12 and 8 hours respectively for the FDA and National Institute for Health and Clinical Excellence (NICE) regulatory documents. This was carried out using the Adobe Acrobat Optical Character Recognition (OCR) search facility, which enabled mapping of citation counts by document and by trial ID. Initially we used the trial prefix followed by the serial number ('WV15670') as ID. This procedure, however, had one major drawback linked to the nature of regulatory documents. As regulatory documents consist of notes, correspondence and reviews, the same trial is cited in a non-standardised way. For example, trial WV15670 is cited as 'WV15670' 15 times, as 'WV_15670' 12 times and simply as '15670' 19 times). Thorough searches must be conducted using all the different terms. As this can be very time-consuming, we decided to compare an Acrobat search with a Boolean string strategy containing all possible citation formats (for example, WV15758 OR WV 15758 OR Trial 15758 OR Trial15758 OR Trials 15758 OR Trials15758 OR 15758 OR study 15758 OR study15758) (this is logically equivalent to 'WV 15758 OR WV 15758') with a term-by-term search (i.e. separately searching for WV15758 and then for WV 15758 and so on). We reasoned that if the yield were comparable, the Boolean strategy would have been faster. The yield of citations of the two strategies was the same for six of seven 'tracker' studies but use of a Boolean string was considerably faster (an average of 3 versus 14 hours) than the term-by-term strategy. The National Institute of Clinical Excellence (NICE) submission citations took two hours to list in a TOC using a Boolean strategy. We adopted the Boolean search strategy to construct our TOC. Ultimately it is possible that a search with the trial numerals ('15670') may be sufficient to identify the vast majority of citations. To validate this method of searching further our methods should be repeated on other sets of regulatory documents.

Once we had reconstructed the trial programmes we submitted the results to GlaxoSmithKline (GSK) and Roche for their input. We received detailed feedback from both but as late as 2011 Roche's list of trials was incomplete. Despite the laboriousness of the methods, we believe we ended up with a far more comprehensive and less biased set of evidence than that available through the current system of journal-based publications. This shift in our data synthesis paradigm was made necessary by the numerous and documented discrepancies between regulatory and published evidence and by the sizeable risk of publication bias of the oseltamivir trial programme. The importance of reconstructing the trial programme by first generating a complete trial list was further reinforced upon discovering bias and oversights in regulators' handling of the trial programme. Regulators focus on a few mutually agreed "pivotal" trials whose data analyses are replicated by the FDA but not by the European Medicines Agency (EMA). Both largely ignored trial M76001, the largest oseltamivir treatment trial conducted prior to initial registration of the drug (and still unpublished). While the manufacturer may not have offered it as a "pivotal" trial, far smaller and even ongoing studies were

included in the evidence base to support Roche's year 1999 New Drug Application number 021087 (Treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than two days). The depth of the EMA scrutiny is harder to assess as we could find no reports of trial site visits or of data analysis replication, but we identified a pooled analysis of treatment trials, very similar to the Kaiser 2003 analysis which formed the basis for the EMA conclusion that oseltamivir affected complications reported, for example, on EMA's 4 October 2012 Summary of product characteristics (SmPC) (<http://www.bmj.com/tamiflu/ema>). We requested Modules 3, 4 and 5 (individual listings, demographic data and the statistical analysis report) from the EMA. However, for most oseltamivir trials, the EMA do not have the relevant documents and neither apparently do National Competent Authorities (email from the EMA, 24 May 2011; email from Dutch regulator MEB, 20 July 2011). This means that the Modules do not appear to have been either submitted to or requested by regulators, raising questions as to the extent of scrutiny of the clinical trials during the regulatory review of oseltamivir in Europe.

Our new method

Reviewing huge quantities of complicated data and linked comments is a very difficult and delicate process. The main problem is not so much the appraisal following standard rules and possible synthesis of data (as when we review published information), but the reconstructions and logical threading of a trial programme generating huge amounts of data needing appraisal. Also the manufacturer's full regulatory submission, which may have even more information than a full clinical study report, remains confidential. Most of the essential data required are available in clinical study reports, together with masses of less important data, but as we have explained even in this case there may be important omissions, such as mislaid diary cards for follow-up. Manufacturers are under obligation to provide regulators with all data requested to enable them to reach a decision: in doing so they produce vast submissions. None of the authors (all experienced systematic reviewers) had any experience of reviewing regulatory information. Given the laborious and painstaking process we tried to identify a quicker and equally reliable way of reviewing regulatory information but could not find any obvious shortcuts. However, we believe that providing a critical overview of a trial programme rather than minute dissection of each trial is necessary. This can be done by identifying the important topics in the trial programme (such as the effects of the drug on symptoms, infection, complications, transmission and well-being) and following them throughout the programme, knitting the evidence into a coherent narrative. This includes carrying out a high-level overview of the mode of action of the drug in different populations for different indications. Understanding any drug's mode of action is core to correct reporting of its strengths and limitations. In addition, a large part of the regulatory submission is made up of chemistry, microbiological, animal model pharmacodynamic and pharmacokinetic studies, which are important for shedding light on the trial programme but which seldom feature in systematic reviews. We are unsure as to whether this information could be considered as core information but an exhaustive review of a trial programme should include reviews dedicated to such topics.

These methods were crucial in discovering major concerns in trial conduct and validity, including the lack of comparability between arms induced by subset analysis and by the randomisation-analysis fork, high positivity rate of influenza, high gastrointestinal events in the placebo arms, possibly active placebo content and possible procedural breaches several trials, which are concerning. Overall, the safest and more conservative option appears to carry out analyses on the basis of the intention-to-treat (ITT) population, in which units of randomisation and analysis are the same and many of the potential problems listed are either not present or minimised.

Our novel methodology remains a work in progress.

Regulatory comments

Reviewing regulatory comments was an essential way to deepen our understanding of the trial programme. From early on in our review we hoped that a close reading of regulatory material would allow us to understand the reason for discrepancies between US and European regulators' conclusions regarding the effects of oseltamivir, particularly (but not limited to) their purported effect on complications (Doshi 2009). We were interested in what led the FDA to have far more cautious and conservative statements - as witnessed in the Tamiflu product label and FDA letters - in comparison to European regulators. Our access to huge amounts of FDA regulatory data allowed for many insights but gave us little visibility of manufacturers' responses.

Some of the statements made by the manufacturer in the clinical study reports, and subsequently in contemporaneous publications and advertisements, appeared unsupported by the evidence provided at the time. The FDA drug regulatory reviewers' comments, although laborious to summarise and contextualise (because of the non-availability of the whole pharmaceutical submission), were confirmed by our reading of the clinical study reports. However, we were unable to find a statement explaining how the FDA reviewed each New Drug Application (NDA). FDA reviewing methods appeared to be a mixture of spot checks, re-run of statistical analyses and on-site inspections. An FDA methods volume or standard operational procedure may be among the documents not available from the web but accessible through a Freedom of Information (FOI) request. Neither the FDA nor the EMA have inventories of held documents, making it very difficult to know what to ask for under FOI rules. We concentrated on downloading or asking for specific clinical study reports and related documents or reviewers' comments on a particular NDA. The quantity of information held by regulators is likely to be large. For example, New Drug Application 21-246, the use of Tamiflu in the treatment of influenza in children submitted to the FDA on 15 June 2000 consisted of 137 volumes of study documents and possibly several electronic files. Although we do not know exactly how long a volume was, we have seen references to up to hundreds of pages in each volume.

Requesting specific documents and packages of information is especially important to allow a more efficient and timely reviewing process when confronted with a large volume of evidence, most of which could be of peripheral value. A request for a specific document is likely to be dealt with far more efficiently than a generic request for "all documentation relating to oseltamivir". This is one of the reasons why developing a TOC for any drug or family of drugs (no matter how time-consuming) is an absolute prerequisite for any serious attempt at reviewing regulatory evidence. This

introduces another very difficult problem: how to handle huge quantities of structured information and the ethics of drawing conclusions from what is still a fragmentary (albeit sizeable) evidence base.

Overall the FDA assessment of the performance of oseltamivir was "modest". This adjective appears six times in a 50-page review document (FDA 1999c). For example, in the Division Director Memorandum dated 25 October 1999, under the heading "Public health role of antiviral treatment" the FDA states: "The clinical relevance of the modest treatment benefit is a highly subjective question" (FDA 1999c, PDF page 3). The FDA refused to accept claims of oseltamivir's effects on influenza complications as "false or misleading" statements in promotional materials (FDA 2000f). An FDA warning letter seems to imply, for example, that oseltamivir's mode of action is "proposed" or "possibly" [that proposed by the manufacturers] i.e. not certain (FDA 2000f). However, FDA reviewers appear to have missed important problems in Roche's clinical trials (such as the imbalance in the numbers of individuals classified as influenza-infected in oseltamivir treatment trials). Most of all, no one seems to have questioned the coherence of the evidence with the proposed mode of action of the drug.

Summary of main results

For the first time a Cochrane review is based on all relevant full clinical study reports of a class of drugs integrated by regulatory comments. Also for the first time, all clinical study reports of trials in a manufacturer's programme (regardless of their relevance to the review) are available to readers without any restriction (apart from minimal redactions to protect anonymity further). The role of Roche and GSK in making this possible should be recognised, as well as that of the *BMJ*, which kept the issue in the public eye until it was resolved.

The evidence we have presented and synthesised shows that both neuraminidase inhibitors (NIs) in this review have symptom-relieving effects, especially for self reported outcomes. They appear to have symptom-relieving properties that make people with influenza-like illness and self reported, investigator-mediated, unverified pneumonia feel better by shortening symptom duration and reducing the frequency of symptoms such as cough. For oseltamivir, this effect perhaps extends to cardiac symptoms, despite the short duration of treatment (five days). We are unsure what to make of this finding but we think it deserves further investigation.

The issue which triggered our change of evidence-seeking methods is partly resolved: no definitions of secondary illnesses were given anywhere in the clinical study reports (for example "pneumonia" was defined as "pneumonia" in the case report forms (Table 1) and diagnostic criteria were not given); clinical diagnosis in the absence of criteria and without X-ray has only a moderate chance of being correct.

We could not decide the level of diagnostic ascertainment of diagnosis of pneumonia and other complications, as it is unclear from the clinical study reports. Definitions of pneumonia were not given and the algorithm for classification of an event as pneumonia was not supplied. In oseltamivir trials, the case report form trigger for recording of adverse events and secondary illness was a question to the participant posed by the investigator. A typical phrasing is as follows: "Secondary illness reminder: Has

the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline?" This was followed by a yes/no box to be ticked and an additional form was to be filled out by the investigator for collecting details on the secondary illness. A record of medications outside trial allocation was elicited in addition to the participant's diary card. The original and Medical Dictionary for Regulatory Activities (MedDRA) terms suggest diagnoses for all secondary illnesses and adverse events but there is no indication how the original and preferred terms were assigned. We therefore considered these outcomes to be "self reported, investigator-mediated, unverified" outcomes. For a subset of trials, secondary/intercurrent illness and adverse event data were collected on a

single, one-page form. In our meta-analyses, we called this sub-analysis "Trials which collected data on non-specific adverse events or secondary/intercurrent illness form". For a different subset of trials, case report forms contained space to record diagnostic tests such as chest X-rays, tympanometry and sinus X-rays for all secondary illness but there was no reporting of such variables in the clinical study reports ([Figure 12](#); [Figure 13](#); [Figure 14](#); [Figure 15](#)). In our meta-analyses, we called this sub-analysis "Trials which collected data on specific 'Diagnosis of Secondary Illness' form". None of the complications were defined as primary outcomes in any trial, which may explain the poverty of data definition.

Figure 12. Sample "Adverse event or intercurrent illness" form (oseltamivir study M76001)

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Tamiflu® (oseltamivir phosphate)



PART IV - CLINICAL DOCUMENTATION



Adverse event or intercurrent illness

Page 31 Patient initials¹

V 0512 CRTN: CRF number:

Adverse event or intercurrent illness:

Initial assessment

Event²
Record only one event on this page (maximum of 100 characters)

Date of onset Initial intensity

mild ☐
 moderate ☐
 severe ☐
 life threatening ☐

Follow-up information

Is this a serious adverse event?
 yes ☐ → *report within one working day of occurrence to Innovex by telephone or telefax*
 no ☐

SAE number⁸

Test drug adjustment³
 none ☐
 discontinued ☐ → *complete patient's completion of study record*

Is this event a secondary illness⁹ related to influenza? yes ☐
 no ☐

Relationship to test drug
 unrelated ☐
 remote ☐
 possible ☐
 probable ☐

Most extreme intensity⁴, 7

mild ☐
 moderate ☐
 severe ☐
 life threatening ☐

Outcome
 resolved - no sequelae ☐ → *specify date* Date resolved
 resolved - with sequelae ☐ → *specify date*
 unresolved¹⁰ ☐
 death⁵ ☐ → *complete patient death record*

Did this adverse event lead to hospitalization?
 yes ☐ → *record on next page*
 no ☐

Comments on AE

Was treatment given for this event*
 yes ☐ → *complete below*
 no ☐

Name of treatment⁵ (or medical procedure) <i>(maximum of 40 characters)</i>	Start date mm/dd/yy	End date mm/dd/yy	Continuing at outcome of AE
1 			☐
2 			☐
3 			☐
4 			☐
5 			☐

*If there are more than 5 treatments please mark ☐. Record additional treatments on the additional treatments page.

M76001

Figure 13. Sample "Secondary illness" form (oseltamivir study WV15670)

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Tamiflu® (oseltamivir phosphate)

PART IV - CLINICAL
DOCUMENTATION

Secondary illness

page 37

Secondary illness^{1, 2}

If a secondary illness became a SAE, please complete adverse event page.

Event _____
Record only one event on this page

Date of onset |_|_| |_|_| |_|_|
 dd mm yy

Date resolved |_|_| |_|_| |_|_|
 dd mm yy

Was treatment given for this event
yes ☐ → record any drug therapy below
no ☐

Treatment³ (or medical procedure) for this event		Total daily dose⁴		Date	
Name of treatment (or medical procedure)		mg		dd/mm/yy	
1	_____	_ _	_ _	start	_ _ _ _ _
				end	_ _ _ _ _
2	_____	_ _	_ _	start	_ _ _ _ _
				end	_ _ _ _ _
3	_____	_ _	_ _	start	_ _ _ _ _
				end	_ _ _ _ _

24sep97 103v1.02 WV15670

Figure 14. Sample "Diagnosis of secondary illness" form, page 1/2 (oseltamivir study WV15978)

Tamiflu® (oseltamivir phosphate)



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Diagnosis of secondary illness

Date of diagnosis mm dd yy

Diagnostic confirmation: Pneumonia, LRTI, Bronchitis

Diagnosis Pneumonia ☐
Bronchitis ☐
Lower respiratory tract infection ☐ → specify _____

acute ☐
chronic ☐

Which lung(s) are affected? right ☐
left ☐
bilateral ☐

Duration of respiratory secondary illness Days¹

Symptoms	present	absent	duration (days) ¹
1. Cough	☐	☐	
2. Chest pain	☐	☐	
3. Haemoptysis	☐	☐	
4. Tachypnea	☐	☐	
5. Dyspnea	☐	☐	
6. Purulent sputum	☐	☐	
7. Non-purulent sputum	☐	☐	
8. Rigors	☐	☐	
9. Convulsion	☐	☐	

Chest examination

	RIGHT		LEFT	
	anterior	posterior	anterior	posterior
10. Rales	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐
11. Ronchi	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐
12. Crepitations	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐
13. Bronchial breath sounds	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐
14. Pleural rub	upper ☐	☐	upper ☐	☐
	middle ☐	☐	middle ☐	☐
	lower ☐	☐	lower ☐	☐

c26-600

24sep99 183v1.0 WV15978

Figure 15. Sample "Diagnosis of secondary illness" form, page 2/2 (oseltamivir study WV15978)

Tamiflu® (oseltamivir phosphate)



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PART IV - CLINICAL DOCUMENTATION



Diagnosis of secondary illness

page 78

Diagnostic confirmation: Pneumonia, LRTI, Bronchitis (continued)

Vital signs

Temperature¹ °F

Sitting measurement

Respiratory rate per minute

Chest X ray

Was chest X ray performed?

yes ☐

no ☐

Are there any clinically significant abnormalities noted in the chest X ray?

yes ☐ → Specify infiltrate ☐

no ☐ consolidation ☐

other ☐ → specify

Microbiology

Was sputum gram stain performed?

yes ☐ → Specify below

no ☐

epithelial cells cells/Lpf

WBC cells/Lpf

organisms present ☐

absent ☐

Was sputum culture performed?

yes ☐ → If organism/pathogen found specify below

no ☐

organism/pathogen

colony count cfu/Lpf

24sep99 185v1.0 WV15978

In meta-regression of all 32 included studies that reported on "pneumonia", we found evidence that treatment effects for pneumonia are statistically different depending on the method of diagnosis. Unclear objective diagnosis was associated with an apparent 46% reduction in pneumonia due to treatment with neuraminidase inhibitors, whereas the use of objective criteria in the data collection showed no evidence of effect, with a risk ratio (RR) of 1.0. Age group (adults versus children), drug (oseltamivir versus zanamivir) and indication (treatment versus prophylaxis) showed no evidence of association with treatment effect.

Meaningful conclusions on the effect of either NI on complications of influenza are difficult to draw based on the trial evidence. In part this was due to the lack of standardised definitions. In addition, meta-analyses of these outcomes that lacked definitions were based on few events and therefore not robust. Caution is therefore urged in interpreting the meta-analysis result, which suggests that 100 patients (67 to 451) need to be treated with oseltamivir for one less self reported, investigator-mediated, unverified pneumonia. The same applies to the zanamivir treatment result, which suggests a reduced risk of self reported, investigator-mediated, unverified bronchitis in adults (number needed to treat to benefit (NNTB) 56, 95% confidence interval (CI) 36 to 155). The evidence suggested oseltamivir had a similar effect, although the result was non-significant.

As stated above, there is no evidence that definitions of complications in either paediatric, elderly or adult trials were ever prepared and incorporated in the trials' design. Therefore, the reporting of cases of 'otitis media', 'pneumonia', 'sinusitis' or 'bronchitis' are of unclear significance and importance, making it impossible to attribute a cause and draw conclusions (FDA 2000d). This is probably why the US Food and Drug Administration (FDA)-approved oseltamivir package insert, since 17 November 2000, has consistently stated: "serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications." The original product label did not contain such a statement but on 14 April 2000, after oseltamivir was approved for sale in the United States, the FDA sent Roche an untitled letter about "Misleading Efficacy Claims" that the FDA had noted in Roche's promotional materials (FDA 2000a, PDF page 3). One of the statements that Roche made was: "Tamiflu reduces incidence of secondary complications (i.e. bacterial infections) by 45%." The FDA commented: "Further, you have claimed reductions in severity and incidence of secondary infections with Tamiflu that are misleading because they are not supported by substantial evidence" (FDA 2000a, PDF page 3). We do not know how Roche responded to the FDA but in subsequently available Roche promotional material information, Roche's statements were consistent with the FDA's demands (Doshi 2009).

There is uncertainty in the "complications" and "secondary illnesses" outcome definition therefore we carried out an analysis on the data from adult treatment trials on those complications classified as serious or those which led to study withdrawal. For oseltamivir, there was no evidence that treatment affected such complications (risk difference (RD) 0.07%, 95% CI -0.78 to 0.44) (Analysis 1.20; Analysis 1.55). This outcome could not be assessed in oseltamivir prophylaxis due to an insufficient number of events. For zanamivir, there was no significant evidence of a treatment effect

on such complications (RD -0.04%, 95% CI -0.64 to 0.24) (Analysis 3.7; Analysis 4.8). This outcome could not be assessed in children due to an insufficient number of events.

Contrary to the FDA, the European Medicines Agency (EMA)'s oseltamivir 'Summary of Product Characteristics' states that oseltamivir significantly reduces the incidence of "specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics" in individuals of 13 years of age and older. This claim is based on "a pooled analysis of all influenza-positive adults and adolescents (N = 2413) enrolled into treatment studies", of which 1063 were in the placebo group and 1350 were in the oseltamivir-treated population (EMA 2010). This statement appears in the EMA files as early as 2001 (EMA 2001). These exact denominators appear in the Kaiser 2003 meta-analysis.

The design of the trials, as defined in the protocol with amendments, statistical analysis plan and case report forms, does not allow any further inferences. The effect on outcomes that were originally considered of secondary or tertiary importance (such as bronchitis and pneumonia) would have been clarified with better clinical definitions and investigations, as some of the serious adverse events were. These benefited from a paragraph-length narrative, which reported most of the salient features of the event.

Our previous decision to analyse the effects of oseltamivir and zanamivir on the ITT population has been confirmed for oseltamivir with the demonstration of the effect on antibody responses in participants in treatment trials, although no such effect is discernible for zanamivir. This effect leads to the introduction of selection bias with a significantly reduced probability of being diagnosed with influenza and an imbalance in the two arms if the intention-to-treat-influenza-infected (ITTI) population is analysed. The effect of oseltamivir on antibodies appears to be carried over to children with influenza-like illness. Its finding contradicts statements made by the manufacturer.

The seeming incomparability between arms of the influenza-infected subpopulations in the oseltamivir trials raises the question of how an appropriate analysis should be conducted. If influenza-infected groups are comparable (as appears to be the case in zanamivir treatment trials) then an appropriate analysis strategy (based on Senn 2004) would be to determine first the effect of treatment in the ITT population. If there is evidence of a treatment effect, then treatment by infected status interaction could be tested. If there was evidence of an interaction, then estimates of treatment effect could be derived separately for the influenza-infected and non-influenza-infected subpopulations. However, this analysis should be conducted on the ITT population using a single appropriate statistical model, obviating the need to conduct separate analysis on the influenza-infected subpopulation. Roche used geometric mean titres indicating antibody responses in the ITTI population to support their statement that oseltamivir does not affect antibody responses (for example, in Table 16 and linked text of Module 1 of trial WV15799). However, the use of such measures can be misleading. What are required for such an analysis are data on how many ITT population participants responded by arm, at what level of antibody response and how many were tested. Such data could not be identified with certainty. A further effect of choosing a subpopulation analysis (ITTI in treatment trials and ITTIINAB (ITT influenza-infected index cases who had negative virology at baseline) in prophylaxis trials) as the primary analysis

is the restriction of the generalisability of results. This is especially so in the case of design flaws (for example, in the case of the post-exposure prophylaxis trial [WV15799](#), where all index cases were not treated and around 55% of participants were dropped from the ITTINAB analysis). In this cluster-trial design households should be included as random-effects in the analysis to take account of within-household correlations.

A significant but slight reduction of the proportion with serum antibody (mostly haemagglutination inhibition (HAI) antibody) titre rise by four-fold or more among those who were tested was shown in this review. This was consistent with the evidence from animal tests using a sub-clinical dose of oseltamivir in influenza A/H1N1-infected mice ([Takahashi 2010](#)). [Takahashi 2010](#) reported a non-significant slight reduction of haemagglutinin (HA) specific IgG antibody in serum and spleen, while they reported about an 80% significant reduction of HA specific secretory IgA antibody (s-IgA Ab) in nasal wash and bronchoalveolar fluids (BALF) on day 12. From this evidence, they warned that the risk of re-infection may increase in patients showing a low mucosal IgA antibody response following oseltamivir administration. These experiments were done because they had the unexpected finding that paediatric influenza patients treated orally with oseltamivir for five days had significantly low levels (about 60% reduction on day five) of anti-influenza S-IgA nasopharyngeal fluids compared to levels in patients not treated with oseltamivir ([Sawabuchi 2009](#)). Their findings are consistent with our findings that serum HA inhibition (HAI) antibody response was decreased by oseltamivir administration, though s-IgA Ab could not be analysed in our study because the data were not reported in the clinical study reports ([Sawabuchi 2009](#); [Takahashi 2010](#)). These findings are also consistent with the evidence on the mode of action of oseltamivir from animal models (Module 2 of [Mendel 1998](#); [WV15670](#); [WV15671](#)) and from viral challenge, randomised, placebo-controlled studies in humans ([Hayden 1999](#)).

Pro-inflammatory cytokines, including interleukin 6 (IL-6), tumour necrosis factor alpha (TNF- α) and interferon gamma (IFN- γ), were completely suppressed by oseltamivir administered 28 hours after the experimental inoculation of influenza virus, while the reduction of viral titre in nasal lavages was partial ([Hayden 1999](#)).

There is decisive evidence that administration of oseltamivir in animals challenged by respiratory syncytial virus (RSV) that lacks a neuraminidase gene showed a symptom-relieving effect (decreased weight loss) and inhibition of viral clearance ([Moore 2007](#)). These effects were accompanied by a decreased CD+8 T cell surface sialoglycosphingolipid GM1 level, which is regulated by the endogenous sialidase/neuraminidase in response to viral challenge along with suppression of cytokine expression ([Moore 2007](#)). They are consistent with those findings from the pharmaceutical company and their investigators. The findings of the study by [Moore 2007](#) suggest a risk of infection and exacerbation of infection by pathogens other than influenza virus in spite of the apparent reduction of symptoms from infection.

Sufficient plasma concentration of oseltamivir carboxylate from orally administered oseltamivir phosphate may act directly on the host endogenous neuraminidase to reduce (or suppress) the immune response even at the dose of 20 mg twice a day for five days. However, the bioavailability of inhaled zanamivir seems to be very broad: about 10% to 70%, as estimated by the area under the curve (AUC) data from the inhalation and intravenous study from the Japanese Summary Basis of Approval (JSBA). The

difference in peak concentration (Cmax) was much larger (6 to 37-fold). This means that inhaled zanamivir could reach a high enough concentration to reduce the immune response, if it is administered at a high dose or a for long period, or if the patient is very susceptible. In fact, a double-blind, placebo-controlled trial using healthy volunteers to investigate the effect of zanamivir treatment (20 mg/day for 14 days) on the humoral immune response to influenza vaccine showed that the zanamivir group responded with significantly lower antibody titres to the H1N1 ([Cox 2001](#)). Pro-inflammatory cytokines, including IL-6, TNF- α , IFN- γ and other chemokines, were almost completely suppressed in the viral challenge randomised controlled trial (RCT) using a very high dose (600 mg) of intravenous zanamivir before inoculation of the influenza virus in human adults ([Fritz 1999](#)).

These findings all suggest that the low immune response, with a low level of pro-inflammatory cytokines, induced by the action of oseltamivir carboxylate may reduce the symptoms of influenza irrespective of an inhibition of influenza virus replication, which is widely believed to be the main mode of action of NIs.

In addition, the potential hypothermic or antipyretic effect of oseltamivir (but not zanamivir) as a central nervous system depressant may also contribute to the apparent reduction of host symptoms ([Ono 2008](#); [Ono 2013](#)).

Zanamivir had no effect on pneumonia symptoms in treatment trials, even when the diagnosis was supported by a chest X-ray; nor did it affect antibody responses, but it did affect bronchitis. We think that this shows an undeniable symptom-relieving effect of both drugs, which also applies to more severe, if undefined, syndromes. Both drugs relieve influenza-like illness symptoms by around 0.6 to 0.7 of a day, although this is first relief and not necessarily complete relief. In the case of oseltamivir, the mix up with the follow-up cards does not allow us to draw any conclusions on a possible length of the duration of symptom relief. Also of note is the fact that this important information came to light from the FDA reports and not from the clinical study reports of the relevant trials ([WV15670](#); [WV15671](#)). This points to the incomplete nature of reporting in the clinical study reports and the important role of Summary Basis of Approval (SBA) regulatory information.

In a subgroup analysis we found no evidence of a difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups. Both subgroups showed strong evidence of treatment effect of 0.5 to 0.7 days reduction in time to first alleviation of symptoms. This strongly supports our hypothesis that these drugs do not have an influenza-specific effect.

Oseltamivir relieves symptoms in otherwise healthy children, but no effect was noted with zanamivir, which may be due to the limited power of the two eligible trials with just over 700 children in total. However, oseltamivir does not have any effect on asthmatic children with influenza-like illness, a population which should benefit most from its use. One explanation for this finding is in the nature of the young asthmatic population, which is well cared for and used to regular powerful medications and close follow-up. The incremental benefit of oseltamivir is thus likely to be undetectable in such a population. An alternative explanation could be the higher susceptibility of the immune system to suppression by oseltamivir carboxylate in asthmatic children compared with those in the placebo group. The finding that oseltamivir administered

to asthmatic children reduces symptoms faster than in placebo recipients at the beginning of the study, but during the off-treatment period more recovered later than those administered placebo, gives some support to this explanation.

There is no evidence of an effect of oseltamivir on hospitalisations. Hospitalisations are an important but poorly defined outcome in the oseltamivir protocols, inconsistently reported in the clinical study reports and overlooked in the zanamivir protocols and reports.

The oseltamivir trials did not detect any influenza-related deaths, reflecting the relatively benign nature of influenza in the study populations. The zanamivir trials detected eight deaths, of which only two were likely to be due to influenza and both occurred in the intervention arms. All the trials were likely to be underpowered to detect differential effects on mortality, but the absence of deaths in placebo recipients again underlines the benign nature of influenza. In fact mortality in Japan during the 2009A/H1N1 influenza outbreak was 198 among about 20 million influenza patients (one in 100,000 infected). Early deterioration leading to death was observed more frequently in oseltamivir compared to zanamivir or no antivirals recipients ([Hama 2011](#)).

Overall the two drugs have similar benefits but quite different toxicity profiles.

On average, for every 28 (14 to 112) adults treated with oseltamivir there will be one more report of nausea and for every 22 (14 to 42) adults and 19 (10 to 57) children there will be one more report of vomiting. Oseltamivir seems to have an apparent protective effect on diarrhoea, contrary to the other evidence of gastrointestinal disturbance. This finding might be as an effect of a placebo containing dehydrocholic acid or it might be one of the results of the influenza-like illness symptom-relieving effects (similar to relief of tachycardia and palpitation). The other apparent gastrointestinal events, such as nausea and vomiting, may be the results of central nervous disorders indicated by "only day 1 increase of vomiting" in treatment trials in children.

For every 62 (41 to 411) adults exposed to zanamivir there will be one less case of nausea and vomiting, but no such effect was visible in children, probably because of a lack of power. Zanamivir does not appear to affect the frequency of bowel movements.

In the prophylaxis data set, "influenza without laboratory confirmation" (i.e. influenza-like illness) was only partially reported in the oseltamivir clinical study reports and not reported in the zanamivir clinical study reports, except for [NAI30034](#) in which no significant reduction was observed (9% versus 10%). As a consequence we are unable to report on that outcome. The size of the reduction in influenza symptoms in oseltamivir prophylactic trials is inferior in magnitude to that seen in hand washing to prevent severe acute respiratory syndrome (SARS), based on seven case-control studies (odds ratio (OR) 0.77, 95% CI 0.70 to 0.84, I^2 statistic = 68%, RD -0.12, -0.16 to 0.08, I^2 statistic = 26%), the NNTB being approximately 50 for prophylaxis with oseltamivir and eight with hand washing ([Jefferson 2011a](#)).

There is a significant reduction in the proportion of patients with symptomatic influenza with both NIs. However, these findings do not reflect the true efficacy for prevention of influenza, because

they conceal the positivity of laboratory testing (measured through tests of viral shedding and four-fold antibody titre rise).

We found an apparent prophylactic effect of zanamivir on pneumonia (which was not defined in case report forms) when it was used for 14 to 28 days. However, we found no evidence of significant effects on other complications and no evidence of an effect of oseltamivir on complications or hospitalisations.

Oseltamivir induced nausea in people undergoing prophylaxis but there was insufficient evidence to show an association with vomiting.

On-treatment renal adverse events were three times more common in the oseltamivir arms compared to the placebo arms, with 150 treated patients leading to one additional event. The two participants who died in the oseltamivir arms both experienced acute renal failure while on-treatment, although only one of those events was listed as an adverse event. The unlisted event was in a 91-year old female who was "withdrawn from the study on Study Day 15 because her estimated creatinine clearance was less than 30 mL/min. The screening laboratory examinations, that were carried out 10 days before the start of study treatment, were normal". Hyperglycaemic adverse events (aggravated diabetes mellitus or hyperglycaemia) were also more common in the oseltamivir arms, with eight events in total (one in [WV15673/WV15697](#), two in [WV15708](#) and five in [WV15825](#)) compared to none in the corresponding placebo arms. These data are only presented descriptively as they are too few (< 10) to meta-analyse formally, as prespecified in our analysis plan.

Finally, oseltamivir caused headaches and psychiatric harms in adult prophylaxis trials. Headaches are one of the most prominent harms of oseltamivir. There is evidence of a dose-response effect in prophylaxis trials [WV15673/WV15697](#) ($P = 0.013$), in which headaches were observed in 202/519, 225/520 and 242/520 participants in the placebo, oseltamivir 75 mg once daily and 75 mg twice daily arms, respectively.

In the psychiatric category, several rare and severe single events (nervousness, aggression, hallucinations, psychosis, suicide ideation and paranoia) were reported significantly more frequently in the intervention arm. Added to other more frequently reported but not significantly different events (such as depression and confusion) this gave a large effect and a relatively small number needed to treat to harm of 94 (36 to 1538). The importance of such a finding lies in the distribution of oseltamivir to large numbers of asymptomatic individuals following pandemic plans. There were no prophylaxis trials in children that met our inclusion criteria, therefore we cannot report on prophylaxis harms in this important population.

The question of why oseltamivir treatment trials failed to identify a clear association between oseltamivir and psychiatric harms, although a weak dose-dependent association was observed, is a moot point. It is possible that influenza-like illness and influenza symptoms masked the harms in those who were already symptomatic and therefore recruited in the treatment trials (and influenza-type symptoms were excluded as adverse events to be reported). The reporting issue of compliharms may have helped to mask such events. Alternatively, it could be that these events are rare in the populations studied and that there was insufficient power to detect an association. The CI was wide (0.43 to 2.03) and

does not rule out a doubling in risk due to treatment - as was found in the prophylaxis trials. It is also possible that the risk of psychiatric harm increases with increasing dose (as the data from trials [WV15670](#) and [WV15671](#) suggest) and increasing duration of treatment (as the prophylaxis trials suggest).

[Toovey 2008](#) assessed the issue and failed to find an association between neurological and psychiatric adverse events and oseltamivir exposure. The outcomes studied were not based on the a priori definition of psychiatric adverse events as defined in the clinical study reports. The definition was constructed post hoc based on a selected group of adverse events taken from the psychiatric, neurological and injury body systems in the reports. The issues are described fully in [Jones 2012](#) and Toovey's response is in [Toovey 2012](#). [Toovey 2008](#) reviewed only retrospective observational studies and did not review three prospective cohort studies conducted in Japan.

A meta-analysis of three prospective cohort studies of neuropsychiatric adverse events (NPAEs) in Japanese children show a pooled odds ratio for abnormal behaviours due to oseltamivir exposure of 1.55 (95% CI 1.21 to 1.98; $P = 0.0005$) without significant heterogeneity ([Hama 2010](#)). In one prospective study of several thousand children with influenza carried out to test the hypothesis of a causal relation between oseltamivir and neuropsychiatric events, abnormal behaviour was observed more frequently in oseltamivir recipient children than in controls (RR 1.57, 95% CI 1.34 to 1.83). Abnormal behaviour was observed in 3.4 per 100 person day (or 13.8%) in the oseltamivir group, compared to 2.2 per 100 person-days (or 8.8%) in the control group ([Yorifuji 2009](#)). Reanalysis of this study population, focusing on delirium and unconsciousness, also showed a significant association between oseltamivir and neuropsychiatric events, especially in the very early phase of the illness within a day of commencement of fever ([Fujiita 2011](#)). These indicate that prospective and intentional collection with this scale of participants may be necessary in treatment RCTs.

Animal toxicity study results firmly support the effect of oseltamivir on the central nervous system. One of these is the hypothermic effect of oseltamivir (but not zanamivir) administered orally, intraperitoneally ([Ono 2008](#); [Ono 2013](#)) and intracerebroventricularly ([Ono 2013](#)). The other is that intraduodenal or intravenous administration of oseltamivir to mature rats induced respiratory arrest shortly followed by cardiac arrest. These studies clearly show central depressant effects of oseltamivir ([Kimura 2012](#)). Moreover in the post-marketing toxicology phase studies by Roche, many symptoms that the manufacturer considered "item-related" were observed: alterations in respiration including decreased respiratory rate/gasping and altered mucous membrane/skin colour (pale) prior to death. Although the manufacturer denied the causality ([Freichel 2009](#)), symptoms at two hours after administration that showed dose-related increase were lack of olfactory orientation, lack of cliff aversion and low or very low arousal. Twenty-four of 52 pups that did not exhibit cliff aversion were later found dead. Fourteen of 17 animals with low or very low arousal died thereafter. These findings are consistent with the clinically observed psychiatric symptoms in the RCTs and post-marketing spontaneous reports.

Zanamivir was well tolerated. However, a potentially active placebo may have masked the occurrence of bronchospasm in zanamivir trials.

Treatment trials were mostly under-recruited and often their results pooled post hoc in two or even three trials, and yet they showed very high influenza positivity rates. One possible explanation for this lies in the intensive surveillance carried out in the predefined trial centre areas and the restricted time span of recruitment during high likelihood of positivity periods. This may be why many centres with low levels of recruitment are listed in the clinical study reports; this limits the generalisability of the results to everyday life.

In a primary or secondary prophylaxis indication the postulated central effect of oseltamivir is confined to suppressing symptoms, as infection was not prevented even when oseltamivir was administered prior to the inoculation of influenza virus both in animals ([Mendel 1998](#)) and in humans ([Hayden 1999](#)) and the prophylaxis trials. However, the central problem remains the incompatibility of the two contrasting claims of its activity against antibody production. If, as reported in many documents, oseltamivir does not interfere with antibody production (see, for example, [FDA 2011a](#); [Roche Investigators' Guide](#)), how is it possible that oseltamivir prevents cases of influenza when part of the definition of prevented cases in oseltamivir trials was based on absence of antibody response?

The apparent ability of oseltamivir to interfere with antibody response calls into question the mode of action of the drug and puts in doubt the proposed effects of oseltamivir. One possibility in treatment trials is that oseltamivir administration, by interfering with antibody production, has the effect of selecting the strongest antibody responders in the ITTI subpopulation. These individuals are classified as influenza cases and are included in the oseltamivir arm of the ITTI population. This selected subpopulation probably represents the healthiest or those least likely to experience complications. An alternative consequence could be that interference with antibody production in the oseltamivir arm led to active arm participants being more likely to develop complications due to impaired immune function.

Evidence from prophylaxis and secondary prophylaxis trials suggests that in addition to the apparent similar mode of action as in the treatment studies, suppression of viral shedding in nasal swab may be of importance. In the former, participants who become positive (i.e. who are subsequently classified as cases of influenza) in the oseltamivir arms are the few who mount a strong response despite oseltamivir interference. The remainder (who are significantly more than in the placebo arm) are classified as prevented or avoided cases. However, as prophylaxis clinical study reports do not report antibody responses and viral isolate results for the ITT populations either, it is impossible to tell whether this proposed mode of action fits all the evidence. The effect of oseltamivir on nasal shedding is consistent with the proposed mode of action of NIs in preventing the virus from leaving the host respiratory epithelial cells, which are covered by a mucous layer. Compared with the rather small reduction of symptoms of influenza-like illness and reduction in antibody rise (up to 10%) by both oseltamivir and zanamivir, the extent of the reduction of symptomatic influenza is almost half. This may be due to reduction of influenza viruses in the nasal swab sample.

In prophylaxis there is no evidence that oseltamivir reduces symptomatic influenza-like illness. Oseltamivir reduces the number of prophylaxis participants testing positive (based on antibody rise and/or culture test). However, this finding is weakened by oseltamivir's interference with the viral replication on

the swab and effect on antibody production. In addition oseltamivir does not affect asymptomatic influenza and there is no evidence that it interferes with person-to-person spread.

Similarly to the FDA (FDA 1999c; FDA 2000c) because of the problems with the design of study [WV15799](#) we could not draw any conclusions on the ability of oseltamivir to interrupt viral transmission.

This is important as the results of trial [WV15799](#) formed part of the WHO3 rationale for use of the drug to interrupt transmission from person to person and allow time before the arrival of vaccines in the event of a pandemic furnishing a seemingly powerful rationale for stockpiling oseltamivir.

This shows the importance of availability of full clinical study reports, something the WHO did not have.

Antibody suppression seems stronger for oseltamivir than zanamivir, probably due to the difference in bioavailability. It may be that evidence of other effects, such as hyperglycaemia and renal impairment (though significance was marginal) in the prophylaxis trials may be due to inhibition of the host's endogenous neuraminidase, which impairs the cell function of various organs ([Hama 2008](#)). Overall, the significance of oseltamivir for nasal shedding is unclear but problems with sampling and culture undermine any claims as to its secondary prophylactic properties, as the FDA made clear in its response (FDA 1999c).

The dose-response increase in psychiatric events in the "pivotal" oseltamivir treatment trials and the increase in vomiting only on day one in treatment trials in children may be due to the sudden onset of the central action of unchanged oseltamivir ([Hama 2008](#)). Brain concentration of unchanged oseltamivir increases during the early phase of influenza in juvenile animals ([Freichel 2009](#)), due to a reduced or low function of p-glycoprotein, a major transporter of oseltamivir at the blood-brain barrier ([Hama 2008](#); [Kimura 2012](#)). The likely centrally mediated mode of action of oseltamivir is supported by the finding of adverse events in healthy people in prophylaxis trials. However, these effects may also be derived from a delayed action associated with host endogenous neuraminidase inhibition by oseltamivir ([Hama 2008](#)), because this appeared after more than a week's exposure the drug and lasted for more than two weeks. Other effects, such as pain in the limbs, hyperglycaemia or diabetic events, reduction of antibody rise and reduction of cytokine induction, may also be due to the suppression of the host's endogenous neuraminidase by oseltamivir ([Moore 2007](#)). Pain in the limbs and metabolic control events (mainly hyperglycaemia) were in excess in the oseltamivir arms, but we did not carry out a formal meta-analysis, as they were not prespecified in our analysis plan and the number of events was below 10 for metabolic events.

Statements made about the capacity of oseltamivir to interrupt viral transmission and reduce complications are not supported by any data we have been able to access.

We have not reviewed other NIs, such as laninamivir and peramivir, or other antivirals, such as the adamantanes (amantadine and rimantadine), or antipyretic/anti-inflammatory agents either. Laninamivir and peramivir may be more potent as NIs, because their bioavailability is far higher than zanamivir and may affect the host's endogenous neuraminidase. Adamantanes are well known centrally active agents and may be more harmful than

oseltamivir and zanamivir. Anti-inflammatory antipyretics (except paracetamol) may be more toxic than NIs ([Hama 2008](#)). Hence, the other NIs, adamantanes and anti-inflammatory antipyretics may not be alternatives to oseltamivir and zanamivir.

Overall completeness and applicability of evidence

We used the Cochrane seven-domain 'Risk of bias' instrument to assess bias. The availability of partial or complete clinical study reports decreased the uncertainty and allowed definitive judgements to be made. Previous unclear risk of bias became certainty of bias or certainty of absence of bias. Certainty or low levels of uncertainty are due to our expectations regarding the complete clinical study reports. We were expecting to have all relevant and consistent information available for our reviews, but when it was not, our judgements changed because we found gaps in the availability of information and inconsistent information. We are still uncertain whether the complete study reports represent an exhaustive and coherent source of trial narrative and data.

In the case of treatment trials, conclusions and generalisations are drawn from a subpopulation in which the two arms do not appear comparable due to the apparent ability of oseltamivir to interfere with influenza antibody production. The effect of oseltamivir on the gastrointestinal tract appears to be notable, although a definitive statement will only be possible once the mode of action and dosage of dibasic calcium phosphate dihydrate and dehydrocholic acid have been clarified. The high percentage of influenza infections appears to be in contrast with the need to pool or delay several trials and the small recruitment size of others because of a lack of influenza circulation. In the case of post-exposure prophylaxis trials, the selection of the infected population has the effect of excluding from the analysis large percentages (in some cases over 50%) of participants. This brings the generalisability of the results of these trials into question.

Much has been made in the trial programmes of viral nasal voidance as a marker of effect. However, its measurement was unreliable in treatment trials as this verbatim quote from the FDA review shows: "Duration of viral shedding was measured from treatment initiation to the time of the first negative virus culture with no subsequent positive cultures. Upon reviewing a list of viral shedding patterns provided by the applicant on 8/16/99, two problems emerged: (1) the pattern of virus shedding was fluctuating in at least 33 subjects (i.e. pos-neg-pos-neg, with or without a subsequent negative result). (2) In at least 100 subjects, the last virus shedding sample was the first negative sample in sequence, meaning there was not a subsequent negative confirmation. Given the fluctuating pattern of virus shedding, to estimate the duration of viral shedding based on the occurrence of a single first negative data poses a high level of uncertainty" (FDA 1999c).

In all programmes, the effect on complications was based on unclear and potentially unreliable definitions, often at the discretion of local clinicians and confirmation (e.g. radiological confirmation of pneumonia) was not consistently reported when it did occur. In the ITT population, the correct population for analysis, there is no credible effect of oseltamivir against pneumonia as the significance of the term "pneumonia" is not clarified.

In the case of post-exposure prophylaxis trial [WV15799](#), nasal voidance was measured only in symptomatic subjects as an

adjunct to protocol version H. However, this does not prevent the manufacturers from making claims of effect for all these outcomes.

Other general requirements, such as presentation within 36 to 48 hours, raise questions about the generalisability of the research evidence. However, underlying all our doubts is the conflicting evidence on the mode of action of the drug.

Most of the trials were substantially under-recruited and so had insufficient power individually to answer the research question.

Quality of the evidence

We assessed all full clinical study reports of relevant trials. An example of the kind of detail available in complete clinical study reports and the importance of the trial timeline in assessing the presence of bias is the observation that of the clinical study reports for the included trials, only one contained a protocol that predated the beginning of participant enrolment, only two had statistical analysis plans that clearly predated participant enrolment and three had clearly dated protocol amendments. No oseltamivir clinical study report included a clear date of unblinding.

All reports in our review were sponsored by the manufacturers. It is known that published studies sponsored by the pharmaceutical industry are more likely to have outcomes favouring the sponsor compared to studies which have other sponsors (Lexchin 2003; Lundh 2012). As the evidence relates to published studies, we do not know whether the findings are applicable to clinical study reports.

Potential biases in the review process

The main limitation of our study is our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents, such as randomisation lists. Randomisation lists appeared to be of two types. The first was a pre-randomisation list of random codes with which participants' IDs cannot be matched with the participant IDs used within other sections of the clinical study report. The second was a post hoc randomisation list to which individual participants can be matched but the original generated codes are not shown. In both cases the truly random generation of the sequence could not be properly assessed because either the original codes are not provided or original codes cannot be matched to patients.

We have created methods and procedures to address the risk of reporting bias that we identified in published trials, but remain uncertain about the success of these new methods.

Agreements and disagreements with other studies or reviews

Several reviews of NIs are now available (Burch 2009; Cooper 2003; Falagas 2010; Tappenden 2009; Turner 2003), including several separate versions of our previous reviews (Jefferson 2006; Jefferson 2009a; Matheson 2007; Shun-Shin 2009). All are mainly based on published information and reach similar conclusions to our 2006 review, which sparked the reader's comment and subsequent investigation and change of methods.

Following publication of our review update in December 2009, Roche asked the Harvard-based academics Hernan and Lipsitch to repeat the Kaiser analysis to confirm or reject Kaiser's conclusions

(Hernan 2011). They were not provided with any funding to carry out this analysis and Roche ultimately provided them with patient-level data sets and Module 1 for the 10 Kaiser trials and one more treatment trial (WV16277). An important methodological difference between Hernan and Lipsitch's analysis and that of Kaiser was Hernan and Lipsitch's decision to privilege a true ITT analysis over the sub-population analysis featured in the Kaiser analysis. Our Cochrane review also analyses the ITT population.

The Kaiser analysis concluded that oseltamivir provided two statistically significant reductions: in lower respiratory tract complications and in hospitalisations.

Hernan and Lipsitch evaluated lower respiratory tract complications and found a statistically significant, but smaller, reduction in the risk of these complications.

Hernan and Lipsitch omitted evaluating the Kaiser paper's conclusion that oseltamivir reduced the risk of hospitalisation. They wrote, "it was not possible to assess the potential benefit for high-risk participants who are hospitalised, because the sample size of most studies was too small to consider hospitalisation as an outcome."

Hernan and Lipsitch do not elaborate on or highlight their apparent methodological disagreement with the Kaiser 2003 analysis and it is not reflected in the news article published on the Harvard website entitled "Oseltamivir effect on complications confirmed by reanalysis" (<http://ccdd.hsph.harvard.edu/NewsEvents/Oseltamivir-reanalysis>). In fact, Hernan and Lipsitch did not confirm one of the key conclusions of the Kaiser paper (Kaiser 2003).

Unfortunately, the Hernan-Lipsitch analysis has been cited by influential bodies such as the European Centre for Disease Prevention and Control (ECDC) as "confirmation of the original Kaiser meta-analysis" (http://ecdc.europa.eu/en/activities/sciadvise/_layouts/forms/Review_DispForm.aspx?ID=561&List=a3216f4c%2Df040%2D4f51%2D9f77%2Da96046dbfd72) despite the fact that Hernan and Lipsitch did not confirm one of the key conclusions of the Kaiser paper (Kaiser 2003).

For complications, while Hernan and Lipsitch clearly produced similar results to Kaiser, we do not think that this means the result is more credible. In view of our findings, we suggest that these results should be interpreted with caution. We have published our preliminary comments (Cochrane Neuraminidase Inhibitors Review Team 2011). The approach Hernan and Lipsitch took in analysing data was insufficient to provide a credible, independent check on validity and reinforces the importance of detailed, critical assessment of entire trial programmes, with access to full-length study reports. Our analysis questions the coherence between the evidence and the proposed mode of action of oseltamivir.

The Ebell 2012 review concluded that there was "no evidence that oseltamivir reduces the likelihood of hospitalisation, pneumonia or the combined outcome of pneumonia, otitis media and sinusitis in the ITT population". This conclusion was based on Module 1 of the 10 Kaiser trials plus WV16277. These are the same 11 trials as Hernan 2011.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of the findings of this review, clinicians and healthcare policy-makers should urgently revise current recommendations for use of the neuraminidase inhibitors (NIs) for individuals with influenza. Our findings confirm that both oseltamivir and zanamivir reduce the time to symptomatic improvement in adults (but not asthmatic children) with influenza-like illness. The size of this effect is small, approximately half a day. It is unclear whether this is superior to treatment with commonly used antipyretic medications. However, we did not find any credible evidence that either oseltamivir or zanamivir reduce the risk of complications of influenza, particularly pneumonia, nor reduce risk of hospitalisation or death. Moreover, even in individuals at higher risk of complications, such as children with asthma or the elderly, we found no evidence of a beneficial effect for reducing risks of complications.

Based on these findings there appears to be no evidence for patients, clinicians or policy-makers to use these drugs to prevent serious outcomes, both in annual influenza and pandemic influenza outbreaks. Practice recommendations and drug labelling needs to be changed to reflect these findings.

When used as prophylactic agents to prevent the occurrence of influenza in individuals or families, our findings again suggest a minimal effect on prevention. Based on this, there is little support for their use as prophylactic agents, for example, during influenza epidemics. Given that oseltamivir is now recommended as an essential medicine for the treatment of seriously ill patients or those in higher-risk groups with influenza (H1N1 2009) ([WHO 2013a](#); [WHO 2013b](#)), this is of some concern.

Reasons why prophylaxis treatment is not clinically meaningful include: 1) according to modelling studies, for prophylactic treatment to be effective, 80% of the population require at least eight weeks of treatment, which has not been trialled ([Longini 2004](#)); 2) models assume the relative risk reduction observed in low risk populations, transfers directly to populations at higher risk (i.e. an absolute treatment effect of 31%, approximately 15-fold higher than the absolute effects we observed in prophylaxis trials ([Longini 2004](#)); 3) A high proportion of people, at least two-thirds require recognisable influenza symptoms; 4) treatment has to be effective against both asymptomatic and symptomatic infections (which it is not), in modelling studies asymptomatic infections are assumed to be 50% as infectious as symptomatic infections ([Longini 2004](#)); 5) because the influenza season can last four to five months, any secondary strategy, such as vaccination, would have to be widely available at the end of the eight week treatment period, and 6) a full understanding of the effect of the treatment in prophylaxis is unknown because symptomatic influenza-like-illness without laboratory-confirmation was only fully reported in one study. This study (NAI30034) showed no difference in proportion of patients with symptomatic influenza-like-illness (with or without lab confirmation) (RR 0.90, 95% CI 0.73 to 1.11).

The small benefits we noted in symptomatic improvement and the lack of credible evidence for an effect on serious complications needs to be balanced with the adverse effects found with these drugs in meta-analyses, especially diabetic/hyperglycaemic, renal

and neuropsychiatric effects in all those people for whom the World Health Organization (WHO) recommend use.

Our results do not discount the potential benefit of using zanamivir and oseltamivir in individuals under particular situations, for example in immunocompromised or in compassionate cases, where few other therapeutic options may exist. However, NIs themselves may be immunosuppressants. Our findings do not support the stockpiling of NIs, nor oseltamivir's inclusion in the WHO's list of essential drugs.

The rationale for undertaking the current review and the methods and pressures that needed to be employed to obtain and evaluate the evidence for these drugs has significant implications for the robustness of the scrutiny that new drugs undergo prior to entering widespread clinical use. We believe that several steps now need to be put in place to provide patients, clinicians and policy-makers with the most transparent assessment of the relative benefits and risks of new drugs.

First, our findings imply that numerous national and international bodies appear willing to accept biased or incomplete trial reports seemingly at face value. This ready willingness is in contrast with the considerable time and effort needed to change their recommendations. Second, published trials are unlikely to provide the level of detail to allow the results of a drug trial to be properly evaluated and risk presenting a partial and potentially biased report of trial conduct and findings. This has implications not only for the reporting of trials but also the weight that can be applied to published studies alone. Third, clinicians and policy-makers should be cautious in interpreting and using the findings of systematic reviews including only published studies, particularly those that comprise only a portion of an entire drug trial programme, or which contain only a portion of the results of trials. There have been many systematic reviews of NIs, none assessing the full trial programme or full trial results, thus limiting their validity. We suspect a similar situation exists for other drugs. Fourth, clinical policy-makers at the national and international level should raise the level of scrutiny needed in the cases of drugs that are likely to be used by large numbers of people who are either asymptomatic or have short, self limiting illnesses such as influenza ('public health drugs') and where the potential for benefit (and harm) is vital. Given the weight of these decisions (with serious implications for both correct and incorrect decisions), policy-makers should not face the barrier of being denied access to what sponsors regard as commercially sensitive information.

Without concerted efforts from multiple stakeholders to put the above measures in place, it is not possible to provide objective assessment of the benefits and risks of new drugs. This risks not only patients potentially missing out on effective treatments, but also patients being exposed to either ineffective (or harmful) treatments.

Implications for research

Our findings have implications for research on the mechanism of action of NIs, with special regard to any direct central action of oseltamivir and the inhibitory effect of the host endogenous neuraminidase of various organs and systems. We could not reach a consensus on whether further trials are warranted and whether current trials should be discontinued.

The considerable body of evidence from randomised controlled trials (RCTs) included in this review indicates either no effect or a relatively small absolute effect size against the complications of influenza. Such an effect, even if statistically significant, would be too small to warrant treatment with NIs in a primary care setting, especially since effective diagnosis and treatments for rare complications (such as pneumonia) are available. Lack of evidence of an effect on hospitalisations probably indicates lack of severity in the first place. Assuming an influenza incidence rate of 2% (similar to that in the control arms of oseltamivir treatment trials), to detect a 25%, clinically significant reduction in pneumonia, 21,500 participants would have to be enrolled in a clinical trial.

Our calculation is likely to underestimate population size, as the 2% incidence rate was derived from trials that used enhanced ad hoc surveillance systems. Any trial design would have to ensure that the presence of complications is ascertained using objective diagnostic criteria (for example, with confirmation using imaging or laboratory testing for pneumonia). Such trials would also have to consider the ethical implications of conducting studies where the estimate of benefit (based on 11 RCTs) in otherwise healthy people is likely to be small, and would have to be balanced against the apparent risks of adverse effects from NIs. We think research should be aimed at more effective preventive measures and early identification of complications.

Based on the length of time it has taken to provide a definitive answer on the efficacy of the NIs, the challenges in obtaining the full information and the methods that we needed to develop to conduct the evidence synthesis, we believe the main implication of our review is the need for reform of multiple components of the research and development, regulatory and assessment pathway of new drugs.

Pharmaceutical sponsors of drug trials should follow a data access and sharing procedure similar to that of the European Medicines Agency (EMA) and sponsors should make all full clinical study reports available to be downloaded from their websites and shared freely once a regulatory decision has been made. Redactions should be kept to the minimum. Part of this process needs to include a full list of the entire drug development programme, to avoid assessment of an incomplete set of trials. Researchers and industry employees who are listed in trial documents should be considered to have legal responsibility for the conduct and reporting of a trial.

Regulators should post an inventory of their documentary holdings on their websites with a brief description of the main content and size of each file. They should make all information available shortly after making a registration decision on a drug and within a reasonable time period. The information should be in electronic format and anonymised (i.e. participants' details should be removed to prevent each person being identified but no further).

Trial registries have improved the reporting of new trials. However, on their own they will not be adequate to resolve the problems we encountered. The completeness of trial registries needs to be tested with a random sampling procedure. Clear instructions for the reporting and updating of their content should be promulgated and penalties imposed on breaches of these procedures. Trial registration should include the original and final versions of a trial protocol, with a full declaration of dated amendments. Procedures for trial unblinding and dates of unblinding should be routinely

reported. Registration should be made compulsory for all studies in which human beings are randomly assigned to experimental arms. Ethical and consent procedures for all trials should include obligations of the trial sponsor to ensure results are made public. Failure to report the existence of a trial on humans and to make results available should be considered as an ethical breach of conduct and subject to appropriate penalties.

The methods used to conduct our evidence synthesis need to be repeated across further interventions and by other researchers and may need to be refined further. Given the considerable resources involved in using these methods, a system is needed to prioritise reviews of important drugs so that such methods are reserved for drugs that meet certain conditions. Priority could perhaps be given to first drugs of a new family, drugs considered to be innovative or those that are likely to have a big market impact. Such reviews should be publicly funded and be independent from both regulators and manufacturers. Researchers who conduct these 'high scrutiny' reviews need to be free of recent ties to either government or the pharmaceutical industry. Systematic review groups such as The Cochrane Collaboration should consider both adopting these methods for other drugs and whether perhaps to scrutinise the published reviews of prioritised drugs.

Finally, all documentary evidence relating to a trial on humans (including clinical study reports, regulatory documents, evidence syntheses) should be archived electronically with no statute of limitations.

Authors' note: in reviewing over 2 GB of data there is the possibility of mistakes. The authors would be grateful if readers could identify these. We promise that if we concur the record will be amended accordingly.

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REFERENCES

References to studies included in this review

167-101 {published data only}

GSK. Investigation of the efficacy of GG167 (zanamivir) in the treatment of influenza viral infections (late Phase II study: dose comparison study). Data on file.

JNAI-01 {published data only}

GSK. Investigation of the efficacy of CG167 in the treatment of influenza viral infections (phase II study) (Protocol No JNAI-01). Double blind, double dummy, randomized, placebo controlled, parallel group, multicenter study to investigate safety and route of administration of CG167 when inhaled, CG167 10 mg, or the combination of inhaled CG167 10 mg plus intranasal CG167 6.4 mg, administered twice daily for 5 days in the treatment of influenza A and B viral infections. Data on file.

JNAI-04 {published data only}

GSK. A multicenter two way layout randomized placebo-controlled double-blind trial parallel group comparative trial on the efficacy and safety of GG167 (zanamivir) 10 mg twice a day and 20 mg twice a day in the treatment of influenza type A and type B infections (late Phase II study: dose comparison study) (Protocol No. JNAI-04). Data on file.

JNAI-07 {published data only}

GSK. A multicenter two way layout randomized placebo-controlled double-blind trial parallel group comparative trial on the efficacy and safety of GG167 (zanamivir) 10 mg twice a day and 20 mg twice a day in the treatment of influenza type A and type B infections (late Phase II study: dose comparison study) (Protocol No. JNAI-07). Data on file.

JV15823 {published data only}

No authors listed. A randomized, placebo-controlled, multicenter study of oseltamivir (Ro 64-0796) in the treatment of influenza in Japanese subjects (Translation of summary Japanese report - of 29 pages). Data on file.

JV15824 {published data only}

No authors listed. Phase 3 study for prophylaxis of influenza with Ro64-0796 (15 page summary from Japanese). Data on file.

M76001 {published data only}

McGarty T. A randomized, double-blind, placebo-controlled, multicenter study of efficacy based on the time to treatment of influenza infection with the neuraminidase inhibitor Ro 64-0796 (also known as GS 4104). Data on file.

ML16369 {published data only}

No authors listed. A double-blind, randomized, placebo-controlled multicenter study of oseltamivir phosphate in the treatment of influenza infection in China. Data on file.

NAI30008 {published data only}

No authors listed. A double-blind, randomized, placebo-controlled, parallel group, multi-center study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for five days in the treatment of influenza in patients

12 years or over diagnosed with asthma or chronic obstructive pulmonary disease. Data on file.

NAI30009 {published data only}

Alfors S, Keene O, Grice R, Hammond J, Hendricks V, Martin N, et al. A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered by inhalation twice daily for five days in the treatment of symptomatic influenza A and B viral infections in children ages 5-12. Data on file.

NAI30010 {published data only}

Hunter S, Reilly L, Sharp S, West M, Alfors S, Hammond J, et al. A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within families. Data on file.

NAI30011 {published data only}

No authors listed. A randomised, double-blind, placebo-controlled study to evaluate the impact of inhaled zanamivir treatment on workplace attendance due to influenza A and B infections. Data on file.

NAI30012 {published data only}

No authors listed. A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for five days in the treatment of symptomatic influenza A and B viral infections in subjects aged over 65 years. Data on file.

NAI30015 {published data only}

No authors listed. A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for five days in the treatment of symptomatic influenza A and B viral infections in armed services personnel. Data on file.

NAI30020 {unpublished data only}

No authors listed. A double-blind, randomised, placebo-controlled, multicenter study in 2 parallel groups, to investigate the efficacy and safety of inhaled zanamivir (10 mg bd. via Diskhaler), for 5 days, in high risk patients with symptomatic influenza A and / or B infection. Data on file Synopsis only available.

NAI30028 {published data only}

No authors listed. A double-blind, randomised, placebo-controlled, multicenter study in 2 parallel groups, to investigate the efficacy and safety of inhaled zanamivir (10 mg bd via Diskhaler), for 5 days, in children aged 5 to 12 years with symptomatic influenza A and / or B infection. Data on file.

NAI30031 {published data only}

No authors listed. A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the

efficacy and safety of inhaled zanamivir 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within households. Data on file.

NAI30034 {published data only}

No authors listed. A double-blind, randomized, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day for 28 days in the prevention of symptomatic influenza A and B viral infections in community-dwelling high-risk populations. Data on file.

NAIA/B2008 {published data only}

No authors listed. A double-blind, randomized, placebo-controlled, multicenter, parallel-group study to investigate the efficacy and safety of zanamivir administered twice or four times a day for the treatment of influenza A and B viral infections. Data on file.

NAIA/B2009 {published data only}

No authors listed. A double-blind, randomised, placebo-controlled, multicentre, parallel-group study to demonstrate the efficacy and safety of zanamivir in the prevention and/or progression of influenza A and B viral infections. Data on file.

NAIA2005 {published data only}

MacLeod A, Gummer M, Raniga K, Hirst H, Keene O, Ossi M, et al. A double-blind, randomised, placebo-controlled multi-centre study to investigate the efficacy and safety of inhaled and intranasal zanamivir in the treatment of influenza A and B viral infections. Data on file.

NAIA2006 {published data only}

No authors listed. A double-blind, randomised, placebo-controlled multicentre study to investigate the efficacy and safety of zanamivir therapy in the prevention of progression of influenza A and B viral infections. Data on file.

NAIA3002 {published data only}

Elliott M, Flack N, Keene O, Szymborski P, Vega R (PharmaResearch, Inc). A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults. Data on file.

NAIA3003 {published data only}

No authors listed. A double-blind, randomized, parallel-group, multi-center study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day compared to the standard of care in controlling nursing home influenza outbreaks. Data on file.

NAIA3004 {published data only}

No authors listed. A double-blind, randomized, placebo-controlled, parallel-group, multi-center study to investigate the efficacy and safety of inhaled zanamivir 10 mg once a day in controlling nursing home influenza outbreaks. Data on file.

NAIA3005 {published data only}

Elliott M, Hunter S, Flack N, Crisp A, Szymborski P, Vega R. A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered once a day for 28 days in the prevention of symptomatic influenza A and B viral infections in community dwelling adults. Data on file.

NAIB2005 {published data only}

Leong J, Brennan J, Gummer M, Keene O, Wightman K. A double-blind, randomised, placebo-controlled, parallel-group, multi-centre study to investigate the efficacy and safety of inhaled plus intranasal zanamivir in the treatment of influenza A and B viral infections. Data on file.

NAIB2006 {published data only}

No authors listed. A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir in preventing progression of influenza A and B viral infections. Data on file.

NAIB2007 {published data only}

Perich R, Solterbeck A, Keene O, Leong J, Raniga K, MacLeod A. A double-blind, randomised, placebo-controlled, parallel-group, multi-centre study to investigate the efficacy and safety of inhaled and inhaled plus intranasal zanamivir in the treatment of influenza A and B viral infections. Data on file.

NAIB3001 {published data only}

Campion K, Gummer M, Keene O. A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of zanamivir administered twice daily in the treatment of influenza A and B viral infections in adults. Data on file.

NAIB3002 {published data only}

Man CY, Keene ON, Challoner T (Challoner Associates). A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults. Data on file.

NV16871 {published data only}

No authors listed. A double-blind, randomized, stratified, placebo-controlled study of oseltamivir in the treatment of influenza in children with asthma. Data on file.

PE-01 {unpublished data only}

No authors listed. A trial to investigate efficacy to reduce development of influenza symptoms in influenza infected patients treated with GG167 (protocol number PE-01 phase II clinical trial). A double-blind double-dummy, randomized, placebo-controlled, parallel group, multicenter study to investigate the efficacy reducing development of influenza symptoms and, safety and rout of administration of GG 157 when orally inhaled GG 167 10 mg, 6.4 mg nebulized intranasally or the combination of inhaled GG167 10 mg plus intranasal GG167 6.4 mg was administered twice day for 5 days in the treatment of influenza A and B viral infections. Data on file.

WV15670 {published data only}

Dorkings J. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomized controlled trial. Data on file.

WV15671 {published data only}

Dorkings J. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. Data on file.

WV15673/WV15697 {published data only}

No authors listed. Efficacy of Ro 64-0796 when used as chemoprophylaxis against natural influenza infection. Data on file.

WV15707 {published data only}

Grosse M. A multi-center, randomized, double-blind, placebo-controlled, parallel group study of oseltamivir treatment in elderly patients with influenza. Data on file.

WV15708 {published data only}

No authors listed. A double-blind randomised placebo controlled study of Ro 64-0796 (also known as GS4104) used in elderly subjects for the prevention of clinical influenza during influenza season. Data on file.

WV15730 {published data only}

Dorkings J. A double-blind, stratified, randomized, placebo controlled study of Ro 64-0796 (GS4104) in the treatment of influenza infection in adults. Data on file.

WV15758 {published data only}

No authors listed. A double-blind, randomized, stratified, placebo-controlled study of Ro 64-0796 (also known as GS 4104) in the treatment of children with influenza. Data on file.

WV15759/WV15871 {published data only}

Gerster T. A double-blind, randomized, stratified, placebo-controlled study of oseltamivir phosphate (Ro 64-0796, also known as GS 4104) in the treatment of influenza in children with chronic asthma. Data on file.

WV15799 {published data only}

No authors listed. A double-blind randomised placebo controlled study of Ro 64-0796 (also known as GS4104) for the prevention of clinical influenza post exposure in families. Data on file.

WV15812/WV15872 {published data only}

McCarvil M. A double-blind, stratified, randomised, placebo controlled study of Ro 64-0796 (also known as GS4104) in the treatment of influenza in chronically ill adults. Data on file.

WV15819/WV15876/WV15978 {published data only}

No authors listed. A double-blind, randomized, stratified, placebo-controlled study of Ro 64-0796 (also known as GS4104) in the treatment of influenza infection in elderly patients. Data on file.

WV15825 {published data only}

No authors listed. A double-blind, randomised, placebo-controlled study of Ro 64-0796 (also known as GS4104) used in

elderly subjects for the prevention of clinical influenza during the influenza season. Data on file.

WV16277 {published data only}

No authors listed. A double-blind, randomised, stratified, placebo-controlled study of oseltamivir in the treatment of influenza infection in patients. Data on file.

References to studies excluded from this review
105934 {published data only}

A post-marketing surveillance to monitor the safety of RELENZA (zanamivir) administered in Korean subjects according to the prescribing information. Data on file.

107485 {published data only}

An open label, single-dose, five-way crossover study examining relative oral bioavailability of zanamivir with bioenhancing excipients following direct release into mid-small intestine using gamma scintigraphy and the IntelliSite Companion Capsule in healthy subjects. Data on file.

108127 {published data only}

An open-label, non-randomized, single-dose study to evaluate serum zanamivir pharmacokinetics following intravenous administration to human subjects with renal impairment compared to subjects without renal impairment. Data on file.

112311 {published data only}

Special drug use investigation for Relenza (resistant appearance). Data on file.

112312 {published data only}

Special drug use investigation for Relenza (efficacy). Data on file.

113268 {published data only}

Drug use investigation for Relenza. Data on file.

113502 {published data only}

Prophylactic efficacy of Relenza against influenza A and B. Data on file.

113625 {published data only}

A randomized, placebo controlled, 3-way crossover study to investigate the safety, tolerability, and pharmacokinetics of repeat dose zanamivir/placebo 10 mg administered twice daily for 5 days by a rotahaler compared to the diskhaler in healthy subjects. Data on file.

113678 {published data only}

An open-label, multi-center, single arm study to evaluate the safety and tolerability of intravenous zanamivir in the treatment of hospitalized adult, adolescent and pediatric subjects with confirmed influenza infection. Data on file.

114045 {published data only}

Collection of patients' background information Relenza® sentinel site monitoring program in Japan. Data on file.

114373 {published data only}

A phase III international, randomized, double-blind, double-dummy study to evaluate the efficacy and safety of 300 mg or 600 mg of intravenous zanamivir twice daily compared to 75 mg of oral oseltamivir twice daily in the treatment of hospitalized adults and adolescents with influenza. Data on file.

167-02 {published data only}

A study of GG167 single blind, single administration - phase I. Data on file.

167-03 {published data only}

A study of GG167 single blind, single administration - phase I. Data on file.

167-04 {published data only}

A study of GG167 single blind, single administration - phase I. Data on file.

167-05 {published data only}

A study of GG167 single blind, single administration - phase I. Data on file.

167T3-11 {published data only}

(Zanamivir trial. Title unknown). Data on file.

ADS-TCAD-PO206 {published data only}

A randomized open label study comparing the efficacy, safety, and tolerability of oral administration of amantadine and ribavirin with oseltamivir versus oseltamivir to influenza A virus infected immunocompromised subjects. Data on file.

BP21288 {published data only}

A single-center, open-label, single dose, exploratory study in Caucasian and Japanese healthy subjects to investigate the pharmacokinetics of oseltamivir and its metabolite in plasma and cerebrospinal fluid. Data on file.

C94-009 {published data only}

Cass LM, Efthymiopoulos C, Bye A. Pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration to healthy volunteers. Clinical Pharmacokinetics. 1999;36 Suppl 1:1-11. Not posted to GSK CTR.

C94-085 {published data only}

Cass LM, Gunawardena KA, Macmahon MM, Bye A: Pulmonary function and airway responsiveness in mild to moderate asthmatics given repeated inhaled doses of zanamivir. Respiratory Medicine 2000;94(2):166-73. Posted to GSK CTR.

GCP/95/045 {published data only}

A study to investigate the pharmacokinetics of GG167 in subjects with impaired renal function. Data on file.

JNAI-02 {published data only}

(Zanamivir trial. Title unknown). Data on file.

JNAI-03 {published data only}

(Zanamivir trial. Title unknown). Data on file.

JP15734 {published data only}

Single ascending oral dose study of tolerability, safety and pharmacokinetics (including effect of food) of the neuraminidase inhibitor Ro 64-0796 in healthy male volunteers. Data on file.

JP15735 {published data only}

Multiple oral dose study of the tolerability, safety and PK of the neuraminidase inhibitor Ro64-0796: direct PK comparison between Japanese and Caucasian subjects. Data on file.

JV16284 {published data only}

Phase II clinical study of oseltamivir phosphate (Ro64-0796) for the treatment of influenza in children. Data on file.

JV21490 {unpublished data only}

* Post-marketing clinical study of oseltamivir phosphate on nighttime ECG in healthy adult male subjects. Data on file 2008.

M76006 {published data only}

Early administration of oral oseltamivir increases the benefits of influenza treatment. Data on file.

ML17279 {unpublished data only}

An observational study to assess the accuracy of diagnosis of influenza in community pharmacies. Data on file.

ML17713 {published data only}

Phase IV study on Tamiflu® capsule 75 in the elderly aged 80 years or older (a single dose oral administration study for assessing pharmacokinetics in the elderly not infected with influenza virus). Data on file.

ML19340 {unpublished data only}

Impact of oseltamivir (Tamiflu®) in post-exposure prophylaxis influenza on mortality and morbidity in institutionalised elderly people. [Impact de l'oseltamivir (Tamiflu®) en prophylaxie antigrippale post-exposition, sur la mortalité et la morbidité des personnes âgées institutionnalisées.]. Data on file.

ML20542 {published data only}

Evaluation of combination therapy with oseltamivir and zanamivir versus monotherapy in the treatment of virologically confirmed influenza in primary care a randomised double blind controlled trial study. Data on file.

ML21954 {published data only}

Efficacy and safety of combination therapies with oseltamivir & zanamivir or oseltamivir & amantadine versus oseltamivir monotherapy in the treatment of seasonal influenza A infection. Data on file.

ML22789 {published data only}

An unblinded, comparative, randomized study of influenza A/H1N1 2009 resistance in patients with standard and double dose oseltamivir treatment. Data on file.

ML22872 {published data only}

Viral shedding/resistance with double duration oseltamivir in infected patients (New Zealand). Data on file.

ML22879 {published data only}

Viral shedding/resistance with standard dose/duration oseltamivir in infected patients (UK). Data on file.

ML25018 {published data only}

A study of the relative oral bioavailability of the anti-flu medicine oseltamivir (Tamiflu®) in patients in the intensive care unit. Data on file.

ML25087 {published data only}

Viral shedding/resistance with double dose oseltamivir in infected patients (Australia). Data on file.

ML25094 {published data only}

Nasogastric administration of OP in infected patients with respiratory failure. Data on file.

ML25157 {published data only}

Oseltamivir pharmacokinetics in morbid obesity. Data on file.

ML25176 {published data only}

Open-label pharmacokinetic of oseltamivir in healthy obese Thai adult subjects. Data on file.

ML25179 {published data only}

A randomized, double-blinded controlled trial comparing high vs standard dose oseltamivir in severe, influenza infection in ICU. "ROSII Study". Data on file.

ML25265 {published data only}

Probing the functional expression of carboxyl esterase in preterm neonates using oseltamivir: a pragmatic observational study. Data on file.

ML25266 {published data only}

Plasma levels of oseltamivir in H1N1 infected patients supported by extracorporeal membrane oxygenation: a single-centre cohort study. Data on file.

MP20691 {published data only}

Effect of probenecid on the pharmacokinetics of oseltamivir. Data on file.

MV20043 {published data only}

A prospective study to assess household transmission of influenza and emergence and transmissibility of drug resistance to oseltamivir following treatment of children with influenza A and B. Data on file.

MV20050 {published data only}

High-dose versus standard-dose oseltamivir for the treatment of severe influenza and avian influenza: a phase II double-blind, randomized clinical trial. Data on file.

MV22926 {published data only}

A study on higher-dose oseltamivir treatment's impact on viral clearance and clinical recovery in adults hospitalized with influenza. Data on file.

MV22949 {published data only}

A study of the pharmacology of oseltamivir (Tamiflu) in pregnancy. Data on file.

MV22951 {published data only}

Pharmacokinetics of Tamiflu® (oseltamivir) in patients receiving extracorporeal membrane oxygenation (ECMO) and or continuous venovenous hemodialysis (CVVHD). Data on file.

MV22963 {published data only}

Pharmacokinetics of oseltamivir in critically ill adult patients. Data on file.

MV22970 {published data only}

Observational study on the pharmacokinetics of oseltamivir in the treatment of influenza during lactation. Data on file.

NAI106784 {published data only}

Phase I, open-label study to evaluate steady-state serum and pulmonary pharmacokinetics following intravenous administration of zanamivir in healthy adult subjects. Data on file.

NAI108166 {published data only}

Phase 1, open-label study to evaluate potential pharmacokinetic interactions between orally-administered oseltamivir and intravenous zanamivir in healthy Thai adult subjects. Data on file.

NAI10901 {published data only}

A double-blind, randomised, placebo-controlled study to evaluate the effect of inhaled zanamivir 10 mg od for 28 days on anti-haemagglutinin antibody production (HAI titre) following co-administration with Fluvirin™ trivalent influenza vaccine in healthy adult subjects. Data on file.

NAI10902 {published data only}

An open label, randomized evaluation of the direct measurement of zanamivir concentrations in respiratory secretions following a single dose inhalation of 10 mg RELENZA™ via DISKHALER in health volunteers. Data on file.

NAI40012 {published data only}

An open-label, multi-center study of the patient instructional leaflet for RELENZA DISKHALER. Data on file.

NAIA1009 {published data only}

Pharmacokinetics of zanamivir (GG167) following inhaled administration in pediatric subjects with signs and symptoms of respiratory illness. Data on file.

NAIA2010 {published data only}

Pilot, cluster randomised, open, single centre, parallel group study to evaluate the efficacy and safety of zanamivir in controlling influenza outbreaks and preventing the development of resistant influenza cases in a high risk nursing home population, compared with usual care. Data on file.

NAIB1001 {published data only}

Cass LMR, Brown J, Pickford M, Fayinka S, Newman SP, Johansson CJ, et al. Pharmacoscintigraphic evaluation of lung

deposition of inhaled zanamivir in healthy volunteers. Clinical Pharmacokinetics 1999 36:Suppl 1 (21-31). Not posted to GSK CTR.

NAIB1002 {published data only}

A study to evaluate the effect of repeat doses of GG167 dry powder on pulmonary function and bronchial hyper-responsiveness in asthmatic subjects. Data on file.

NAIB1007 {published data only}

A GG167 Pharmacokinetic Study to Select a Regimen for Prophylaxis. Data on file.

NCT00297050 {published data only}

A phase I double-blind, placebo-controlled, dose-escalating study to evaluate the safety and tolerability of intravenous peramivir in healthy subjects. Data on file.

NCT00416962 {published data only}

An open-label, multiple dose, randomized, three-period crossover study in healthy volunteers to evaluate the effect of co-administration of amantadine 100 mg BID and oseltamivir 75 mg BID on the pharmacokinetic properties of amantadine and oseltamivir. Data on file.

NCT00867139 {published data only}

TCAD vs. monotherapy for influenza A in immunocompromised patients. Data on file.

NCT00957996 {published data only}

A phase 3, open-label, randomized study of the antiviral activity, safety, and tolerability of intravenous peramivir in hospitalized subjects with confirmed or suspected influenza infection. Data on file.

NCT01063933 {published data only}

A pharmacokinetic/pharmacodynamic and safety evaluation of investigational intravenous peramivir in children with influenza disease (CASG 117). Data on file.

Not applicable (registry) {published data only}

(Oseltamivir trial. Title unknown). Data on file.

NP15525 {published data only}

Multiple ascending oral dose study of the tolerability, safety and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in healthy volunteers. Data on file.

NP15717 {published data only}

Study of the PD and PK of the neuraminidase inhibitor Ro 64-0796 (GS4104) in the treatment of volunteers experimentally infected with human influenza B virus. Data on file.

NP15718 {published data only}

An excretion balance and pharmacokinetic study of Ro 64-0796 after a single oral dose of 14C-labelled Ro 64-0796 and an intravenous dose of 14C-labelled Ro 64-0802 in healthy male subjects. Data on file.

NP15719 {published data only}

Study of the pharmacokinetics and absolute bioavailability of the neuraminidase inhibitor Ro 64-0796. Data on file.

NP15728 {published data only}

An open-label study of the effect of cimetidine and probenecid on the pharmacokinetics of Ro 64-0796/GS4104 in healthy subjects. Data on file.

NP15729 {published data only}

An open-label bioequivalence and food effect study of the clinical trial and market formulations of Ro 64-0796 in healthy subjects. Data on file.

NP15743 {unpublished data only}

No authors listed. A palatability study of the neuraminidase inhibitor (Ro 64-0796), formulated as an oral formulation. Data on file.

NP15757 {published data only}

No authors listed. Study of the pharmacokinetics and pharmacodynamics of the neuraminidase inhibitor Ro 64-0796 (GS4104) in the prophylaxis of experimental infection of volunteers with the human influenza B virus. Data on file.

NP15810 {published data only}

An open-label bioequivalence and food effect study of the clinical trial and market formulations of Ro 64-0796 in healthy subjects. Data on file.

NP15826 {published data only}

An open-label study of pharmacokinetics of Ro 64-0796/GS4104 in children. Data on file.

NP15827 {published data only}

Study of the pharmacodynamics of the neuraminidase inhibitor in the treatment of subjects experimentally infected with the human influenza B virus. Data on file.

NP15881 {published data only}

Palatability testing of the neuraminidase inhibitor Ro 64-0796 in children. Research Report No. W-144154/27 October 1999. Data on file.

NP15901 {published data only}

An open-label, two-way crossover pharmacokinetic drug interaction study of neuraminidase inhibitor Ro 64-0796/GS4104 and amoxicillin in healthy volunteers. Data on file.

NP15912 {published data only}

Palatability testing of the neuraminidase inhibitor Ro 64-0796 in children. Data on file.

NP16472 {published data only}

A single center, open label, multiple dose oral oseltamivir suspension study in end-stage-renal disease (ESRD) patients on hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD). Data on file.

NP22770 {published data only}

An open-label, multiple dose, randomized, three-period crossover study in healthy subjects to evaluate the effect of co-administration of oseltamivir (RO0640796) 75 mg twice daily and rimantadine 100 mg twice daily on the pharmacokinetic properties of oseltamivir and rimantadine. Data on file.

NP25138 {published data only}

A study of intravenous oseltamivir [Tamiflu] in infants with influenza. Data on file.

NP25139 {published data only}

A study of intravenous Tamiflu (oseltamivir) in children with influenza. Data on file.

NP25140 {published data only}

PK and safety of multiple ascending doses of iv oseltamivir in healthy adults. Data on file.

NV20234 {published data only}

A randomized, double-blind trial evaluating conventional and high dose Tamiflu in the treatment of influenza in immunocompromised patients. Data on file.

NV20235 {published data only}

A double-blind, randomized, placebo controlled multicenter trial of oseltamivir for the seasonal prophylaxis of influenza in immunocompromised patients. Data on file.

NV20237 {published data only}

An influenza resistance information study (IRIS). Data on file.

NV22155 {published data only}

A randomized, multicenter trial of oseltamivir [Tamiflu] doses of 75 mg for 5 or 10 days versus 150 mg for 5 or 10 days to evaluate the effect on the duration of viral shedding in influenza patients with pandemic (H1N1) 2009. Data on file.

NV22158 {published data only}

Avian/pandemic influenza registry final report, 30 August 2012. Data on file.

NV25118 {published data only}

A randomized, multicenter, parallel study of the safety, pharmacokinetics and the effect on viral activity of intravenously administered Tamiflu [oseltamivir] in patients with influenza over 13 years of age. Data on file.

NV25182 {published data only}

A prospective, observational safety study in children ≤ 24 months of age receiving oseltamivir for the treatment or prophylaxis of influenza infection. Data on file.

NV25655 {published data only}

An open-label, prospective, single oral dose study evaluating the pharmacokinetics, safety and tolerability of oseltamivir (Tamiflu) in adult subjects on peritoneal dialysis (PD) using a rapid cycle regimen to simulate automated peritoneal dialysis (APD) and in adult subjects with creatinine clearance from 10-30 mL/min not on dialysis. Data on file.

PP15974 {published data only}

A single oral dose, multi-center, open label study of the pharmacokinetics, safety and tolerability of Ro 04-0796/GS4104 in ESRD subjects on hemodialysis and peritoneal dialysis. Data on file.

PP16351 {published data only}

An open label study of the pharmacokinetics of oseltamivir (Ro 64-0796) in children aged 0 - 5 years old after a single dose. Data on file.

PP16361 {published data only}

Double-blind, randomized, placebo controlled, single ascending i.v. dose study of the tolerability (with emphasis of nausea and vomiting), safety, pharmacokinetics of oseltamivir (Ro 64-0796) and its active metabolite oseltamivir carboxylate (Ro 64-0802) in healthy male volunteers. Data on file.

PV15615 {published data only}

GS97802 - challenge flu A treatment. Data on file.

PV15616 {published data only}

GS-97801 challenge flu A treatment. Data on file.

WP15517 {published data only}

Single ascending oral dose study of the tolerability, safety and pharmacokinetics (including effect of food) of the neuraminidase inhibitor GS4104 in healthy volunteers. Data on file.

WP15525 {published data only}

Multiple ascending oral dose study of the tolerability, safety and pharmacokinetics of the neuraminidase inhibitor, GS4104 in healthy volunteers. Data on file.

WP15647 {published data only}

Multiple ascending oral dose study of the tolerability, safety and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in healthy elderly volunteers. Data on file.

WP15648 {published data only}

Multiple oral dose study of the pharmacokinetics, tolerability and safety of the neuraminidase inhibitor Ro 64-0796 in patients with renal impairment. Data on file.

WP15676 {published data only}

Study of the safety and pharmacokinetics of the neuraminidase inhibitor Ro 64-0796 in healthy volunteers when administered concomitantly with paracetamol (acetaminophen). Data on file.

WP15979 {published data only}

An open-label, relative bioavailability study of the phase III pediatric clinical trial and market formulations of Ro 64-0796 in healthy volunteers. Data on file.

WP16094 {published data only}

An open-label, three-way crossover, pharmacokinetic drug interaction study of neuraminidase inhibitor Ro 64-0796 and aspirin in healthy subjects. Data on file.

WP16134 {published data only}

An open label bioequivalence and food effect study of the enteric coated and immediate release formulations of oseltamivir in healthy subjects. Data on file.

WP16137 {published data only}

An open-label, bioequivalence study of the phase III pediatric clinical trial and market oral suspension formulations of Ro 64-0796 in healthy volunteers. Data on file.

WP16225 {published data only}

An open-label, relative bioavailability study of the market suspension (with improved process), the clinical trial suspension and market capsule formulation of Ro 64-0796 (Tamiflu, oseltamivir) in healthy subjects. Data on file.

WP16226 {published data only}

A study of the pharmacokinetics of oseltamivir (Ro 64-796) and its active metabolite Ro 64-0802 following single oral dosing of Ro 64-0796 to healthy volunteers and patients with moderate hepatic impairment. Data on file.

WP16254 {published data only}

A pharmacokinetic drug interaction study of oseltamivir (Ro 64-0796) and antacid in healthy volunteers. Data on file.

WP16263 {published data only}

A randomized, double blind, parallel group, placebo controlled study of the effect of oseltamivir on ECG intervals in healthy subjects. Data on file.

WP16295 {unpublished data only}

* A randomized, open label study of the site of absorption of oseltamivir in healthy subjects using an Enterion capsule. Data on file.

WP17721 {published data only}

Clinical pharmacokinetics of cyclosporine or mycophenolate with and without a concurrent single dose of oseltamivir phosphate in patients with a renal transplant. Data on file.

WP18308 {published data only}

Comparison of the pharmacokinetics of Ro 64-0802 following a single dose of oseltamivir phosphate either in a capsule or a drinking solution. Data on file.

WP20727 {published data only}

A combined single ascending dose, multiple ascending dose and exploratory bioavailability study to investigate the safety, tolerability and pharmacokinetics of intravenous Ro 64-0796 in healthy volunteers. Data on file.

WP20749 {published data only}

Oseltamivir treatment for children less than 24 months of age with influenza. Data on file.

WP21272 {published data only}

An open-label, randomized 2-period crossover study to investigate the pharmacodynamics, pharmacokinetics, safety and tolerability of warfarin, and the pharmacokinetics, safety

and tolerability of oseltamivir, when given in combination. Data on file.

WP22849 {published data only}

An open label, prospective, pharmacokinetic/ pharmacodynamic and safety evaluation of oseltamivir (Tamiflu®) in the treatment of infants 0 to < 12 months of age with confirmed influenza infection. Data on file.

WV15731 {published data only}

A double-blind, randomized, stratified pilot study of Ro 64-0796 (also known as GS4104) in children with influenza. Data on file.

WV16139 {published data only}

(Oseltamivir trial. Title unknown). Data on file. [Mentioned in EMA EPAR dated 23 March 2006 pdf page 14 but possibly same trial as WV 16193]

WV16193 {published data only}

A randomized, open-label, parallel group study of oseltamivir used for management of influenza in households. Data on file.

References to studies awaiting assessment
JPRN-JapicCTI-111647 {published data only (unpublished sought but not used)}

Kashiwagi S, Watanabe A, Ikematsu H, Awamura S, Okamoto T, Uemori M, et al. Laninamivir octanoate for post-exposure prophylaxis of influenza in household contacts: a randomized double blind placebo controlled trial. *Journal of Infection and Chemotherapy* 2013;**19**:740-9.

ML20589 {published data only}

Economic and social benefits of treating and preventing influenza in aged care facilities. Data on file.

ML20910 {published data only}

A randomized, open label study to evaluate the effect of Tamiflu on viral shedding and on serum and cytoplasmic inflammatory cytokine concentrations in patients with laboratory-confirmed influenza. Data on file.

ML21776 {published data only}

Pilot study to develop a model to evaluate nosocomial transmission of influenza. Data on file.

MV21118 {published data only}

A double-blind, randomized, placebo-controlled study of early oseltamivir treatment of influenza in children 1-3 years of age. Data on file.

MV21737 {published data only}

A phase 4, multi-center, randomized, double blind, placebo controlled study, to evaluate the safety of inhaled zanamivir 10 mg versus placebo and oral oseltamivir 75 mg versus placebo for influenza prophylaxis in healthy volunteers for 16 weeks. Data on file.

MV21879 {published data only}

Efficacy of oseltamivir in reducing the duration of clinical illness, viral shedding, and transmissibility reduction within households among participants in an influenza disease burden surveillance cohort in urban Dhaka, Bangladesh. Data on file.

MV22841 {published data only}

Viral shedding/resistance with standard dose/duration oseltamivir in infected patients (South Africa). Data on file.

MV22940 {published data only}

A randomised controlled trial on the effect of post-exposure oseltamivir prophylaxis on influenza transmission in nursing homes (PEPPIE). Data on file.

NCT00419263 {published data only}

A phase II, multicenter, randomized, double-mask, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza. Data on file.

NCT00453999 {published data only}

A phase II, multicenter, randomized, double-mask, double-dummy study comparing the efficacy and safety of peramivir administered intravenously once daily versus oseltamivir administered orally twice daily in adults with acute serious or potentially life-threatening influenza. Data on file.

NCT00486980 {published data only}

A phase 3 multicenter, randomized, double blind, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza. Data on file.

NCT00555893 {published data only}

Monitoring influenza severity and transmission on Tamiflu (MISTT). Data on file.

NCT00610935 {published data only}

A phase 3 multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of intramuscular peramivir in subjects with uncomplicated acute influenza. Data on file.

NCT00705406 {published data only}

A phase II, multicenter, randomized, placebo-controlled, study to evaluate the efficacy and safety of intramuscular peramivir 600 mg in subjects with uncomplicated acute influenza. Data on file.

NCT00958776 {published data only}

A phase 3, multicenter, randomized, double-blind, controlled study to evaluate the efficacy and safety of peramivir administered intravenously in addition to standard of care compared to standard of care alone in adults and adolescents who are hospitalized due to serious influenza. Data on file.

NCT00980109 {published data only (unpublished sought but not used)}

Anekthananon T, Pukritayakamee S, Ratanasuwan W, Jittamala P, Werarak P, Charunwatthana P, et al. Oseltamivir

and inhaled zanamivir as influenza prophylaxis in Thai health workers: A randomized, double-blind, placebo-controlled safety trial over 16 weeks. *Journal of Antimicrobial Chemotherapy* 2013;**68**:697-707. [NCT00980109]

NCT01032837 {published data only (unpublished sought but not used)}

Dharan NJ, Fry AM, Kieke BA, Coleman L, Meece J, Vandermause M, et al. Clinical and virologic outcomes in patients with oseltamivir-resistant seasonal influenza A (H1N1) infections: results from a clinical trial. *Influenza and Other Respiratory Viruses* 2012;**6**:153-8.

NV20236 {published data only}

An open label, multicenter trial of oseltamivir prophylaxis of seasonal influenza in children. Data on file.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

167-101

Methods	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study of zanamivir for the prophylaxis of influenza infection. Phase III study Location, number of centres: Japan, 5 centres Duration of study: 36 days (duration of administration: 28 days)
Participants	Number screened: not available Number randomised: 319 (zanamivir: 161; placebo: 158) Number completed (participants for efficacy analysis): 317 (zanamivir: 161; placebo: 156) M = 26.5%, F = 73.5% among 317 Mean age: 33.6 years Baseline details: all (at least most) Japanese; 1 (0.6%) vaccinated in zanamivir group, 0 in placebo group (within 8 months) Inclusion criteria: 1. Male or female healthcare workers aged 18 years and above at the time of the study 2. Participants who were able to take the first dose of study medication following notification of an influenza outbreak by the investigator 3. Participants who were willing and able to give written informed consent to participate in the study (if the subject is aged less than 20 years old, written informed consent is necessary from the subject itself and from the parental authority) 4. Able to use the diskhaler properly

167-101 (Continued)

5. Participants were willing and able to adhere to the protocol and the instructions of the investigator
6. Participants who, in the opinion of the investigator, could complete the symptom-diary card

Exclusion criteria:

1. Participants who have influenza-like illness (one or more of fever 37.5 °C or more, headache, sore throat, feverishness, muscle or joint pain, or cough) prior to the study during this influenza season
2. Participants who have any underlying illness which could influence the efficacy and safety assessment
3. Participants who were known or suspected to be hypersensitive to any component of the study medication (GG167, lactose) and relief medications (acetaminophen and dextromethorphan)
4. Participants who had received an investigational drug in the previous 3 months
5. Participants who had received any influenza antiviral therapy in the previous 7 days, e.g. amantadine
6. Participants who were pregnant, breast-feeding or intending to become pregnant during the study
7. Evidence of, or history of, such things as alcoholism, drug abuse, psychiatric disorders
8. Other conditions which the investigator decide inappropriate for participants of the study

Definition of patient populations for analysis

Intention-to-treat population: N = 319 (zanamivir: 161; placebo: 158): number randomised irrespective of the study medication

This is a secondary population for the analysis of efficacy data

Population for efficacy analysis:

Full analysis set (FAS): N = 317 (zanamivir: 161; placebo: 156)

All randomised participants except those who did not take at least 1 dose of study agent or whose efficacy data were not available. This is the secondary population for the analysis of efficacy

Non-vaccinated set (NVS) (N = 316) (zanamivir: 160; placebo: 156)

All non-vaccinated randomised participants who took at least 1 dose of study drug. This is the primary population for the analysis of efficacy

Per-protocol set (PPS) (N = 315) (zanamivir: 159; placebo: 156) [needs translation]

Safety population (N = 317) (zanamivir: 161; placebo: 156)

All randomised participants except those who met the exclusion criteria and did not take at least 1 dose of study agent. Primary population for analysis of safety data. This is the secondary population for the analysis of efficacy

Interventions	Zanamivir 10 mg once daily Placebo
Outcomes	The primary efficacy endpoint was the proportion of subjects who, during prophylaxis (d1 to d28), developed symptomatic, laboratory-confirmed influenza A or B infection (1) "Symptomatic influenza" was defined as the presence of at least 2 of the following influenza symptoms: fever of 37.5 °C or more, headache, sore throat, feverishness, myalgia, cough. Symptoms must have been present concurrently for 3 consecutive diary card entries (approximately 1.5 days) (2) Laboratory confirmation of influenza infection was a positive result by any of the following methods: culture or seroconversion

167-101 (Continued)

The secondary efficacy endpoint

1. Proportion of subjects who, during prophylaxis (d 3 to d 28), developed symptomatic, laboratory-confirmed influenza A or B infection that satisfied the 2 conditions above (1) and (2)
2. Proportion of subjects who, during prophylaxis (d 1 to d 28), developed laboratory-confirmed influenza infection
3. Proportion of subjects who, during prophylaxis (d 1 to d 28), developed laboratory-confirmed influenza infection and developed fever of 37.5 °C or more
4. Proportion of subjects who, during prophylaxis (d 1 to d 28), developed fever of 37.5 °C or more irrespective of the laboratory test results
5. Number of days, out of 28, the subject recorded use of relief medications (acetaminophen and cough suppressant)
6. Maximum recorded score on diary card
7. Development of secondary complications of influenza
8. Other outcomes to explore unique aspects of zanamivir based on the results

Safety outcome:

The safety measure was adverse events. Adverse events were defined as any unwanted or unexpected events. However, symptoms that were observed or did not worsen were not included as adverse events (pg 69 to 71/122; protocol)

Notes	Study period: 20 December 1999 to 3 March 2000 There was notable inconsistency in the results across different outcomes (see 'Risk of bias' section). The time period for assessment of antibody rise may have been inappropriate and increased the risk of bias in observed effects on outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	1. Participants were medical workers. There may have been selection bias prior to randomisation. pg 32/96 (CSR-PTC) and pg 36/122 (protocol) 2. The protocol says (pg 43/122, protocol), "study agents were randomly allocated" before distribution of the block (kumi) of study agents. However the random sequence generation method is not described. Randomisation was done before the distribution of the block of the study agents. Each block (kumi) contained 6 packages of study agents (3 packages for zanamivir and 3 packages for placebo) for 6 participants
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Incomplete outcome data (attrition bias) Symptoms	High risk	Unequal proportion of drop-outs between groups
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Unequal proportion of drop-outs between groups

167-101 (Continued)

Incomplete outcome data (attrition bias) Safety data	High risk	Unequal proportion of drop-outs between groups
Selective reporting (reporting bias)	High risk	The placebo contained lactose, which may cause bronchospasm in some participants. Hence the placebo used in this study may be a good control for the efficacy analysis but is not a good control for the safety analysis, because it increases the probability of adverse events in the control (lactose) group
Other bias	High risk	Use of healthcare workers could have resulted in under-reporting of adverse events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both treatments were identical in colour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No evidence of code-breaking

JNAI-01

Methods	Double-blind, randomised, placebo-controlled, parallel-group, multicentre trial to investigate the efficacy, safety and route of administration of zanamivir in the treatment of influenza A and B
Participants	Inclusion criteria: Subjects who met the following criteria and were judged to have influenza A or B viral infection by the investigator when influenza A or B was circulating in the region: 1. Otherwise healthy males or females aged 16 to 65 years old. Inpatient or outpatient 2. Have influenza-like illness (fever > 37.5 °C and at least 2 of the following symptoms: headache, myalgia, cough, sore throat) 3. Presenting within 24 hours (at most 36 hours) from influenza-like illness symptom onset 4. Willing to co-operate for the study and able to follow the investigator's instructions Exclusion criteria: 1. Suspected bacterial infection 2. Patients with chronic respiratory disease (including bronchial asthma), cardiovascular disease (excluding hypertension without complications), chronic metabolic disease (including diabetes), hepatic or renal impairment, anaemia or immunosuppression 3. Unstable chronic illness 4. Were receiving other intranasal or oral drug for topical application 5. Females who were pregnant, of child-bearing potential, breast-feeding or trying to become pregnant during the study period 6. Had received an investigational drug in the previous 3 months 7. Judged to be inappropriate for the study by the investigator Populations for efficacy analysis

JNAI-01 (Continued)

Randomised and treated population: 116 cases (A37, B40, C 39). 24 cases (8 cases each) were excluded due to GCP non-compliance

(1) Intention-to-treat population: N = 92 (A29, B32, C31) (116 randomised and treated minus 24 non-compliant with GCP were considered "intention-to-treat population". This is a secondary population for the analysis of efficacy data

(2) Per-protocol population: N = 68 (A25, B19, C24)

(3) Influenza-positive population: N = 56 (A16, B18, C22)

(4) Efficacy population: N = 49 (A15, B14, C20)

Populations for safety analysis: 116 cases (A37, B40, C 39)

Interventions	GG167 10 mg inhaled GG167 inhaled plus intranasal 6.4 mg administered twice daily for 5 days Placebo
Outcomes	Primary: time to alleviation of the 3 major and 5 major influenza symptoms (3 systemic symptoms typical of influenza: fever, headache and myalgia + 2 upper respiratory symptoms: cough and sore throat) Secondary: time to alleviation of individual symptoms (fever, headache, myalgia, cough and sore throat) Safety: incidence of drug-related abnormal symptoms/abnormal laboratory changes
Notes	Random allocation was done prior to the distribution and registration of participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method used for sequence generation not specified
Allocation concealment (selection bias)	Low risk	Centrally controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	High risk	The trial was terminated prematurely
Incomplete outcome data (attrition bias) Complications of influenza	High risk	The trial was terminated prematurely
Incomplete outcome data (attrition bias) Safety data	High risk	The trial was terminated prematurely
Selective reporting (reporting bias)	High risk	Methods of primary outcomes were not predefined in the protocol
Other bias	High risk	Corrected data were used for analysis. Endpoints were not described in the protocol; under-recruitment

JNAI-01 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatments were identical in colour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No breaking of the code allowed

JNAI-04

Methods	Double-blind, placebo-controlled trial of zanamivir in the treatment of influenza viral infection A and B. Late phase II study for dose comparison
Participants	16 years or older with influenza-like symptoms Inclusion criteria: 1. A temperature of 37.5 °C or greater plus at least 2 of the following: headache, muscle pain, cough, sore throat 2. Presenting within 24 hours (at most 36 hours) from influenza-like illness symptom onset 3. In general, aged 16 years or more irrespective of gender and irrespective of whether outpatient or inpatient 4. Not receiving treatment elsewhere for an underlying disease 5. Patient who intends to co-operate with the study and can be expected to follow the doctor's orders Exclusion criteria: 1. Patient suspected of having a bacterial infection 2. Patient with an unstable chronic disease 3. Pregnancy or suspicion of pregnancy as well as person planning to become pregnant during the course of the study and nursing mothers 4. Patient who was prescribed any investigational medication within the last 3 months 5. Any patient the investigator determines to be inappropriate for the study Populations for efficacy analysis Number screened N = 53 (3 were not eligible) Randomised N = 50 (1 was not treated and 1 was excluded due to incomplete informed consent) Randomised and treated population: 48 cases Low-dose active group (LA): 19, high-dose active group (HA): 13 Low-dose placebo group (LP): 10, high-dose placebo group (HP): 6 (1) Intention-to-treat population: 48 cases (LA19, HA13, LP10, HP6) (2) Per-protocol population: 38 cases (LA15, HA10, LP8, HP5) (3) Influenza-positive population: 22 cases (LA11, HA5, LP2, HP4) (4) Efficacy population: 18 cases (LA9, HA4, LP2, HP3)
Interventions	Zanamivir 10 mg twice daily for 5 days Zanamivir 20 mg twice daily for 5 days

JNAI-04 (Continued)

"Low" placebo twice daily for 5 days

"High" placebo twice daily for 5 days

Outcomes	Primary: time to alleviation of the 3 major influenza symptoms (fever, headache and myalgia) Secondary: - Time to alleviation of 5 major influenza symptoms (fever, headache and myalgia + cough and sore throat) - Proportion of subjects with individual influenza-like symptoms (fever, headache, myalgia, feverishness, cough, sore throat, arthralgia, lumbago, chillness, fatigue, nasal symptoms, diarrhoea and poor appetite) Safety: incidence of abnormal symptoms/abnormal laboratory changes, which were not denied as having causality by the investigator	
Notes	The primary and secondary outcomes were not defined in the protocol	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	Centralised randomisation
Incomplete outcome data (attrition bias) Symptoms	High risk	The study was terminated prematurely
Incomplete outcome data (attrition bias) Complications of influenza	High risk	The study was terminated prematurely
Incomplete outcome data (attrition bias) Safety data	High risk	The study was terminated prematurely
Selective reporting (reporting bias)	High risk	Populations of analysis were not predefined
Other bias	High risk	The primary and secondary outcomes were not defined in the protocol
Blinding of participants and personnel (performance bias) All outcomes	High risk	Low and high dose differed in colour
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators were informed of the randomisation codes before unblinding

JNAI-07

Methods	A randomised, placebo-controlled trial of zanamivir in the treatment of influenza viral infection A and B. Late phase II study for dose comparison
Participants	Individuals visiting a participating outpatient centre where influenza A and B were circulating, who were diagnosed as having influenza A and B based on satisfying the following inclusion criteria: 1. A temperature of 37.5 °C or greater plus at least 2 of the following: headache, muscle pain, cough, sore throat 2. Presenting within 24 hours (at most 36 hours) from influenza-like illness symptom onset 3. In general, aged 16 years or more irrespective of gender and irrespective of outpatient or inpatient 4. Patient who intends to co-operate with the study and can be expected to follow the doctor's orders Exclusion criteria: 1. Patient suspected of having a bacterial infection 2. Patient with an unstable chronic disease 3. Pregnancy or suspicion of pregnancy as well as person planning to become pregnant during the course of the study and nursing mothers 4. Patient who was prescribed any investigational medication within the last 3 months 5. Patient who was prescribed amantadine within the last 7 days 6. Any patient the investigator determines to be inappropriate for the study Populations for efficacy analysis Number screened N = 336 (among those 4 were not eligible) Randomised with double-blinded state N = 333 (among those 4 were withdrawn consent) Randomised and treated population under double-blinded state (ITT): 329 cases Low-dose active group (LA): 107, high-dose active group (HA): 111 Low-dose placebo group (LP): 54, high-dose placebo group (HP): 57 (1) ITT (intention-to-treat) population: 329 cases (LA107, HA111, LP54, HP57) (2) FAS (full analysis set: ITT - 5 (consent withdrawn) - 4 (incomplete case record): 318 cases (LA101, HA110, LP51, HP56) (3) Per-protocol population (irrespective of influenza positivity): 244 cases (LA81, HA84, LP38, HP41) (4) Influenza-positive population (irrespective of protocol adherence): 225 cases (LA71, HA82, LP34, HP38) (5) Efficacy population (per-protocol and influenza-positive): 172 cases (LA55, HA63, LP26, HP28) Populations for safety analysis: 329 cases (LA107, HA111, LP54, HP57) Safety outcome: The safety measure was the incidence of abnormal symptoms/abnormal laboratory changes which include or exclude those "causality denied". "Abnormal symptoms or abnormal laboratory findings" are the adverse events defined as newly observed or remarkably worsened symptoms after treatment started or abnormal or worsened laboratory findings compared with those before treatment irrespective of the causal assessment
Interventions	Zanamivir 10 mg twice daily for 5 days Zanamivir 20 mg twice daily for 5 days "Low" placebo twice daily for 5 days

JNAI-07 (Continued)

"High" placebo twice daily for 5 days

Outcomes	Primary: time to alleviation of the 3 major influenza symptoms (influenza, fever, headache) Secondary: time to alleviation of 5 major influenza symptoms Change in antibody titre
Notes	The interventions were distinguishable in appearance

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method used for sequence generation not specified
Allocation concealment (selection bias)	High risk	Low and high doses of intervention differed in colour
Incomplete outcome data (attrition bias) Symptoms	High risk	Case narratives not fully provided
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Only the data for hospitalisation reported
Incomplete outcome data (attrition bias) Safety data	High risk	Symptoms that were part of the subject's influenza-like illness (ILI) according to the opinion of the investigator did not need to be reported as AEs. Only new or worsened symptoms (abnormal symptoms) and laboratory test results (abnormal laboratory tests results) were required to be reported
Selective reporting (reporting bias)	High risk	Populations of analysis were not predefined
Other bias	High risk	Baseline temperatures were almost significantly lower in the zanamivir group than the placebo group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Low and high doses of intervention differed in colour
Blinding of outcome assessment (detection bias) All outcomes	High risk	Low and high doses of intervention differed in colour

JV15823

Methods	Randomised, placebo-controlled, multicentre study of oseltamivir (Ro 64-0796) in the treatment of influenza in Japanese participants
Participants	Over 16 years of age; present within 36 hours of onset of symptoms of fever > 38.0 °C, plus 2 influenza symptoms

JV15823 (Continued)

Interventions	75 mg capsules, Ro 64-0796/V14 batch no. GMZ 0129/03 Matching placebo capsules: Ro 64-0796/V16 batch no. GMZ 0136	
Outcomes	Primary outcome The time to alleviation of all symptoms Secondary outcomes Total symptom score AUC Change in virus titre Time to return to the afebrile state Adverse events	
Notes	The available study report is a 29-page document in Japanese. The design and methods are similar to those of WV 15670 and 15671 (the "pivotal" treatment trials in adults) and the trial was intended as a "bridge" with the Western trial programme. The report does not contain any supporting data (i.e. statistical analysis plan, protocol, amendments, certificates of analysis and audit, randomisation lists, lists of investigators, IRB clearance and individual listings)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not specified as protocol and methods section were not available
Allocation concealment (selection bias)	High risk	Not specified as protocol and methods section were not available
Incomplete outcome data (attrition bias) Symptoms	High risk	92 participants excluded in efficacy analysis because infection with influenza virus could not be verified in the efficacy analysis
Incomplete outcome data (attrition bias) Complications of influenza	High risk	92 participants excluded in efficacy analysis because infection with influenza virus could not be verified in the efficacy analysis
Incomplete outcome data (attrition bias) Safety data	High risk	No drop-outs because of harms were reported but no breakdown by on- and off-treatment status reported
Selective reporting (reporting bias)	High risk	Not specified as protocol and methods section were not available
Other bias	High risk	Not specified as protocol and methods section were not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not specified as protocol and methods section were not available
Blinding of outcome assessment (detection bias)	High risk	Not specified as protocol and methods section were not available

JV15823 (Continued)
All outcomes

JV15824

Methods	Randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of Ro64-0796 for the prophylaxis of influenza A and B
Participants	Participants ≥ 16 years of age and without influenza-like symptoms
Interventions	Ro64-0796/V14 75 mg capsule Ro64-0796/V16 placebo capsule
Outcomes	Primary outcome Rate of occurrence of influenza Secondary outcomes Rate of occurrence for patients infected with non-clinical influenza Rate of occurrence for patients infected with non-symptomatic influenza Rate of occurrence for patients infected with influenza-like disease Safety
Notes	The available clinical study report is a 15-page document translated into English from the Japanese original. The design and methods are similar to those of WV 15697/15673 (the "pivotal" prophylaxis trials in adults) and the trial was meant as a "bridge" with the Western trial programme. The report does not contain any supporting data (i.e. statistical analysis plan, protocol, amendments, certificates of analysis and audit, randomisation lists, lists of investigators, IRB clearance and individual listings)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not specified as protocol and methods section were not available: method of sequence generation not reported
Allocation concealment (selection bias)	High risk	Not specified as protocol and methods section were not available
Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT analysis included all randomised participants; all participants who took at least 1 dose of medication were included in the safety population (CSR G-146); no systematic differences in drop-outs
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	ITT analysis included all randomised participants
Incomplete outcome data (attrition bias) Safety data	High risk	All participants who took at least 1 dose of medication were included in the safety population (CSR G-146); no systematic differences in drop-outs but no breakdown by on- and off-treatment status reported, only aggregate in treatment summary table

JV15824 (Continued)

Selective reporting (reporting bias)	High risk	Not specified as protocol and methods section were not available; unclear if there were any amendments
Other bias	High risk	No reporting of methods; no protocol; 4 participants not registered received the clinical trial drug
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not specified as protocol and methods section were not available
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not specified as protocol and methods section were not available

M76001

Methods	Randomised, double-blind, placebo-controlled, parallel-group study stratified by onset of influenza symptoms. Influenza surveillance programme set up to track outbreak of virus across the United States Location, number of centres: USA (164 centres) Duration of study: 21 (+/-4) days
Participants	Number screened: not available Number randomised: 1459 (oseltamivir: 965; placebo: 482. N randomised but did not receive study drug: 12) Number completed: 1344 M = 44% F = 56% Mean age: 35 years Baseline details: 81% Caucasian Inclusion criteria 1. Ambulatory male and female outpatients, aged ≥ 13 to 80 years of age 2. Symptoms consistent with influenza 3. Fever $\geq 100^\circ\text{F}$ (documented in the office/clinic) PLUS at least 1 respiratory symptom (cough, sore throat, nasal congestion) PLUS at least 1 constitutional symptom (chills/sweats (feeling feverish), headache, myalgia (aches and pains), fatigue) 4. No more than 36 hours post onset of feeling unwell 5. Negative urine pregnancy test in women of childbearing potential 6. Willing and able to comprehend and give written informed consent Exclusion criteria 1. Patients with unstable or uncontrolled renal, cardiac, pulmonary, vascular, neurological or thyroid disorders, diabetes, adrenal disease, hepatitis or cirrhosis. Stable disease is defined as disease not requiring a major change of therapy or hospitalisation for 8 weeks prior to the first dose of study drug 2. Transplant recipients 3. Patients taking systemic steroids or immunosuppressant therapies

M76001 (Continued)

4. Active cancer at any site (patients with basal cell carcinoma or a previous history of cancer in remission and not requiring therapy were eligible)
5. Known HIV infection
6. Pregnant or breast-feeding females
7. Female patients of childbearing potential unable to use an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study therapy
8. Allergy to any excipients in the capsule (section oseltamivir/Ro 64-0796) or acetaminophen (paracetamol)
9. Patients who experienced a previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis within 2 weeks prior to study day 1
10. Received antiviral therapy for influenza within 2 weeks prior to study day 1
11. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry
12. A clinically relevant history of abuse of alcohol or other drugs

Definition of patient populations for analysis
Intention-to-treat (ITT) infected population (N = 1063)

This population was the primary analysis population and was used for summaries and analyses of efficacy parameters and consisted of the same patients as the ITT population but excluded patients who did not have laboratory-confirmed infections. Patients were analysed according to the groups to which they were randomised

ITT population (N = 1447)

The ITT population consisted of all patients who took at least 1 dose of study medication and had at least 1 efficacy measurement. Patients with protocol violations or deviations were retained in the ITT population. Patients were analysed according to the groups to which they were randomised

Safety population (N = 1447)

Not defined

Standard population (N = 932)

This population was used for summaries of selected efficacy parameters. It included all patients who were randomised, who had no major protocol violations or deviations, who had laboratory-confirmed influenza and who received at least the first 6 scheduled doses

Interventions	Intervention: oseltamivir (size 2 capsules) 75 mg bid Control: matching placebo (size 2 capsules) bid For each treatment arm, patients were provided with a blister pack containing 12 capsules for 10 doses (2 extra capsules in case of damage or mishandling) Treatment period: 5 days Follow-up period: 12 to 18 days post-treatment Co-interventions: paracetamol 500 mg was also provided for symptomatic relief, if necessary
Outcomes	Primary outcome Duration of illness Length of time until alleviation of the symptoms of influenza (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches and chills/sweats). The time to alleviation of all 7 symptoms corresponds to the duration over which subsequent area under the curve calculations were made Secondary outcomes 1. Severity of illness

M76001 (Continued)

2. Duration of symptoms
3. Sequelae/complications due to influenza
4. Tertiary efficacy parameters
5. Serology
6. Use of symptom relief medications
7. Quality of life
8. Adverse events

Notes	The final protocol is dated 2 October 1998. There were no amendments to the protocol. The first patients received treatment on 24 December 1998. The Module 2 does not contain the statistical analysis plan, amendments or protocol amendments or certificates of analysis. As a consequence no additional information to further develop the M1 extraction was obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list shows random sequence and centralised phone driven system was used
Allocation concealment (selection bias)	Low risk	Centralised phone driven system: "The randomisation numbers were allocated by a central randomisation service, ICTI (Interactive Clinical Technologies Inc., Princeton, NJ)." "The investigator or study coordinator telephoned the Randomization Center to report their centre's identification number, the patient's initials, date of birth and time from the onset of flu symptoms. The Randomization Center then assigned a unique patient identification number and a corresponding medication number for each patient. The investigator or coordinator entered these numbers in the appropriate place on the case report form."
Incomplete outcome data (attrition bias) Symptoms	High risk	In the absence of IPD and CRFs we cannot account for all participants
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Unclear how complications of influenza were defined clinically
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events (AEs) could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting was inconsistent
Selective reporting (reporting bias)	High risk	Certificate of analysis is missing
Other bias	High risk	Potentially active placebo
Blinding of participants and personnel (performance bias) All outcomes	High risk	Capsule size is reported but no details of colour or taste or contents
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation code was unavailable to monitors or statisticians

ML16369

Methods	Randomised, double-blind, placebo-controlled trial conducted during the influenza epidemic season Location, number of centres: Beijing and Shanghai, China; 7 study centres Duration of study: 21 days
Participants	Number screened: not available Number randomised: 478 (baseline data on ITTI population only: 273 (oseltamivir: 134; placebo: 139)) Number completed: 451 M = (ITTI) 50% F = (ITTI) 50% Mean age: 31 years Baseline details: baseline information only available for the ITTI population Smoking history: 20%; influenza virus: A (62%); B (36.5%); unknown (1.5%) Inclusion criteria 1. Male/female patients with symptoms consistent with influenza: fever $\geq 37.8^{\circ}\text{C}$ PLUS at least 2 of the following symptoms (coryza/nasal congestion, sore throat, cough, myalgia/muscles aches and pain, fatigue, headache or chills/sweats) during an influenza outbreak in the community 2. No more than 36 hours post onset of feeling unwell 3. Aged ≥ 18 and ≤ 65 years of age 4. Willing and able to comprehend and give written informed consent 5. Patients must agree to utilise an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study therapy and females of childbearing potential must have a negative urine pregnancy test prior to drug dosing Exclusion criteria 1. Presentation > 36 hours post onset of feeling unwell 2. Patients with active clinically significant renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease), immunodeficiency disorders, cancer, hepatitis or cirrhosis 3. High likelihood of bacterial infection, based on signs, symptoms or laboratory tests, e.g. WBC $\geq 10.0 \times 10^9/\text{L}$ or N $\geq 90\%$ 4. Patients taking steroids or immuno-suppressant therapies 5. Allergy to any excipients in the capsule (see section 8.1) or paracetamol 6. Asthmatics and patients with COPD 7. Patients who experienced a previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis or received antibiotics for URTI, otitis, sinusitis or bronchitis or antiviral therapy for influenza, e.g. amantadine or rimantadine, within 2 weeks prior to study day 1 8. Dementia or other psychiatric condition that might interfere with the patient's ability to assess influenza symptomatology 9. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry 10. Administration of influenza vaccine less than 12 months prior to study day 1 11. A clinically relevant history of abuse of alcohol or other drugs 12. Pregnant or breast-feeding females 13. Transplant recipients 14. Known HIV infection Definition of patient populations for analysis

ML16369 (Continued)

ITT infected population (N = 273)

The population for primary efficacy analyses was the intention-to-treat-infected (ITTI) population comprising randomised participants who received at least 1 dose of study drug and had laboratory-confirmed influenza (a positive culture on day 1 and/or ≥ 4 -fold increase in HAI antibody between baseline and day 21 of the study)

ITT population (N = 451)

The ITT population consisted of all participants who took at least 1 dose of study medication. The safety population included all participants who received at least 1 dose of study medication and who had at least 1 safety follow-up, whether or not withdrawn prematurely

Safety population (N = 459)

Not defined

Interventions	Intervention: oseltamivir 75 mg (Ro 64-0796) bid Control: matching placebo bid Treatment period: 5 days Follow-up period: up to day 21 Co-interventions: contents of rescue pack of medication provided to study participants not reported
Outcomes	Primary outcome Duration of illness: the median duration was presented for each treatment group together with 95% confidence intervals. Kaplan-Meier graphs of duration of symptoms according to treatment group were provided. Although the primary analysis for the primary parameter was done using the ITTI population, an additional analysis for the primary parameter was done using the ITT population Secondary outcomes 1. Extent and severity of illness 2. Symptoms 3. Symptom relief medications consumption 4. Secondary illness 5. Adverse events
Notes	Conducted during influenza season from January to April 2001. No further information available in 2011 to 2013

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	Randomisation was pharmacy-controlled
Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT population outcome data reported

ML16369 (Continued)

Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on all participants irrespective of compliance with treatment or infection status
Selective reporting (reporting bias)	Low risk	Symptoms and outcomes of primary interest were available for ITT population
Other bias	High risk	No information available on placebo contents; under-recruitment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Participants and staff remained blinded to allocation status throughout the study. The investigator received a sealed envelope for each subject in the trial, for use in emergencies. Each envelope contained the identity of a subject's treatment."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Inadequate information available to ascertain whether outcome assessors were aware of treatment group assignment

NAI30008

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for 5 days in the treatment of influenza in patients aged 12 ≥ years diagnosed with asthma or COPD Location, number of centres: USA (46 centres); UK (36); France (23); South Africa (11); Norway (10); Canada (9); Australia (6); Germany (5); Slovakia (3); Austria (2); Belgium (2); Denmark (2); Sweden (2); Chile (1); Israel (1) Duration of study: 4 weeks
Participants	Males or females aged ≥ 12 years with influenza-like illness
Interventions	Zanamivir (5 mg per inhalation) 2 inhalations twice a day, via Rotadisks/modified Diskhaler Placebo 2 inhalations twice a day, via Rotadisks/modified Diskhaler
Outcomes	Primary outcome: Time to alleviation of clinically significant symptoms of influenza Secondary outcomes: Time to alleviation of clinically significant symptoms of influenza and no use of relief medication Time until the subject returned to normal activities Sleep disturbance measured by the number of nights during the treatment period and during the study period for which the subject recorded Maximum daily temperature Total number of tablets of supplied paracetamol taken over the treatment period

NAI30008 (Continued)

Total number of spoonfuls of supplied cough mixture taken over the treatment period

Incidence of complications of influenza and the incidence of associated antibiotic use

Mean PEFR as recorded on the diary card over the treatment period

FEV1 and PEFR as recorded in the clinic on days 6 and 28

Viral titres from throat swabs

Global assessment of symptoms as recorded by the physician on day 6

Notes Study period: June 1998 to April 2000. Asthmatic patients were excluded after trial commencement; discrepancies in rescue medications were reported and different allocation concealment routines occurred in different centres

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method used in sequence generation not specified
Allocation concealment (selection bias)	Low risk	Unblocked randomisation schedule provided by sponsor
Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT analysis included all randomised participants
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	The authors display data for safety and incidence of complications of influenza based on the ITT population
Incomplete outcome data (attrition bias) Safety data	Low risk	The authors display data for safety and incidence of complications of influenza based on the ITT population
Selective reporting (reporting bias)	Low risk	Outcomes reported as listed in protocol
Other bias	Low risk	Reasons for all protocol amendments were clearly reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sealed envelopes; only in the case of an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the subject, the investigator could unblind a subject's treatment assignment

NAI30009

Methods Randomised, double-blind, placebo-controlled, parallel-group multicentre study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered by inhalation twice daily for 5 days in the treatment of symptomatic influenza A and B viral infections in children ages 5 to 12

NAI30009 (Continued)

Location, number of centres: USA (36 centres); Canada (6); France (7); Germany (6); Belgium (2); Finland (2); Spain (2); Russia (2); Sweden (2); Israel (1) United Kingdom (1)

Duration of study: 14 to 28 days

Participants	Children aged 5 to 12 years with influenza-like illness (ILI)
Interventions	Zanamivir (5 mg per inhalation), 2 inhalations twice daily via Rotadisk/Diskhaler Placebo, 2 inhalations twice daily via Rotadisk/Diskhaler
Outcomes	Primary outcome: time to alleviation of clinically significant symptoms of influenza Secondary outcomes: Time to alleviation of clinically significant symptoms of influenza and no use of relief medication Time until the participant returned to normal activities Incidence of complications of influenza Antibiotic use for complications Mean overall assessment of diary card symptom score over post-treatment Number of days out of study days 2 to 5 where cough was recorded Maximum daily diary card temperature Number of days out of study days 2 to 5 where the participant's parent recorded use of any relief medication Total number of 12-hour periods during which supplied paracetamol was taken over the treatment period Total number of 12-hour periods during which supplied dextromethorphan cough mixture (pholcodine in Europe) was taken over the treatment period Investigator Global Assessment of Symptoms at the study day 3 visit and at the post-treatment visit Day 3 viral titre from throat swab Temperature as measured at the clinic visit on study day 3 for those participants with this assessment
Notes	Study conducted: 11 January 1999 to 19 April 1999. Different methods were used for allocation concealment in different countries

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method used for sequence generation not specified
Allocation concealment (selection bias)	Low risk	An unblocked randomisation schedule was used. Eligible participants were allocated the next (i.e. lowest) sequential participant treatment number available at each centre
Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT population included data for patients with missing diary cards

NAI30009 (Continued)

Incomplete outcome data (attrition bias) Complications of influenza	Low risk	ITT population included data for patients with missing diary cards
Incomplete outcome data (attrition bias) Safety data	Low risk	ITT population included data for patients with missing diary cards
Selective reporting (reporting bias)	High risk	Per-protocol population not defined in the protocol
Other bias	High risk	Use of different relief medications across different centres
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only in the case of an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the participant, could the investigator unblind a participant's treatment assignment. If the investigator broke the blind for an individual participant, the date and reason was recorded on the "status of treatment blind" page in the CRF. The investigator did not reveal the blind to the monitor

NAI30010

Methods	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within families Location, number of centres: USA (11 centres); Canada (2); Finland (1); UK (1) Duration of study: 11 days	
Participants	2 to 5 family members with at least 1 adult and 1 child with presence of influenza-like illness Definition of patient populations for analysis ITT population (N = 1158) Index cases ≥ 5 years and contact cases ≥ 5 years randomised to treatment. Index cases and contact cases < 5 years of age who did not receive treatment, were excluded from the ITT analysis. The family was included if at least 1 randomised family member was in the population Safety population (N = 1158) Index cases and contact cases who took at least 1 dose of study medication. Randomised participants excluded if there was clear evidence of failure to take study medication	
Interventions	Zanamivir powder (5 mg per inhalation) via Rotadisk/Diskhaler Placebo 2 inhalations via Rotadisk/Diskhaler Co-interventions Relief medication pack (contents not specified)	

NAI30010 (Continued)

Outcomes

Primary outcome: proportion of randomised families in whom at least 1 randomised contact developed symptomatic, laboratory-confirmed influenza A or B infection

Secondary outcomes:

Proportion of randomised families in whom at least 1 randomised contact developed laboratory-confirmed influenza A or B infection

Proportion of randomised families in whom at least 1 randomised contact developed laboratory-confirmed influenza A or B infection and where symptoms began anytime from start of treatment to day 11

Proportion of randomised families in whom at least 1 randomised contact developed a febrile illness during days 1 to 11

Proportion of randomised families in whom at least 1 contact case developed laboratory-confirmed influenza infection

Time to alleviation of clinically significant symptoms for randomised index cases

Time to alleviation of clinically significant symptoms and no use of relief medication for randomised index cases

Number of days unable to perform normal activities

Number of days of use of relief medication

Proportion of randomised families in whom at least 1 randomised contact developed a secondary infection

Temperature of randomised index case at clinic visit on study day 5

Notes

In Europe, it was discovered that clinical supplies were incorrectly packed [CSF pg 9]; recruitment was stopped and procedures were put in place to correct this error; all randomised family members received the same treatment as the index case [CSF pg 10] Study period: October 1998 to May 1999

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method used to generate sequence unspecified
Allocation concealment (selection bias)	Low risk	Blocked randomisation provided by sponsor
Incomplete outcome data (attrition bias) Symptoms	Low risk	All randomised participants included in ITT population for efficacy; low number of drop-outs
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	All randomised participants included in ITT population for efficacy; low number of drop-outs
Incomplete outcome data (attrition bias) Safety data	Low risk	Safety population based on randomised participants
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified in protocol and statistical analyses plan

NAI30010 (Continued)

Other bias	High risk	Protocol amendment before participant recruitment Protocol amendments were undertaken during the study, which involved the changing of endpoints and removal of laboratory tests, as well as including new exclusion criteria. In Europe, it was discovered that clinical supplies were incorrectly packed; recruitment was stopped and procedures were put in place to correct this error; all randomised family members received the same treatment as the index case
Blinding of participants and personnel (performance bias) All outcomes	High risk	Incorrect packing of supplies; use of different colours for index and contact cases; randomising all families to same treatment. No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Breaking of the randomisation code was forbidden

NAI30011

Methods	Randomised, double-blind, placebo-controlled study to evaluate the impact of inhaled zanamivir treatment on workplace attendance and healthcare outcomes due to influenza A and B infections	
Participants	Males or females aged 18 years and above with influenza-like illness	
Interventions	4 x 5 mg doses of micronised zanamivir (as dry powder, lactose blend) Matching placebo (lactose only)	
Outcomes	Primary outcome: time to alleviation of influenza symptoms Secondary outcomes: Time absent from work due to influenza symptoms Time to perception of influenza symptom improvement	
Notes	Protocol amendments were undertaken during the study which involved the changing of endpoints and removal of laboratory tests, as well as including new exclusion criteria	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	Low risk	The ITT population is included in the safety data
Incomplete outcome data (attrition bias)	Low risk	The ITT population is included in the safety data

NAI30011 (Continued)

Complications of influenza

Incomplete outcome data (attrition bias) Safety data	Low risk	The ITT population is included in the safety data
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified in the protocol
Other bias	High risk	2 protocol amendments occurred during trial; in 1 of these, there was re-defining of endpoints and removal of a laboratory test for antibody detection
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only in the case of an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the participant, could the investigator unblind a participant's treatment assignment. The investigator was not to reveal the blind to the monitor

NAI30012

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for 5 days in the treatment of symptomatic influenza A and B viral infections in participants aged > 65 years
Participants	Male or female participants aged > 65 years (with or without underlying medical conditions) with ILI
Interventions	Zanamivir (GG167) powder (5 mg inhalations), 2 inhalations, twice daily, for 5 days, via Rotadisk/Diskhaler Placebo, 2 inhalations, twice daily, for 5 days, via Rotadisk/Diskhaler
Outcomes	Primary outcome: time to alleviation of clinically significant symptoms of influenza Secondary outcomes: Time to alleviation of clinically significant symptoms and no use of relief medication Complications of influenza Complications of influenza requiring antibiotic use Time to alleviation of individual symptoms Time to afebrile status Use of supplied paracetamol Global assessment of symptoms by the investigator Time to return to 'how I felt before influenza illness' Time to return to normal activities Viral titre levels at day 2/3, day 6 and day 14

NAI30012 (Continued)

Notes More participants in the placebo group had a high-risk medical condition compared with the zanamivir group, in both the ITT and influenza-positive populations. 2 deaths reported; neither were considered to be related to the drugs but case narratives are blanked out

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	Randomisation code provided by sponsor; unblocked randomisation schedule and sequential participant treatment number
Incomplete outcome data (attrition bias) Symptoms	Low risk	All randomised participants were analysed in the ITT sample for efficacy
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	All randomised participants were analysed in the ITT sample for efficacy
Incomplete outcome data (attrition bias) Safety data	Low risk	The safety population included all participants randomised to treatment and who took at least 1 dose of study medication
Selective reporting (reporting bias)	Low risk	All outcomes specified in the protocol reported
Other bias	High risk	More participants in the placebo group had a high-risk medical condition compared with the zanamivir group, in both the ITT and influenza-positive populations; protocol was amended 8 times during the trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Breaking of the code by opening the hidden portion of the detachable drug label or hidden entry envelope was expressly forbidden. Only in the case of an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the participant, could the investigator unblind a participant's treatment assignment. The investigator was not to reveal the blind to the monitor

NAI30015

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for 5 days in the treatment of symptomatic influenza A and B infections in armed service personnel
Participants	Participants were conscripts of the Finnish Army, living in residential units with influenza-like illness
Interventions	Inhaled zanamivir 10 mg (2 x 5 mg blisters), twice daily, for 5 days, via Rotadisk/Diskhaler

NAI30015 (Continued)

Placebo (2 blisters), twice daily, for 5 days, via Rotadisk/Diskhaler

Outcomes	Primary outcome: time to alleviation of clinically significant symptoms of influenza Secondary outcomes: Time to alleviation of clinically significant symptoms of influenza and no relief medication Time to afebrile status Total symptom score Viral load data Complications Maximum daily diary temperature during treatment Total number of 12-hour periods during which supplied paracetamol was taken over the treatment period Global assessment of symptoms Time to alleviation of individual symptoms	
Notes	No explicit report on randomisation and blinding procedures provided	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided; no information on method of sequence generation
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	Low risk	All randomised participants were analysed in the ITT sample for efficacy
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	All randomised participants were analysed in the ITT sample for efficacy
Incomplete outcome data (attrition bias) Safety data	Low risk	The safety population comprised all randomised participants
Selective reporting (reporting bias)	High risk	Protocol listed "MEP abnormalities (in a sub-set of participants)" as a secondary endpoint but it was not reported in the CSR
Other bias	Low risk	Only 1 protocol amendment comprising typographical corrections
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided

NAI30015 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators received hidden entry envelopes that contained the code break for each treatment number. Breaking of the code by opening the hidden entry envelopes was expressly forbidden except in the event of a medical emergency where the identity of the drug was necessary in order to treat the participant properly. In the event of such an emergency, it was requested that the investigator make every effort to contact the study monitor or designee prior to breaking the code

NAI30020

Methods	Randomised, double-blind, placebo-controlled, multicentre study in 2 parallel groups, to investigate the efficacy and safety of inhaled zanamivir (10 mg bid via Diskhaler), for 5 days, in high-risk patients with symptomatic influenza A and/or B infection
Participants	Eligible participants were adults aged ≥ 18 years, with symptomatic influenza A and/or B infection: feverishness ($> 37.8^{\circ}\text{C}$) and at least 2 of the 4 following symptoms: headache, muscle pains, myalgia, sore throat and cough, also with influenza-quick-test positive and categorised as "high risk" High risk was defined as: males and females aged > 60 years, participants living in an old peoples' home, participants with respiratory disorders including COPD or asthma, participants with diabetes mellitus, chronic renal failure or cardiovascular disorders Exclusions included pregnant women or women at risk of becoming pregnant during the study; participants with a suspected bacterial respiratory infection; participants with a known sensitivity to components of the intervention or placebo treatments or the emergency medications
Interventions	Zanamivir 2 inhalations (5 mg per inhalation) twice daily for 5 days Placebo 2 inhalations (5 mg per inhalation) twice daily for 5 days Participants were additionally provided with paracetamol and cough syrup as symptomatic medication, with guidance to take these only if there was "an acute need"
Outcomes	Primary outcome: time to alleviation of fever (time to first measurement with a temperature $< 37.8^{\circ}\text{C}$, maintained for the following 24 hours) Secondary outcomes: Time to alleviation of the other clinically relevant symptoms Time to return to normal activity Incidence of complications Loss of productivity assessed by number of days taken off work Use of medical services
Notes	Only a synopsis was provided for this trial; a full clinical study report was not available The total number of patients analysed was not clearly reported It appears that intention-to-treat analysis was not performed 43/329 randomised participants took the study drug but were excluded from the analysis according to prespecified exclusion criteria (temperature too low, no diary available, fever stopped before medication taken - Clinical Research Associate findings at investigator's site)

Risk of bias

NAI30020 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method used for sequence generation not specified
Allocation concealment (selection bias)	High risk	Concealment of allocation was not reported
Incomplete outcome data (attrition bias) Symptoms	High risk	Blinding of participants and personnel was not reported
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Blinding of outcome assessors was not reported
Incomplete outcome data (attrition bias) Safety data	High risk	Blinding of participants, personnel and assessors was not reported
Selective reporting (reporting bias)	High risk	Statistical analysis plan was not available and it is not possible to know the pre specification of outcomes
Other bias	High risk	The trial appeared to under-recruit but the numbers of participants are not clearly reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel was not reported
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessors was not reported

NAI30028

Methods	Randomised, double-blind, placebo-controlled, multicentre, comparative study in parallel groups to investigate the efficacy and tolerability of inhaled zanamivir, administered 2 x daily for 5 days
Participants	Children aged from 5 to 12 years with symptomatic influenza A and/or influenza B infection
Interventions	Zanamivir (dry powder for oral inhalation) in a circular foil pack (Rotadisks®) with 4 regularly distributed blisters each containing 5 mg zanamivir blended with 20 mg lactose Placebo Rotadisks® containing 25 mg lactose
Outcomes	Primary outcome: time to alleviation of all the clinically significant symptoms of influenza Secondary outcomes: Time to return to normal activities Complications

NAI30028 (Continued)

Notes The 2 SAEs (febrile convulsion and stomach ache) were considered by the investigators to be zanamivir-related

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random blocks
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled
Incomplete outcome data (attrition bias) Symptoms	High risk	5 participants were excluded from the analysis of efficacy due to insufficient diary card data
Incomplete outcome data (attrition bias) Complications of influenza	High risk	5 participants were excluded from the analysis of efficacy due to insufficient diary card data
Incomplete outcome data (attrition bias) Safety data	High risk	5 participants were excluded from the analysis of efficacy due to insufficient diary card data
Selective reporting (reporting bias)	High risk	The primary endpoint was originally the time to alleviation of the main signs/symptoms of influenza but this was later adjusted to the time to alleviation of fever. The presence of fever was indicated for all participants but the value was not recorded for 11 participants; data for these participants was, therefore, excluded from the per-protocol analysis
Other bias	Low risk	Low number of drop-outs in both groups; reasons reported. All participants included in safety population. There were no protocol amendments
Blinding of participants and personnel (performance bias) All outcomes	High risk	Identical Rotadisks used in both groups; placebo was reported to be lactose. No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were only allowed to break the study blind in an emergency, where knowledge of the participant's study medication was essential on clinical grounds

NAI30031

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within households
Participants	The index case was the first household member for whom a clinical diagnosis of ILI could be made
Interventions	Zanamivir (GG167) powder (5 mg per inhalation) 2 inhalations via Rotadisk/Diskhaler Placebo, 2 inhalations via Rotadisk/Diskhaler

NAI30031 (Continued)

Outcomes

Primary outcome: the proportion of randomised households in which at least 1 randomised contact case developed symptomatic, laboratory-confirmed influenza A or B infection

Secondary outcomes:

The proportion of randomised households in which at least 1 randomised contact case developed laboratory-confirmed influenza infection

The proportion of randomised households for which at least 1 randomised contact case developed symptomatic influenza-like illness (irrespective of laboratory confirmation).

The proportion of randomised households in which at least 1 randomised contact case developed symptomatic, laboratory-confirmed influenza infection, excluding any failures that occurred within 1 day of the start of prophylaxis

The proportion of randomised households in which at least 1 randomised contact case developed laboratory-confirmed influenza and a febrile illness

The number of days out of 28 at least 1 randomised contact case was unable to perform all their normal activities

The number of days out of 28 at least 1 randomised contact case recorded the use of relief medication

The proportion of randomised households in which at least 1 randomised contact case developed any secondary complication of influenza

The proportions of randomised households in which at least 1 randomised contact case develops symptomatic, laboratory-confirmed influenza and the flu type of the index case matches that of all the contact cases who develop influenza

Time to alleviation of clinically significant symptoms of influenza in contact cases developing symptomatic, laboratory-confirmed influenza during prophylaxis

Notes

Some outcomes in the clinical study reports were not listed in the protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided, but sequence generation not specified
Allocation concealment (selection bias)	Low risk	Blocked randomisation schedule was used. Each randomised household contact case was allocated the next (i.e. lowest) sequential treatment number available for that household
Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT population available
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	ITT population available
Incomplete outcome data (attrition bias) Safety data	Low risk	The safety population was defined as all contact cases randomised to treatment who took at least 1 dose of study medication
Selective reporting (reporting bias)	High risk	Several outcomes reported in clinical study reports were not listed in the protocol

NAI30031 (Continued)

Other bias	High risk	Patients receiving antibiotics for bacterial RTI were excluded in the protocol but not in the clinical study reports
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Breaking of code only permitted in emergency

NAI30034

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day for 28 days in the prevention of symptomatic influenza A and B viral infections in community-dwelling, high-risk participants aged ≥ 12 years	
Participants	Community-dwelling males and females aged ≥ 12 years at greatest risk for developing complications from influenza	
Interventions	Zanamivir powder (5 mg per inhalation) 2 inhalations, once daily for 28 days, via Rotadisk/Diskhaler Placebo, 2 inhalations, once daily for 28 days, via Rotadisk/Diskhaler	
Outcomes	Primary outcome: the proportion of randomised participants who, during prophylaxis (days 1 to 28), developed symptomatic, influenza A or B infection confirmed by culture/serology Secondary outcomes: The proportion of randomised participants who developed influenza confirmed by culture/serology The proportion of randomised participants who, during prophylaxis, developed influenza-like illness (ILI); developed a febrile illness	
Notes	Protocol states several other secondary outcome measures; these modifications are not listed in the protocol amendment section: the total number of over-the-counter medications used; the proportion of randomised participants who require a prescription medication; the total number of prescription medications used; the proportion of randomised participants who have an unscheduled healthcare contact; and the total number of unscheduled healthcare contacts	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided; method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation; a blocked randomisation schedule was used. Eligible participants were always allocated the next (i.e. lowest) sequential treatment number available
Incomplete outcome data (attrition bias) Symptoms	Low risk	Low number of drop-outs, reasons reported. There were the same number of participants in the safety population and the ITT population

NAI30034 (Continued)

Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Low number of drop-outs, reasons reported. There were the same number of participants in the safety population and the ITT population
Incomplete outcome data (attrition bias) Safety data	Low risk	Low number of drop-outs, reasons reported. There were the same number of participants in the safety population and the ITT population
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified in protocol
Other bias	High risk	5 protocol amendments, with 1 after trial commencement; amended the definition of confirmed influenza
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, participants and study monitors were unaware of which treatment a participant was randomly assigned to receive. Only in the case of an emergency, when knowledge of the study drug was essential for the clinical management or welfare of the participant, was the investigator permitted to unblind a participant's treatment assignment

NAIA/B2008

Methods	Randomised, double-blind, placebo-controlled, multicentre, parallel-group study to investigate the efficacy and safety of zanamivir administered twice or 4 times a day for the treatment of influenza A and B viral infections
Participants	Males and females aged ≥ 13 years with influenza-like illness; ≥ 18 years in some centres
Interventions	Zanamivir was provided as a solution for intranasal administration at a concentration of 16 mg/ml in saline and as a dry powder for inhalation Placebo was normal saline (for intranasal spray) and dry lactose powder to match zanamivir (for inhalation)
Outcomes	Primary outcome: Time until the alleviation of clinically significant symptoms of influenza Secondary outcomes: Time to eradication of major influenza symptoms Time to alleviation of each of the symptoms in the diary card Combined symptom analysis Time until the patient returned to normal activities Number of days that the overall symptom assessment was recorded Number of days that at least 1 symptom was recorded Number of days that sleep disturbance was recorded as 'not at all' or 'slightly' over the whole period covered by the diary card

NAIA/B2008 (Continued)

Maximum daily temperature

Mean daily number of administrations of supplied paracetamol (acetaminophen) over the treatment period

Mean daily number of administrations of supplied cough mixture over the treatment period

Investigator-rated global assessment of symptoms

Number of cases of hospitalisation resulting from influenza infection

Notes Combined symptom analysis as a secondary endpoint was added to the final analysis plan after the trial commenced (14 May 1996). The symptoms of feverishness, headache, myalgia, cough and sore throat were summarised by the mean symptom score to provide a measure of overall severity

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation codes provided; but method used for sequence generation not specified
Allocation concealment (selection bias)	Low risk	Generated using GWRD program (PACT)
Incomplete outcome data (attrition bias) Symptoms	Low risk	Similar number of withdrawals in both groups (6%)
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Similar number of withdrawals in both groups (6%)
Incomplete outcome data (attrition bias) Safety data	Low risk	ITT population was safety population
Selective reporting (reporting bias)	High risk	Several secondary endpoints were changed; 1 was added to the clinical study reports that was not in the protocol
Other bias	High risk	Protocol amendments do not list changes to secondary endpoints; variation in minimum age for inclusion
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each investigator was provided with a sealed envelope containing the individual code-break envelopes for patients in their centre. These were only to be opened in a medical emergency, where knowledge of the study treatment was essential for further management of the patient

NAIA/B2009

Methods	Multicentre, randomised, double-blind, placebo-controlled trial was designed to investigate the efficacy and safety of zanamivir (inhaled, intranasal, inhaled combined with intranasal versus placebo) in the prevention of and/or reduction in progression of influenza (post-exposure prophylaxis)
Participants	Individuals without flu symptoms aged ≥ 13 years (aged ≥ 18 years in 3 European countries) at risk of developing influenza having been in close contact with an index case
Interventions	Zanamivir (16 mg/mL), 2 intranasal sprays per nostril (0.1 mL per spray) twice daily plus placebo 2 inhalations twice daily Zanamivir (5 mg per inhalation), 2 inhalations twice daily plus placebo 2 sprays per nostril twice daily Zanamivir (5 mg per inhalation), 2 inhalations twice daily plus zanamivir (16 mg/mL), 2 intranasal sprays per nostril (0.1 mL per spray) twice daily Placebo 2 inhalations twice daily plus placebo 2 sprays per nostril twice daily
Outcomes	Primary: the proportion with symptomatic influenza, with laboratory confirmation, during treatment period Secondary: The proportion of patients with a fever (temperature 37.8°C) during the treatment period Number of days over the study period (day 1 to 5) that the patient recorded any symptom on the diary card as 'none' or 'mild' Number of days over the study period (day 1 to 5) that the patient recorded the overall symptom assessment on the diary card as 'none' or 'mild' Investigator-rated global assessment of symptoms (GAS)
Notes	The study aimed to recruit 840 but randomised 575 participants; the protocol was amended 6 times

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Symptom outcomes analysed with intention-to-treat population (all randomised)
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Outcomes analysed with intention-to-treat population (all randomised)
Incomplete outcome data (attrition bias) Safety data	Low risk	Safety outcomes analysed with safety population (all randomised who took at least 1 dose of study treatment)
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported as stated in protocol

NAIA/B2009 (Continued)

Other bias	High risk	Patient-rated assessment not reported as outcome; lack of statistically significant power
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The monitors were blinded as to the study treatment administered. No investigator revealed the blind for study medication prior to trial completion

NAIA2005

Methods	Randomised, double-blind, placebo-controlled multicentre trial, designed to evaluate the efficacy and safety of inhaled and intranasal zanamivir in the treatment of influenza A and B viral infections
Participants	Eligible participants were individuals aged ≥ 13 years generally in good health, enrolled within 48 hours of the onset of influenza-like illness
Interventions	Zanamivir 2 inhalations (5 mg per inhalation) twice a day plus placebo 2 sprays per nostril twice a day Zanamivir 2 inhalations (5 mg per inhalation) twice a day plus zanamivir (16 mg/mL) 2 intranasal sprays per nostril (0.1 mL per spray) twice a day Co-interventions Paracetamol, dextromethorphan hydrobromide and pseudoephedrine hydrochloride
Outcomes	Primary outcome: time to alleviation of major influenza symptoms Secondary outcomes: Time (in days from initiation of treatment) to alleviation of feverishness, headache and myalgia Time (in days from initiation of treatment) to eradication of major signs and symptoms of influenza Time (in days from initiation of treatment) to alleviation and eradication of individual symptoms of influenza Combined symptom analysis Mean daily temperature over the study treatment period Number of days (from initiation of treatment) until the patient was able to return to normal activities Number of days out of days 1 to 10 that the patient recorded any symptom as 'moderate' or 'severe' Number of days out of days 1 to 10 that the patient recorded their overall symptom assessment (OSA) as 'moderate' or 'severe' Number of days out of days 2 to 10 that the patient recorded sleep disturbance as 'moderate' or 'severe' Mean supportive drug use (e.g. paracetamol, cough mixtures and decongestants) over the study treatment period Investigator global assessment of symptoms

NAIA2005 (Continued)

Day at which viral shedding fell below limit of quantitation (core centres only). Area under the viral shedding curve (core centres only)

Notes

A protocol amendment changed 1 exclusion criterion from patients with influenza vaccines administered since August 1993 to patients with influenza vaccines administered since 1 October 1994 during the recruitment period

Major protocol amendments

1. Modified the inclusion criteria to specify fever as a temperature $\geq 37.8^{\circ}\text{C}$ or 100.1°F
2. Changed patient populations from S = subset of patients at centres with experience in virology and X = all patients to C = core centre patients (centres with experience in virology), T = target patients (patients with whom symptom assessments and diary cards were reviewed by study site personnel) and X = all patients
3. Defined target patient population as 1 out of every 6 patients (except core centre patients) who was targeted for additional face-to-face diary card review and clinical symptom assessment by site study staff on days 2, 4 and 8
4. Modified adverse events to include those that were temporally related to study drug administration
5. Clarified the clinical symptom assessment and the diary card review for the core centre and target patients
6. Added section on unscheduled visits and clarified the withdrawal information
7. Revised statistical methods section
8. Changed 1 exclusion criterion from patients with influenza vaccines administered since August 1993 to patients with influenza vaccines administered since 1 October 1994

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Described as randomised; procedure generating randomisation schedule not available
Allocation concealment (selection bias)	Low risk	Centrally generated, pharmacy-controlled randomisation "Each investigator was provided with a sealed envelope containing the individual code break envelopes for patients in their centre."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Withdrawals included in ITT analyses for both efficacy and safety. Data from infected and non-infected participants were available
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Safety population based on randomised participants
Selective reporting (reporting bias)	Low risk	Change in SAP before trial commencement; outcomes reported as outlined in protocol
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events
Blinding of participants and personnel (performance bias)	High risk	No certificates of analysis were provided

NAIA2005 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator, all study staff, patients and the monitors were blinded as to the study treatment (zanamivir or placebo) administered; each investigator was provided with a sealed envelope containing the individual code-break envelopes for patients in their centres. These were to be opened in a medical emergency only, where knowledge of the study treatment was essential for further management of the patient

NAIA2006

Methods	Randomised, double-blind, placebo-controlled, multicentre trial investigating efficacy and safety of zanamivir in preventing progression of influenza A and B from asymptomatic to symptomatic, among cases exposed to suspected index cases	
Participants	Eligible participants were aged ≥ 13 years, with no signs or symptoms of influenza	
Interventions	Zanamivir (16 mg/mL) 2 intranasal sprays per nostril (0.1 mL per spray) twice a day plus placebo 2 inhalations twice a day Zanamivir 2 inhalations (5 mg per inhalation) twice a day plus placebo 2 sprays per nostril twice a day Zanamivir 2 inhalations (5 mg per inhalation) twice a day plus zanamivir (16 mg/mL) 2 intranasal sprays per nostril (0.1 mL per spray) twice a day Placebo 2 inhalations twice a day plus placebo 2 sprays per nostril twice a day	
Outcomes	Primary outcome: the proportion of patients with laboratory-confirmed influenza during treatment plus at least 2 clinically significant symptoms of influenza of 'moderate' or 'severe' severity during the study treatment period Secondary outcomes: The proportion of patients with influenza The proportion of patients with a fever (temperature 37.8°C) during the treatment period Number of days over the study period (day 1 to 5) that the patient recorded any symptom on the diary card as 'moderate' or 'severe' Number of days over the study period (day 1 to 5) that the patient recorded the overall symptom assessment on the diary card as 'moderate' or 'severe' Number of days over the study period (day 1 to 5) that the patient recorded 'moderate' or 'severe' sleep disturbance Number of days over the study period (day 1 to 5) that the patient recorded that they were unable to perform normal activities	
Notes	The aim was to recruit 380 participants. Only 64 contact case participants were recruited and randomised	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified

NAIA2006 (Continued)

Allocation concealment (selection bias)	Low risk	Pharmacy-controlled; codes were in sealed envelopes. No investigator revealed the blind for study medication prior to trial completion
Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT and safety population included all randomised and all who took at least 1 dose of medication respectively
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	ITT and safety population included all randomised and all who took at least 1 dose of medication respectively
Incomplete outcome data (attrition bias) Safety data	Low risk	ITT and safety population included all randomised and all who took at least 1 dose of medication respectively
Selective reporting (reporting bias)	Low risk	Outcomes were reported as stated in the protocol
Other bias	High risk	Inability to recruit adequate numbers, as initially planned
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator, all study staff, patients and the monitors were blinded as to the study treatment administered (zanamivir or placebo). Codes were to be opened in a medical emergency only, where knowledge of the study treatment was essential for further management of the patient

NAIA3002

Methods	Randomised, double-blind, placebo-controlled, multicentre trial to investigate the safety and efficacy of inhaled zanamivir in the treatment of symptomatic influenza A and B in adolescents and adults Location, number of centres: USA (72 centres); Canada (12) Duration of study: 28 days
Participants	Individuals aged ≥ 12 years, with ILI, in locations with influenza circulating in the community
Interventions	Zanamivir (5 mg per inhalation), 2 inhalations twice daily via Rotadisk/Diskhaler Placebo, 2 inhalations twice daily, via Rotadisk/Diskhaler Treatment period: 5 days Follow-up period: 23 days post-treatment Co-interventions: relief pack of medication (paracetamol and cough mixture)
Outcomes	Primary outcome: time until alleviation of clinically significant symptoms of influenza Secondary outcomes: Time to alleviation of clinically significant symptoms of influenza and no use of relief medication

NAIA3002 (Continued)

Maximum daily temperature summarised by area under the curve (AUC) over the treatment period

Time until the participant returned to normal activities

Time to alleviation of each individual symptom

Mean overall influenza score

Mean symptom score for each of the individual symptoms collected on the diary card

Total number of tablets of supplied paracetamol taken

Total number of spoonfuls of supplied cough mixture taken

Global assessment of symptoms at the post-treatment visit

Incidence of complications of influenza

Day 3 viral titre from throat swab

Productivity and healthcare resource utilisation outcomes

Notes

Major protocol amendments

1. Reference to 5 mL spoonfuls of dextromethorphan was deleted
2. Study personnel recorded in CRF, instead of diary card, whether first dose of study medication was given before or after 14:00 hours
3. Secondary complications would be recorded in the CRF
4. Second diary card was to be completed twice a day
5. Appendix 4 defined categories of influenza complications

Study period: October 1997 to April 1998

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	"...packs containing zanamivir or matching placebo were provided by the Pharmaceutical Supplies Department of Glaxo Wellcome Research and Development to Glaxo Wellcome Inc. The supplies were labelled and packed in Clinical Supply Operations at GWI for distribution to the study centres by Simirex, Inc., Mt. Laurel, NJ."
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data for ITT and IP populations available
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	All randomised participants included in ITT for efficacy; and all who took at least 1 dose of medication included in ITT for safety
Incomplete outcome data (attrition bias) Safety data	Low risk	All who took at least 1 dose of medication included in safety population
Selective reporting (reporting bias)	Low risk	All outcomes reported as specified in protocol

NAIA3002 (Continued)

Other bias	Low risk	Protocol amendments were explained and do not appear to have any influence on the outcomes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator, all staff, participants and study monitors were blinded as to the study treatment administered. Breaking of the code by opening the hidden portion of the detachable drug label was expressly forbidden except in the event of a medical emergency where the identity of the drug had to be known in order to treat the participant properly

NAIA3003

Methods	Randomised, double-blind, placebo-controlled, multicentre trial investigating the efficacy and safety of inhaled zanamivir compared with standard care in controlling outbreaks of influenza in nursing homes	
Participants	Participants in nursing homes were randomised when healthy and followed until an outbreak of influenza was declared in that nursing home	
Interventions	Zanamivir 2 inhalations (5 mg per inhalation) once a day plus 1 placebo tablet once a day Placebo 2 inhalations once a day plus 1 rimantadine tablet (100 mg) once a day	
Outcomes	Primary outcome: the proportion of randomised participants who, during prophylaxis, developed a new sign or symptom and had laboratory confirmation of influenza infection Secondary outcomes: The proportion of randomised participants who, during prophylaxis, developed febrile illness The proportion of randomised participants who, during prophylaxis (days 1 to 15) or anytime during the study (days 1 to 28), developed complications of influenza and had subsequent associated laboratory confirmation of influenza infection The proportion of randomised participants who, during prophylaxis (days 1 to 15) or anytime during the study (days 1 to 28), took an antibiotic due to complications of influenza and had subsequent associated laboratory confirmation of influenza infection The proportion of randomised participants who, during days 3 to 15 of prophylaxis, developed a new sign or symptom with subsequent associated laboratory confirmation of influenza infection The proportion of randomised participants who, during prophylaxis, had laboratory-confirmed influenza infection	
Notes	4 protocol amendments were made and do not appear to have any influence on the outcomes. Adverse event data were not extracted from this study because of exposure to rimantadine	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified

NAIA3003 (Continued)

Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	Low risk	All randomised participants included in ITT for efficacy
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	All randomised participants included in ITT for efficacy
Incomplete outcome data (attrition bias) Safety data	Low risk	All who took at least 1 dose of medication included in ITT for safety
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified in the protocol and analysis plan
Other bias	High risk	2 protocol amendments for interim safety analysis; some re-randomisation of patients occurred
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blind. As such, the investigators, participants and study monitors were unaware of which treatment a participant was randomly assigned to receive. Breaking of the code by opening the hidden portion of the detachable drug label was expressly forbidden except in the event of a medical emergency where the identity of the drug was necessary in order to treat the participant properly

NAIA3004

Methods	Randomised, placebo-controlled, multicentre trial performed in 12 nursing homes in Lithuania, the Netherlands and Israel
Participants	Participants without ILI, living in nursing homes
Interventions	Zanamivir 2 inhalations (5 mg per inhalation) once a day Placebo 2 inhalations once a day
Outcomes	Primary: the proportion of randomised participants who, during prophylaxis, developed a new sign or symptom and had laboratory confirmation of influenza infection Secondary: The proportion of randomised participants who, during prophylaxis, developed febrile illness (defined as a temperature of > 99.0 °F or > 37.2 °C) and had laboratory confirmation of influenza infection The proportion of randomised participants who, during prophylaxis (days 1 to 15) or anytime during the study (days 1 to 28), developed complications of influenza and had laboratory confirmation of influenza infection

NAIA3004 (Continued)

The proportion of randomised participants who, during prophylaxis (days 1 to 15) or anytime during the study (days 1 to 28), took an antibiotic due to complications of influenza and had laboratory confirmation of influenza infection

The proportion of randomised participants who, during days 3 to 15 of prophylaxis, developed a new sign or symptom with laboratory confirmation of influenza infection

The proportion of randomised participants who, during prophylaxis, had laboratory-confirmed influenza infection

Notes

There were 12 SAEs during the study. There were 3 deaths, causes as follows: MI during post-prophylaxis follow-up; liver cirrhosis and congestive heart failure (6 months after study completion); pleural effusion and probable lung cancer (3 months after the study). Some re-randomisation of patients occurred

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Symptom outcomes were reported using the intention-to-treat population (all randomised) as specified in the protocol and analysis plan
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Outcomes were reported using the intention-to-treat population (all randomised) as specified in the protocol and analysis plan
Incomplete outcome data (attrition bias) Safety data	Low risk	Safety outcomes were reported using the safety population (all randomised who took at least 1 dose of study medication) as specified in the protocol and analysis plan
Selective reporting (reporting bias)	Low risk	Outcomes were reported as specified in the protocol and analysis plan
Other bias	High risk	The protocol was amended 4 times; twice to allow for interim safety analysis and once to allow for extra recruitment. Some re-randomisation of patients occurred
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, participants and study monitors were unaware of which treatment a participant was randomly assigned to receive. Breaking of the code by opening the hidden portion of the detachable drug label was expressly forbidden except in the event of a medical emergency where the identity of the drug was necessary in order to treat the participant properly

NAIA3005

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study designed to investigate the efficacy and safety of zanamivir given by the inhaled route in the prevention of symptomatic disease caused by influenza A and B viral infections in community-dwelling adults Location, number of centres: USA, 2 centres Duration of study: 35 days
Participants	Males or females 18 years or greater from a university community without symptoms indicative of influenza prior to the prophylaxis phase of the study Definition of patient populations for analysis <i>Intention-to-treat population (N = 1107)</i> Not specified. <i>Safety (N = 1107)</i> All randomised participants who took 1 dose of study drug. Primary population for analysis of safety data <i>Non-vaccinated population (N = 948)</i> All non-vaccinated randomised participants who took at least 1 dose of study drug. Primary population for the analysis of efficacy <i>Per-protocol (N = 891)</i> Not specified
Interventions	Zanamivir (5 mg per inhalation), 2 inhalations once a day via Rotadisk/Diskhaler Placebo, 2 inhalations once a day, via Rotadisk/Diskhaler Treatment period: 28 days Follow-up period: 7 days post-treatment Co-interventions: relief medication provided as paracetamol and cough mixture
Outcomes	Primary outcome: the proportion of non-vaccinated randomised participants who, during prophylaxis, developed symptomatic, laboratory-confirmed influenza A or B infection Secondary outcomes: The proportion of randomised participants who developed laboratory-confirmed influenza infection The proportion of randomised participants who, during days 3 to 28 of prophylaxis, developed symptomatic, laboratory-confirmed influenza infection The proportion of randomised participants who, during prophylaxis, developed a febrile illness with laboratory confirmation of influenza infection. A febrile illness was defined as a temperature of 37.8 °C The proportion of randomised participants who during prophylaxis developed a febrile illness irrespective of laboratory confirmation of influenza The maximum recorded score during days 1 to 28 for each of the symptoms recorded on the diary card The number of days out of 28 the participant was unable to perform all their normal activities The number of days out of 28 the participant recorded use of relief medication The proportion of randomised participants who, during prophylaxis, developed a secondary complication of influenza and had subsequent associated laboratory confirmation of influenza infection

NAIA3005 (Continued)

The proportion of randomised participants who, during prophylaxis, developed a secondary complication of influenza, irrespective of laboratory confirmation of influenza

The proportion of randomised participants who required antibiotics

The proportion of randomised participants who required an OTC medication

The proportion of randomised participants who required a prescribed medication

The proportion of randomised participants who had an unscheduled healthcare contact plus the mean number of unscheduled healthcare contacts

The proportion of randomised participants confined to bed/incapacitated plus the mean duration of incapacity because of influenza

The proportion of randomised participants who missed at least 1/2 day from work/school because of influenza and the mean duration missed from work/school

Notes

ITT population comprised all randomised participants. However, patients who had no diary card data from days 1 to 5 or were withdrawn prematurely from study treatment were not included

Patients who were at risk of developing complications were excluded from the study and the investigators did not list complications as an outcome

Inconsistencies occurred in the Protocol Summary, Study Plan and Study Procedures (Protocol 2 Amendment); cough and sore throat were listed as primary symptoms in clinical study reports but not in the protocol and the investigator global assessment was not listed in the protocol but was listed in the clinical study reports

Study performed prior to influenza season in 1997

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided; but method used to generate randomisation sequence not stated in clinical study reports
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Similar number of participant adverse events in zanamivir and placebo
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Similar number of participant adverse events in zanamivir and placebo
Incomplete outcome data (attrition bias) Safety data	Low risk	Similar number of participant adverse events in zanamivir and placebo
Selective reporting (reporting bias)	Low risk	All outcomes listed in protocol reported
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events. The protocol was amended twice during the course of the study; case narratives and CRFs blank

NAIA3005 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo described as "matching"; no certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Breaking of the code by opening the hidden portion of the detachable drug label was expressly forbidden except in the event of a medical emergency where the identity of the drug had to be known in order to treat the participant properly

NAIB2005

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled and intranasal zanamivir in the treatment of influenza A and B viral infections Location, number of centres: Belgium (3 centres); Finland (1); France (5); Germany (1); Italy (2); Netherlands (1); Norway (6); Spain (5); Sweden (4); UK (4) Duration of study: 28 days
Participants	Male or female aged ≥ 18 years with influenza-like illness for < 48 hours Number screened: not available Number randomised: 197 (zanamivir (inhaled): 64; zanamivir (inhaled and intranasal): 70; placebo: 63) Number completed: 185 M = 53 F = 47 Mean age: 34 years Baseline details: 96% Caucasian; 24% smokers Inclusion criteria 1. Male or female ≥ 18 years 2. Duration of ILI ≤ 48 hours (i.e. feverish and at least 2 of the following symptoms: headache, myalgia, cough, sore throat) 3. In good health except for current respiratory illness 4. Able to use diskhaler and aqueous nasal spray devices 5. Willing and able to adhere to protocol 6. Willing and able to give informed consent to participate in the study 7. Fluent and literate in the language spoken by the investigator and staff Exclusion criteria 1. Suspected bacterial infection 2. Influenza vaccine administered within previous year 3. At risk of developing complications from influenza infections (e.g. chronic active disorders of cardiovascular or pulmonary systems, chronic metabolic disease, hepatic or renal dysfunction, or immunosuppression) 4. Unstable chronic illness 5. Concurrent medical condition that could interfere with evaluations of safety or efficacy (e.g. perennial rhinitis, vasomotor rhinitis)

NAIB2005 (Continued)

6. Currently receiving intranasal or inhaled medication
7. Influenza antiviral therapy in previous 7 days
8. Pregnancy/lactation or likely to become pregnant during study
9. Received investigational drug in previous 30 days
10. Evidence or history of abuse of any drug substance
11. Use of antibiotic within the previous 7 days
12. Intolerance to lactose

Definition of patient populations for analysis
Influenza-positive population (N = 151)

All participants in the ITT population with laboratory-confirmed influenza determined either from pre-treatment diagnostic sample or a positive serology result. If diagnostic sample and serology were both positive but indicated different influenza types, influenza type was assigned according to diagnostic sample result. Secondary population for assessment of efficacy

Intention-to-treat population (N = 197)

All randomised participants included in the treatment group to which they were assigned even if no medication was taken. Primary population for assessment of efficacy

Safety (N = 196)

Participants randomised to treatment who took at least 1 dose of study medication. Participants excluded if there was clear evidence of failure to take any study medication. Used for safety data

Interventions

Zanamivir (5 mg per inhalation) 2 inhalations twice a day plus placebo 2 sprays per nostril (0.1 mL per spray) twice a day

Zanamivir (5 mg per inhalation) 2 inhalations twice a day plus zanamivir (16 mg/mL) 2 sprays per nostril (0.1 mL per spray, equivalent to 1.6 mg zanamivir) twice a day

Placebo 2 inhalations twice a day plus placebo 2 sprays per nostril (0.1 mL per spray) twice a day

Treatment period: 5 days

Follow-up period: 23 days post-treatment

Co-interventions: relief medication described and measured as an outcome but not clear whether this was administered as co-intervention

Outcomes

Primary outcome: time to alleviation of major influenza symptoms

Secondary outcomes:

Time (in days from initiation of treatment) to eradication of major signs and symptoms of influenza

Combined symptom analysis

Mean daily temperature over the study treatment period (days 1 to 5)

Number of days (from initiation of treatment) until the patient was able to return to normal activities

Number of days out of days 1 to 10 that the patient recorded any symptom as 'moderate' or 'severe'

Number of days out of days 1 to 10 that the patient recorded their overall symptom assessment (OSA) as 'moderate' or 'severe'

Number of days out of days 2 to 10 that the patient recorded sleep disturbance as 'moderate' or 'severe'

Mean supportive drug use

NAIB2005 (Continued)

Investigator global assessment of symptoms

Day at which viral shedding fell below limit of quantitation (core centres only)

Area under the viral shedding curve (core centres only)

Notes

The original intention was for 273 patients (91 patients per treatment group) to be recruited but due to the relatively low incidence of influenza, this target was not achieved.

The protocol for this study was amended twice. Both of these amendments were implemented prior to the commencement of recruitment. As a result of both internal discussions and external discussions with regulatory authorities, the statistical methods employed were substantially different from those documented in the protocol.

Cough and sore throat were reported as major symptom in clinical study reports but not in the protocol and discrepancies occurred between the protocol and clinical study reports regarding evaluation of viral shedding

Study period: November 1994 to April 1995

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided; but method used to generate randomisation sequence not stated in clinical study reports
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Data from ITT and IP populations available
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	No systematic differences in drop-out
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on randomised participants
Selective reporting (reporting bias)	Low risk	All outcomes listed in protocol reported
Other bias	High risk	As a result of both internal discussions and external discussions with regulatory authorities, the statistical methods employed were substantially different from those documented in the protocol
Blinding of participants and personnel (performance bias) All outcomes	High risk	The blind was maintained by ensuring that trial medication and placebo had an identical appearance, shape, administration schedule, smell and taste; no certificates of analysis were provided.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator, all study staff, patients and the monitors were blinded as to the study treatment administered. The blind was maintained by ensuring that trial medication and placebo had an identical appearance, shape, administration schedule, smell and taste. 1 envelope was opened for a patient 3 months after the conclusion of their treatment but as this was some time after treat-

NAIB2005 (Continued)

ment, it was not seen to affect the trial. The blind was not broken for any other patients entered into this study

NAIB2006

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study designed to evaluate the efficacy and safety of inhaled zanamivir in the prevention of progression of influenza A and B viral infections
Participants	Male or female ≥ 18 years exposed to an index case with symptoms of influenza-like illness within the previous 48 hours
Interventions	Zanamivir (5 mg per inhalation), 2 inhalations twice a day by Rotadisk/Diskhaler Placebo to match zanamivir, 2 inhalations twice a day by Rotadisk/Diskhaler
Outcomes	Primary outcome: the proportion of patients with laboratory-confirmed influenza during treatment plus at least 2 clinically significant symptoms of influenza of 'moderate' or 'severe' severity during the study treatment period Secondary outcomes: Proportion of patients with a documented fever during the study (temperature $> 37.8^{\circ}\text{C}$) Number of days with any 'moderate' or 'severe' symptoms Number of days overall assessment of symptoms as 'moderate' or 'severe' Number of days with moderate or severe sleep disturbance Number of days patient was unable to perform normal activities Investigator global assessment
Notes	Statistical methods section were revised to allow for stratification of vaccinated participants In the efficacy evaluations, nasal symptoms (nasal congestion, rhinorrhoea) were changed to nasal congestion (blocked, runny nose) Safety and non-vaccinated populations were not defined in the protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided, but method used for sequence generation not specified in clinical study reports
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	High risk	Patients who had no diary card data from days 1 to 5 were withdrawn prematurely from study treatment. Page numbers in clinical study reports blanked
Incomplete outcome data (attrition bias)	High risk	Patients who were at risk of developing complications were excluded from the study and the investigators did not list complications as an outcome. Page numbers in clinical study reports blanked

NAIB2006 (Continued)

Complications of influenza

Incomplete outcome data (attrition bias) Safety data	High risk	Patients were removed from the safety population if there was documented evidence of failure to take any study medication. Page numbers in clinical study reports blanked
Selective reporting (reporting bias)	Low risk	All outcomes listed in the protocol were reported in the clinical study reports. Pages number blanked
Other bias	High risk	Inconsistencies in the protocol summary, study plan and study procedures. Clinical study report pages for this information were censored
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators and participants reported to be blinded but the colour and appearance of the inhalers not described [clinical study reports page blanked out]; no certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No investigator revealed the blind for study medication prior to trial completion [clinical study reports page blanked out]

NAIB2007

Methods	Placebo-controlled, double-blind trial to evaluate the efficacy and safety of inhaled zanamivir and the combination of inhaled plus intranasal zanamivir in the treatment of influenza A and B viral infections Location, number of centres: Australia, New Zealand, South Africa (24 centres) Duration of study: 28 days
Participants	Male or females, aged 13 years and above (aged 16 and above, or aged 18 and above in some centres) with laboratory-confirmed influenza or influenza-like illness as defined by symptoms of feverishness and at least 2 of the following: headache, myalgia, cough, sore throat of less than or equal to 48 hours duration Number screened: not available Number randomised: 554 (inhaled zanamivir: 188; inhaled and intranasal zanamivir: 183; placebo: 183) Number completed: 456 M = 52% F = 48% Mean age: 30 years
Interventions	Zanamivir (5 mg per inhalation) 2 inhalations twice daily plus placebo 2 sprays per nostril (0.5 mL per spray) twice daily Zanamivir (5 mg per inhalation) 2 inhalations twice daily plus zanamivir (1 mg/mL) 2 sprays per nostril (0.5 mL per spray) twice daily Placebo 2 inhalations twice daily plus placebo 2 sprays per nostril (0.5 mL per spray) twice daily Treatment period: 5 days Follow-up period: 23 days post-treatment

NAIB2007 (Continued)

Co-interventions: paracetamol was provided for symptomatic relief

Outcomes	Primary outcome: time to alleviation of clinically significant symptoms of influenza Secondary outcomes: Time (in days from initiation of treatment) to alleviation of individual symptoms of influenza (feverishness, headache, myalgia, cough, sore throat, nasal congestion, weakness and loss of appetite). Alleviation of an influenza symptom was defined as a score of 'none' or 'mild', which had to be maintained over the next 24 hours Time (in days from initiation of treatment) until the patient returned to normal activities. This had to be maintained for the following 24 hours Time (in days from initiation of treatment) until the patient was able to return to usual daily activities and perform these as well as normal Mean symptom score. The 5 symptoms of feverishness, headache, myalgia, cough and sore throat were summarised by the mean symptom score over days 1 to 5 of treatment Number of days over the study period (days 1 to 5) that the patient recorded their overall symptom assessment (OSA) as 'moderate' or 'severe' Number of days over the study period (days 1 to 5) that at least 1 symptom was rated as 'moderate' or 'severe' Number of days over the study period (days 2 to 5) that sleep disturbance was recorded as 'moderate' or 'severe' Maximum daily temperature summarised over the study treatment period (days 1 to 5) Mean daily paracetamol use over the study treatment period (days 1 to 5) Investigator-rated global assessment of symptoms (GAS). The influenza infection status of patients rated by the investigator at the post-treatment visit as 'none', 'mild', 'moderate' or 'severe' Incidence of secondary infections
Notes	Due to logistic difficulties in receiving the results of influenza diagnostic tests within 48 hours of influenza symptom onset, some patients were recruited on the basis of a clinical diagnosis of influenza Cough and sore throat were reported as major symptoms in clinical study reports but not in the protocol Protocol amendment 3 necessitated revising the definition of serious adverse events and time line changes for the reporting adverse events. Amendments were also made to definitions for primary and secondary efficacy parameters and statistical analyses were modified Protocol amendment 4 was made to the age range included (13 to 65 years, 16 to 65 years and 18 to 65 years, respectively) and inclusion or exclusion of patients with asthma, to meet local regulatory and ethics committee requirements Study period: May 1995 to May 1996

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided; method of sequence generation not described in clinical study reports
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled allocation

NAIB2007 (Continued)

Incomplete outcome data (attrition bias) Symptoms	Low risk	ITT and IP population data available for symptom relief
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Attrition does not appear to be significantly different between groups; reasons for attrition reported
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on randomised participants
Selective reporting (reporting bias)	High risk	Protocol amendment 3, which necessitated revising the definition of serious adverse events and timeline changes for reporting adverse events. Cumulative day of alleviation used to report primary outcome rather than mean or median; this was not specified in the protocol
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events. Amendments were also made to definitions for primary and secondary efficacy parameters, inclusion/exclusion of participants; and statistical analyses were modified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Each investigator was provided with a sealed envelope containing the individual code-break envelopes for patients in their centres but colour and appearance were not reported; no certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...the monitors were blinded as to the study treatment administered." No investigator broke the blind for study medication prior to trial completion

NAIB3001

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir administered twice daily in the treatment of influenza A and B viral infections in adults Location, number of centres: Australia (6 centres); New Zealand (4); South Africa (3) Duration of study: 28 days
Participants	Males or females aged ≥ 12 years (age mean 37) with laboratory-confirmed influenza or influenza-like illness Number screened: not specified Number randomised: 455 (zanamivir: 227; placebo: 228) Number completed: 428 Definition of patient populations for analysis <i>Influenza-positive population (N = 321)</i> Secondary population for assessing efficacy. Defined as all participants the safety population who had confirmed influenza. Participants were included in this population if baseline culture test was positive

NAIB3001 (Continued)

or if rapid diagnostic test was positive or if serology results confirmed influenza infection (≥ 4 -fold increase in influenza antibody from day 1 to day 28)

Sensitivity analysis also performed for primary endpoint on population of patients confirmed as influenza-positive by either culture or serology

ITT population (N = 455)

Primary population for assessing efficacy. All randomised patients, regardless of whether or not the study drug was actually taken or completion of study. Participants analysed according to assigned treatment group irrespective of which medication they took during the study

Safety population (N = 455)

Primary population for the analysis of safety data. Defined as all participants randomised to treatment who took at least 1 dose of study medication. Randomised patients were excluded if there was clear evidence of failure to take study medication. Participants were analysed according to treatment group of the actual medication they took the majority of the time

High risk population (N = 76)

All patients in safety population at greater risk of complications if they became infected with influenza. Analysis of 'high risk' population restricted to primary endpoint, complications, adverse event incidence and serious adverse event incidence

All participants ≥ 65 years were in this population. In addition, conditions thought to predispose patients to greater risk of complications from influenza included concurrent cardiovascular conditions (excluding hypertension), concurrent respiratory conditions (asthmatics excluded if unmedicated), concurrent metabolic conditions and those who were immunocompromised

Interventions	Zanamivir (5 mg per inhalation) 2 inhalations twice a day Placebo 2 inhalations twice a day Treatment period: 5 days Follow-up period: 23 days post-treatment Co-interventions: paracetamol and cough mixture were provided for symptomatic relief
Outcomes	Primary outcome: time until alleviation of major signs and symptoms of influenza Secondary outcomes: Time to eradication of major signs and symptoms of influenza. Major signs and symptoms of symptoms of influenza were defined as fever, headache, myalgia, sore throat and cough. Eradication was defined as a score of 'none' for all symptoms, which had to be maintained over the next 24 hours Time to alleviation of each of the diary card symptoms calculated separately Time until the patient returned to normal activities. This was defined as the first day on which the patient recorded that they were able to carry out all their usual daily activities. This was required to be maintained for 24 hours (2 consecutive diary card entries) Mean symptom score over post-treatment assessments on days 1 to 5 and on days 1 to 14 Maximum daily temperature, the maximum of the temperatures was obtained for each day. The weighted mean of these values was calculated over the study treatment period. The AUC was calculated using trapezoidal methods Sleep disturbance. The definition of sleep disturbance described in the protocol (i.e. mean number of days when sleep was disturbed 'not at all' or 'slightly') was changed to number of days out of days 2 to

NAIB3001 (Continued)

14 for which the patient recorded 'moderate', 'quite a bit' or 'severe' sleep disturbance. This change was made prior to blinding the study and described in the data analysis plan (DAP)

Number of tablets of paracetamol taken over the treatment period (days 1 to 5) and days 1 to 14

Number of spoonfuls of cough mixture taken over the treatment period (days 1 to 5) and days 1 to 14

Incidence of complications of influenza and associated antibiotic use

Investigator global assessment of symptoms

Notes

The study was conducted by 22 investigators in 3 countries (Australia, New Zealand and South Africa); only 13 of these investigators recruited patients

The protocol defined the influenza-positive population as a subset of the intention-to-treat population. This was changed in the data analysis plan to be a subset of the safety population. For this study, both populations were the same so the change was irrelevant

Investigator global assessment of symptoms was not described in the protocol but planned prior to blinding the study

Protocol amendment:

At 3 Australian centres an additional study protocol was designed to collect pharmacoeconomic data was instigated. This involved interviews with influenza-positive patients after their day 28 visit

Study period: recruitment commenced in May 1997 and rolled over to 1998

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided; but method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias) Symptoms	Low risk	Based on ITT and IP populations
Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	Based on randomised participants. The safety population included all patients randomised to treatment who took at least 1 dose of study medication
Selective reporting (reporting bias)	Low risk	Outcomes listed in protocol reported in clinical study reports
Other bias	High risk	Exposure to lactose in test drugs may have underestimated true risk of asthma events. Investigator global assessment of symptoms was not defined in the protocol but was planned prior to unblinding the study and specified in the DAP. It is not clear why the patient assessment was not included to assess concordance

NAIB3001 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Unclear if Rotadisks were identical in shape and appearance; no certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No code-break envelopes were opened in this study

NAIB3002

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for 5 days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults Location, number of centres: multicentre study in Europe: Belgium (2 centres); Denmark (3); Finland (2); France (10); Germany (5); Holland (1); Italy (2); Norway (7); Spain (1); Sweden (6); UK (3) Duration of study: 28 days
Participants	Males or females aged ≥ 12 years (mean age: 37 years) with influenza-like illness (ILI) Number screened: not available Number randomised: 356 (zanamivir: 174; placebo: 182) Number completed: 349 Definition of patient populations for analysis <i>Influenza-positive population (N = 277)</i> Primary population for assessing efficacy. Defined as all participants in safety population with confirmed influenza. Participants considered influenza-positive if positive result obtained from any of: baseline culture or polymerase chain reaction (PCR) assay, or if participants showed seroconversion (≥ 4-fold increase in convalescent antibody titres compared with baseline demonstrated by haemagglutination inhibition) <i>ITT population (N = 356)</i> All randomised participants, regardless of whether study drug was taken or study completion. Participants who did not take medication to which they were randomised included in treatment group assigned. This was the secondary population for assessing efficacy <i>Safety population (N = 356)</i> All participants who took at least 1 dose of study medication. Participants only excluded from safety population if clear evidence of failure to take study medication. Participants who did not take medication to which they were randomised would have been included in the treatment group of the actual medication they took the majority of the time. This was the primary population for the analysis of safety data <i>High risk (N = 32)</i> Defined as those who could experience more prolonged or severe illness, or suffer complications from influenza due to age or underlying medical condition
Interventions	Four 5 mg doses of micronized zanamivir (as dry powder, lactose blend) or matching placebo (lactose only)

NAIB3002 (Continued)

Treatment period: 5 days

Follow-up period: 23 days post-treatment

Co-interventions: paracetamol and cough mixture were provided for symptomatic relief

Outcomes	Primary outcome: time until alleviation of clinically significant symptoms of influenza Secondary outcomes: Time to alleviation of clinically significant symptoms and no use of relief medication Time until the participant returns to normal activities Time to alleviation of each individual symptom score Mean overall influenza score Mean symptom score for each of the individual symptoms collected on the diary card Maximum daily temperature Total number of tablets of supplied paracetamol Total number of spoonfuls of supplied cough mixture Global assessment of symptoms at the post-treatment visit Incidence of complications of influenza and associated antibiotic use
Notes	Protocol amendments - Reference to '5 mL' spoonfuls of dextromethorphan deleted - Study personnel recorded whether first dose of study medication given before or after 14:00 hours - Secondary complications were to be recorded in the CRF - The second diary card including symptom assessments and relief medication use, to be completed twice a day. Questions relating to productivity and normal activities completed once a day - Consent form amended to include statement that participant's doctor/nurse would also need to take a throat swab on day 6 - Categories to be used to document influenza complications were defined - Protocol amendment 2 applied to all centres in Denmark, France, Holland, Italy and Norway: minimum age for inclusion was to be 18 years in response to Ethics/Regulatory issues in those countries - Protocol amendment 3 was standard administrative amendment to meet requirements of French law no. 88-1138, of 20 December 1988 and modified by French Law No. 94-630, of 25 July 1994 - Protocol amendment 01 was applicable to all of the investigators. It corrected typographical errors and inconsistencies and included further categories to be used to assess secondary complications of influenza Study period: recruitment planned for between October 1997 and April 1998

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation list provided; but method of sequence generation not specified
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled randomisation
Incomplete outcome data (attrition bias)	Low risk	Based on ITT and IP populations

NAIB3002 (Continued)

Symptoms

Incomplete outcome data (attrition bias) Complications of influenza	Low risk	Insufficient evidence to indicate that administration of zanamivir affects antibody response in similar way to oseltamivir. The influenza-positive population is less likely to reflect a non-randomised comparison
Incomplete outcome data (attrition bias) Safety data	Low risk	All 356 participants randomised to treatment were included in the safety population; missing diary cards were accounted for in analysis
Selective reporting (reporting bias)	Low risk	Primary and secondary endpoints reported as specified in protocol
Other bias	High risk	3 protocol amendments in the course of the study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unclear if Rotadisks were identical in shape and appearance; no certificates of analysis were provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...study monitors were blinded as to the study treatment administered." The code-break envelopes were to be opened only in the event of a medical emergency where knowledge of the treatment received was absolutely necessary for management of the participant. Prior to breaking the blind the investigator was asked to discuss the matter with the study monitor or designee

NV16871

Methods	Randomised, double-blinded, placebo-controlled, parallel-group trial of the effect of treatment with oseltamivir on improving rate of recovery from influenza-mediated asthma symptoms and exacerbations in children (6 to 17 years) with asthma Location, number of centres: 50 centres in 10 countries mostly in Eastern Europe
Participants	A total of 329 randomised of whom 28.6% (i.e. less than estimated rate of 50%) had laboratory-confirmed influenza; ITTI population had 51 placebo and 43 oseltamivir patients
Interventions	Oseltamivir by weight dosing bid for 5 days or placebo
Outcomes	Primary efficacy outcome was % change in FEV1 from days 1 to 2 to day 6 measured by spirometry. Study stratified for asthma severity at baseline (mild or moderate/severe) and time from influenza symptoms onset to first study drug dose (< 24 hours or ≥ 24 hours)
Notes	There was no significant difference in outcomes between the 2 groups, though a trend in favour of oseltamivir was reported. Secondary outcomes based on diary symptoms appeared to show faster recovery, reduced rate of complications and reduced use of antibiotics in the oseltamivir group. In terms of safety the overall incidence of adverse events was higher in the oseltamivir group than the placebo group (24% versus 21%). This was mainly due to a higher incidence of gastrointestinal events (10% versus 6%), of which vomiting (8% versus 2%) was most significant The definition of the M2 Module itself was not clear in the 614 page PDF reviewed and despite page by page review some things, e.g. the certificates of analysis, were not found and protocol amendments or statistical analysis plan amendments were also not reported. No additional information from M2 changes the original summary and risk of bias

Risk of bias

NV16871 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list shows random sequence and centralised phone-driven system was used
Allocation concealment (selection bias)	Low risk	Centralised phone system
Incomplete outcome data (attrition bias) Symptoms	High risk	In the absence of IPD and CRFs we cannot account for all participants
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Unclear how complications of influenza were defined clinically
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified either as symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same participant in different categories
Selective reporting (reporting bias)	High risk	SAP and certificates of analysis and amendments are missing. GCP infringements noted in 2 centres
Other bias	High risk	Placebo content unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo colour and taste not clear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Centrally randomised scheme

PE-01

Methods	A double-blind, double-dummy, randomised, placebo-controlled, parallel group, multicentre study to investigate the efficacy and safety of oral and inhaled GG167 in reducing the development of influenza symptoms
Participants	Inclusion criteria: Index case: Individuals who the investigator diagnosed as having symptoms of influenza A and B by the following criteria: individuals who satisfied the following conditions for influenza infection between the commencement of the symptoms and the first presentation to the participating centre, were willing to participate in the study and could be expected to follow the investigator's orders: 1. Participants with feverishness or a temperature of 37.5 °C or greater at the first presentation 2. At least 2 of the following: headache, muscle pain, sore throat, cough Contact:

PE-01 (Continued)

Person who had any following chance of contact with an index case within 4 days after the commencement of influenza symptoms of the index case and was diagnosed that he/she may be infected with influenza:

1. Sleeping in the same room as the index case (such as inpatients)
2. Working in the same room as the index case (such as co-workers)
3. Living in the same home as the index case (such as family)

Participants had to be at least 16 years old, understand how to use the investigational agents and intend to co-operate with the study and could be expected to follow the investigator's orders

Exclusion criteria:

1. Person who had feverishness within 48 hours prior to the first presentation day or a temperature 37.0 °C or more at the first presentation day
2. Person who had 2 or more symptoms of the following symptoms within 48 hours prior to the first presentation day: headache, muscle pain, sore throat, cough, nasal symptoms and general fatigue
3. Person who had at least 1 of the following symptoms of "score 2" or more: headache, muscle pain, sore throat, cough, nasal symptoms and general fatigue
4. Person suspected of having a bacterial infection
5. Patient with an unstable chronic disease
6. Pregnancy or suspicion of pregnancy as well as person planning to become pregnant during the course of the study and nursing mothers
7. Patient who was prescribed any investigational medication within the last 3 months
8. Patient who received influenza vaccine within the last 1 year
9. Any patient the investigator determines to be inappropriate for the study

Definition of patient populations for analysis

ITT population N = 44 (IH 11, IN 11, IH + IN 11 and PL 11)

Protocol compatible population: N = 40 (IH9, IN 11, IH + IN 10, PL 10)

Safety population: N = 44 (IH 11, IN 11, IH + IN 11 and PL 11)

Safety outcome

The safety measure was the incidence of abnormal symptoms/abnormal laboratory changes in which causality determinations were not completely denied. "Abnormal symptoms or abnormal laboratory findings" are the adverse events defined as newly observed or remarkably worsened symptoms after treatment started or clinically untoward abnormal or abnormally changed laboratory findings after treatment started irrespective of the causal assessment

Interventions	Orally inhaled zanamivir 10 mg + intranasally nebulised placebo Orally inhaled placebo + intranasally nebulised zanamivir 6.4 mg Orally inhaled zanamivir 10 mg + intranasally nebulised zanamivir 6.4 mg Orally inhaled placebo + intranasally nebulised placebo
Outcomes	Primary: the proportion of subjects who, during prophylaxis (day 1 to day 5), developed symptomatic influenza Secondary: • The proportion of subjects who, during prophylaxis (day 6 to day 10), developed symptomatic influenza • The proportion of subjects who, during prophylaxis (day 1 to day 10), developed symptomatic influenza

PE-01 (Continued)

- The number and proportion of subjects who, during prophylaxis (day 1 to day 5 or day 6 to day 10), developed symptomatic influenza

Notes

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of sequence generation not specified
Allocation concealment (selection bias)	High risk	Not described
Incomplete outcome data (attrition bias) Symptoms	High risk	The trial was terminated prematurely
Incomplete outcome data (attrition bias) Complications of influenza	High risk	The trial was terminated prematurely
Incomplete outcome data (attrition bias) Safety data	High risk	The trial was terminated prematurely
Selective reporting (reporting bias)	High risk	Analysis, including primary outcomes, was planned after study unblinding
Other bias	High risk	Under-recruitment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificate of analysis
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not described

WV15670

Methods	Randomised, double-blind, placebo-controlled study in people with symptoms of influenza. Centres were activated to recruit participants during an influenza outbreak in the locality, detected using standardised surveillance techniques Location, number of centres: 51 centres in Europe, 11 in Canada and 1 in Hong Kong Duration of study: 21 (+/- 4 days)
Participants	Number screened: not available Number randomised: 719 (oseltamivir 75 mg: 242; oseltamivir 150 mg: 242; placebo: 235) Number completed: 688

WV15670 (Continued)

M = 51%

F = 49%

Mean age: 37.4

Baseline details

Inclusion criteria:

1. Fever $\geq 38^{\circ}\text{C}$
2. At least 1 respiratory symptom (cough, sore throat, nasal symptoms)
3. At least 1 constitutional symptom (headache, myalgia (aches/pains), sweats/chills (feeling feverish), prostration (fatigue))
4. No more than 36 hours post onset of feeling unwell
5. Aged ≥ 18 and ≤ 65 years of age
6. Willing and able to comprehend and give written, informed consent
7. Willing to utilise an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study therapy
8. Negative urine pregnancy test prior to drug treatment (females of childbearing potential)

For the purposes of analysis and definition of the study populations, the criteria were adjusted to accept a baseline temperature of 37.8°C and entry into the studies up to 40 hours post onset of illness, thereby accounting for differences between criteria evaluated at time of entry and criteria at time of first dose

Exclusion criteria:

1. Active, clinically significant, renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease) or immunodeficiency disorders, cancer, hepatitis or cirrhosis
2. Transplant recipients
3. Use of steroids or immuno-suppressant therapies
4. Pregnant or breast-feeding females
5. Known HIV infection
6. Allergy to any excipients in the capsule or paracetamol
7. Asthmatics in receipt of chronic therapy for asthma
8. Participants who experienced a previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis within 2 weeks prior to study day 1
9. Receipt of antibiotics for URTI, otitis, sinusitis or bronchitis or antiviral therapy for influenza within 2 weeks prior to study day 1
10. Participation in a clinical study with an investigational drug within 4 weeks prior to screen/study day 1
11. Administration of influenza vaccine less than 12 months prior to study day 1
12. A clinically relevant history of abuse of alcohol or other drugs
13. Presentation > 36 hours post onset of feeling unwell

Definition of patient populations for analysis

ITTI population (N = 425)

Participants who were discovered to have been infected with laboratory-confirmed influenza

ITT population (N = 726)

All randomised participants irrespective of influenza status

Interventions

Intervention:

1. Oseltamivir 75 mg bid, given as size 2 capsules (total daily dose 150 mg)

WV15670 (Continued)

2. Oseltamivir 150 mg bid, given as size 2 capsules (total daily dose 300 mg)

Control: placebo size 2 capsules

Treatment period: 5 days

Follow-up period: 12 to 20 days post-treatment

Co-interventions: participants were provided with a rescue pack of paracetamol (500 mg) for symptomatic relief. The amount of medication was noted on the participant's diary card. Participants were requested not to use any other medication for the relief of symptoms during the study treatment period. However, if any other medication was taken, this was to be recorded

Outcomes

Primary outcome: duration of illness, defined as the length of time to first alleviation of the symptoms of influenza (nasal congestion, sore throat, cough, aches and pains, fatigue, headaches and chills/sweats). This was calculated from 'time 0' (study drug initiation) to the time at which all 7 symptoms were alleviated

Secondary outcomes:

1. Severity of symptoms
2. Virus shedding
3. Serology
4. Symptoms
5. Temperature
6. Proportion of participants with fever
7. Symptom relief medication use
8. Secondary illnesses, predefined as sinusitis, otitis, bronchitis, pneumonia and other chest infections (as well as recurring symptoms noted on the diary card once alleviation of that symptom had been considered to occur)
9. Proportion of household contacts who developed an influenza-like illness following the illness of the trial participant
10. Virology
11. Return to baseline health status (i.e. pre-flu health)
12. Virus type (e.g. A/H1N1, A/H3N2, B, etc.)
13. Time to afebrile state
14. Symptom relief medication usage over the dosing period
15. Viral resistance
16. Proportion with infection
17. Pharmacokinetic evaluation: plasma and urine samples
18. Adverse events

Notes
Protocol amendments

1. (7 January 1998) defined the exclusion and withdrawal criteria for participants participating in the study at the Hong Kong centre who were found to be infected with the influenza A/H5N1 virus. Since May 1997, 18 individuals have been diagnosed with influenza infection caused by a new human pathogen influenza A/H5N1, of whom 6 have died as a result. This virus, previously associated with avian influenza, has apparently crossed species and resulted in a pathogenic infection in man. The vast majority of influenza infections occurring in Hong Kong at the time of the study were of the non-virulent strain types influenza A/H1N1, H3N2 or influenza B. However, it was considered that in view of the apparent virulence of the A/H5N1 strain type, participants enrolled into this study, which was placebo-controlled, might be placed at undue risk. This risk was specific to Hong Kong, as this strain type has not so far been identified outside of this region
2. The influenza A/H5N1 virus type is known to be sensitive to amantadine. Throat swabs were taken from all participants entered into the trial prior to the first dose of study drug. In the Hong Kong region, a rapid diagnostic technique (the polymerase chain reaction, PCR) was used to test the swab eluates for the presence or absence of influenza A/H5N1. If any participant was found to be harbouring this strain type, they were to be withdrawn from the study without breaking the blind and offered

WV15670 (Continued)

amantadine at the discretion of the investigator and if the participants condition merited such intervention

3. (16 February 1998) revised the analyses and definition of secondary and tertiary parameters in the study. Following an experiment to assess the use of a standardised protocol for quantitative viral culture, significant variability was detected between the 2 virology laboratories with respect to these assays. Further work continued in order to elucidate the mechanisms of this variability and to further validate the methods. However, due to the lengthy period of time required to complete this work, virus titre was removed as a secondary parameter in this study and the information analysed post-database close. The major virology parameter in these studies thus became the duration of virus shedding following inclusion into the trial. It was also believed that peak virus titre might have occurred prior to baseline for a significant number of participants entering the trial and hence this particular parameter was not analysed

Study period: December 1997 to April 1998

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Some discrepancies noted from the Module 2 summary regarding the treatment group assignment of participants experiencing adverse events. This does not necessarily affect the method for generating the randomisation sequence but could affect ITT and safety populations
Allocation concealment (selection bias)	Low risk	"The randomisation numbers were generated by a central randomisation service, ICTI (Interactive Clinical Technologies inc., Princeton, NJ, USA)." "The investigator telephoned the centre to report the participant's initials, date of birth and smoking history. The randomisation number was then supplied by the centre in the form of a message on an interactive voice response system (IVRS). The investigator entered the randomisation number in the appropriate place on the case report form."
Incomplete outcome data (attrition bias) Symptoms	High risk	Appendix 19 (time to alleviation of all symptoms (ITT population)) has summary info for ITT. However, the extent of missing data is unknown for this outcome
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Incomplete outcome data on complications is very likely given the inadequacies present in the way info on complications was collected. In summary, this was to ask patients to self report complications at day 8 and day 21 (follow-up visit at end of the study)
Incomplete outcome data (attrition bias) Safety data	Low risk	AEs could be classified as either symptoms of influenza, complications of influenza and AEs. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	Secondary illnesses were patient-reported The body of the clinical study reports states that complications requiring antibiotic treatment were specified a priori, but even in the final version of the protocol for which we have the full text, there is no predefined list of secondary illnesses (i.e. no mention of pneumonia, bronchitis, sinusitis or otitis in the protocol), nor did complications have anything to do with antibiotic treatment according to the protocol, nor does the CRF mention specific secondary illnesses by name In addition, the protocol does not pre-specify any secondary illnesses. They first appear in the RAP and are in the core report (Module 1). The protocol indicates that the data would be collected, so the absence of mention of secondary illnesses as an outcome (even tertiary) is not easily explicable

WV15670 (Continued)

		In addition, the decision of ITTI selection for primary outcome for reporting itself may be the selective reporting bias at the start, because this could break the balance between both groups. This bias may have both factor of patient selection (selection bias) and reporting selection (reporting bias), although they were prespecified
Other bias	High risk	The protocol reports that dehydrocholic acid and dibasic calcium phosphate dihydrate were in the oseltamivir as well as placebo capsules. It is not clear why it is reported in another clinical study report that the dehydrocholic acid was added to the placebo to match the bitter taste of oseltamivir The certificate of analysis reports capsule No 1 (placebo) contains 6.13 mg of dehydrocholic acid. Placebo contained dehydrocholic acid but the dosage was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"In order to maintain blinding, each participant had 2 bottles of medication for each dose interval. 1 capsule was administered from each bottle twice per day at approximately 12 hour intervals. The first dose was administered during the first (day 1) visit Each bottle was labelled with the participant number and contained identical capsules of either active compound or placebo. Those participants receiving 75 mg bid received 1 capsule containing 75 mg from 1 bottle and a matching-capsule containing placebo from the other bottle at each dosing. Participants receiving doses of 150 mg bid received 1 capsule containing 75 mg active drug from each bottle at each dosing."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the randomisation code was available at the Study centre, to the Roche Monitors, Statisticians or at Roche Headquarters. In the event of a medical emergency the blind could be broken, if this was considered absolutely necessary to properly manage the participant, by contacting the randomisation centre. The blinding was not required to be broken for any participant during the study."

WV15671

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study design in participants presenting with influenza-like illness Location, number of centres: USA, 57 centres Duration of study: 12 days (+/- 4 days)
Participants	Number screened: not described Number randomised: 627 (oseltamivir 75 mg bid: 209; oseltamivir 150 mg bid: 210; placebo: 208) Number completed: 581 M = 49% F = 51% Mean age: 32.6

WV15671 (Continued)

Baseline details

Inclusion criteria:

Fever $\geq 100^{\circ}\text{F}$ plus

1. 1 of cough, sore throat or nasal symptoms, plus:
2. 1 constitutional symptom (headache, malaise, (feeling unwell), myalgia (aches and pains), sweats/chills (feeling feverish), prostration (fatigue))
3. No more than 36 hours post onset of feeling unwell (protocol violation up to 40 hours)
4. ≥ 18 and ≤ 65 years
5. Comprehension/willingness to give written consent
6. Agreement to utilise an effective method of contraception throughout study period and for 1 reproductive cycle following cessation of study therapy. Negative urine pregnancy test prior to dosing

Exclusion criteria:

1. Clinically significant disorders/conditions (renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease), immunodeficiency disorders, cancer, hepatitis or cirrhosis)
2. Receipt of transplant
3. Steroids/immuno-suppressant therapies
4. Pregnant or breast-feeding females
5. HIV infection
6. Allergy to any excipients in the capsule or paracetamol
7. Chronic therapy for asthma
8. Previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis or received antibiotics for URTI, otitis, bronchitis or sinusitis or antiviral therapy for influenza within 2 weeks prior to study day 1
9. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry
10. Vaccination against influenza less than 12 months prior to study day 1
11. Clinically relevant history of abuse of alcohol or other drugs
12. Presentation > 36 hours post onset of symptoms

Definition of patient populations for analysis
Intention-to-treat infected population (N = 375)

All participants who took 1 dose of the study drug and were subsequently discovered to have laboratory-confirmed influenza

Standard population (N not presented)

As for the ITTI population, except that this was further restricted to those who took at least 5 doses of the study drug

ITT population (N = 615)

All participants who took at least 1 dose of the study drug. Following a request from the regulators this population was included in hypothesis testing for the primary efficacy endpoint

Interventions

Intervention:

1. Oseltamivir 75 mg bid, given as size 2 capsules (total daily dose 150 mg)
2. Oseltamivir 150 mg bid, given as size 2 capsules (total daily dose 300 mg)

Control: matching placebo capsules (2) for Ro 64-0796 (GS 4104) orally bid for 5 days

Treatment period: 5 days

Follow-up period: 12 to 20 days post-treatment

WV15671 (Continued)

Co-interventions: rescue pack consisting of paracetamol (500 mg) for symptomatic relief

Outcomes	Primary outcome: time to alleviation of symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headache and chills/sweats) as derived from participant symptom questionnaire. Calculated from time 0 (study drug initiation) to the time at which all 7 symptoms were alleviated. Participants who withdrew prior to the alleviation of symptoms were censored at the time of withdrawal Secondary outcomes: 1. Extent and severity of illness 2. Viral shedding 3. Serology 4. Symptoms 5. Temperature 6. Proportion of participants with fever 7. Symptom relief medication usage 8. Adverse events
Notes	Protocol amendments Protocol amendment D (16 February 1998) revised the analyses and definition of secondary and tertiary parameters in the study. Virus titre was removed as a secondary outcome following the detection of significant variability between 2 virology laboratories with respect to these assays. The major virology parameter in these studies thus became the duration of virus shedding following inclusion into the trial. It was also believed that peak virus titre might have occurred prior to baseline for a significant number of participants entering the trial and hence this particular parameter was not analysed Study period: December 1997 to April 1998

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Telephone access available
Allocation concealment (selection bias)	High risk	"Randomisation was conducted by a central randomisation service by telephone. The investigator/study coordinator telephoned the randomisation centre giving the participants initials, date of birth and smoking history and the treatment number was then supplied by the centre. The randomisation number was entered in the appropriate place on the participant's Case Report Form by the investigator."
Incomplete outcome data (attrition bias) Symptoms	High risk	Missing data imputed but number missing not provided. Higher attrition in treatment groups for fever
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Diagnosis of complication not standardised and based on objective criteria. Method of diagnosis was based on local centre definitions. Unknown what effect this could have on classification of outcome
Incomplete outcome data (attrition bias) Safety data	High risk	AEs could be classified as either symptoms of influenza, complications of influenza and AEs. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	Missing summary table of hospitalisations. ITT data provided in Modules 3 to 5

WV15671 (Continued)

Other bias	High risk	Unknown what effect additional substances in placebo could have on AEs. Number of centres in Module 1 not consistent with Module 2 (60 versus 57)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo used "In order to maintain the double blind nature of the study, participants received 2 capsules twice daily for all treatments." "The identification number was added by the investigator at the time of randomisation" "No open key to the code was available at the Study centre..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The identification number was added by the investigator at the time of randomisation." "No open key to the code was available at the Study centre, to the Monitors, Statisticians or at Gilead/Roche Headquarters"

WV15673/WV15697

Methods	Combined analysis of 2 randomised, double-blind, placebo-controlled trials. Participants were requested to return to the clinic when investigators determined that influenza was present in the community Location, number of centres: USA; 6 centres Duration of study: 8 weeks
Participants	Number screened: not specified Number randomised: 1562 (oseltamivir 75 mg: 520; oseltamivir 150 mg: 521; placebo: 521) Number completed: 1505 M = 37% F = 63% Mean age: 34 years. Baseline details: 80% Caucasian; 11% African-American; 3% Hispanic Inclusion criteria: 1. Healthy adults 2. 18 to 65 years of age Exclusion criteria: 1. Recent vaccination Definition of patient populations for analysis ITTI population Not applicable ITT population (N = 1559) All participants randomised to treatment and who took at least 1 dose of study medication
Interventions	Intervention:

WV15673/WV15697 (Continued)

1. Oseltamivir 75 mg once daily plus placebo (total daily dose: 75 mg)
2. Oseltamivir 75 mg twice daily (total daily dose: 150 mg)

Control: placebo twice daily

Treatment period: 6 weeks

Follow-up period: 2 weeks post-treatment

Co-interventions: none specified

Outcomes	Primary outcome: laboratory-confirmed clinical influenza during the 6-week treatment period Secondary outcomes: 1. Asymptomatic influenza infection (virus shedding/4-fold increase in antibody to influenza virus in the absence of clinical symptoms of influenza) 2. Non-clinical influenza (symptoms not meeting the criteria for clinical influenza but confirmed to be influenza virus infection through detection of influenza virus shedding/4-fold increase in antibody to influenza virus) 3. Influenza-like illness not caused by influenza virus 4. On- and off-treatment adverse events
Notes	Study period not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Absence of information on randomisation procedure
Allocation concealment (selection bias)	High risk	The Module 1 (PDF page 23) reports: "The participant's randomisation numbers were generated by Roche and incorporated into double-blind labeling. No open key was available at any of the study sites or to any Roche personnel involved with the study". We presume this means that Roche generated the codes and stuck them on the packaging and ICTI allocated through phone in.
Incomplete outcome data (attrition bias) Symptoms	High risk	Effect of oseltamivir on antibody response impacting on diagnosis
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	Original protocol missing
Other bias	High risk	The data set for the study is aggregated from 2 separate trials. The placebo event rates for influenza infection are very different and their aggregation conceals the variation between the results of the different studies. We tried

WV15673/WV15697 (Continued)

separating estimates of effect for individual participants in the 2 trials. We failed because although participants' ID codes and centres were known, centre codes were redacted from individual participant listings, which meant that we could not disaggregate results by trial for use in meta-analysis

Blinding of participants and personnel (performance bias) All outcomes	High risk	Capsule size but no details of colour, taste or contents was reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available"

WV15707

Methods	Randomised, double-blind, placebo-controlled, parallel-group study. Stratification by vaccination status (current season or not) and chronic obstructive airways disease (present/absent) Location, number of centres: Australia, South Africa and South America, 13 centres Duration of study: 21 +/-4 days
Participants	Number screened: not described Number randomised: 26 (oseltamivir: 17; placebo: 9) Number completed: 25 M = 59% F = 41% Mean age: 71.5 years Baseline details Inclusion criteria: 1. Male or female patients 2. ≥ 65 years 3. Symptoms of influenza, including temperature (> 37.5 °C) 4. At least 1 respiratory symptom (cough, sore throat or nasal congestion) 5. At least 1 constitutional symptom (chills/sweats, headache, myalgia (aches and pains) fatigue) Exclusion criteria: Not described Definition of patient populations for analysis ITTI population (N = 12) Analysis of participants according to the groups to which they were randomised, having received at least 1 dose of study treatment and laboratory-confirmed influenza virus infection ITT population (N = 26)

WV15707 (Continued)

Analysis of participants according to the groups to which they were randomised, having received at least 1 dose of study treatment, irrespective of influenza infection status

Standard population (N not reported)

Population with no major protocol violations or deviations and laboratory-confirmed influenza, who received at least the first 6 scheduled doses within 72 hours/first 5 doses within 72 hours and went on to take 9 or 10 doses. Analysis according to treatment received

Interventions	Intervention: oseltamivir 75 mg bid (total daily dose 150 mg) Control: placebo (provided as size 2 capsule containing dehydrocholic acid, dibasic calcium phosphate dihydrate and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate) Treatment period: 10 days Follow-up period: 7 to 15 days post-treatment Co-interventions: not specified
Outcomes	Primary outcome: duration of illness (time to alleviation of symptoms) Secondary outcomes: 1. Area under the curve (AUC) of the composite symptom score 2. Virus shedding 3. Quality of life 4. Adverse events
Notes	Study period not specified No viral swab data were collected on South American patients. This population was therefore excluded from the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation service by phone
Allocation concealment (selection bias)	Low risk	Central randomisation service
Incomplete outcome data (attrition bias) Symptoms	High risk	In the absence of IPD and CRFs we cannot account for all participants
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	Outcomes of primary interest for the ITT population not made available to the review authors

WV15707 (Continued)

Other bias	High risk	Placebo contained dehydrocholic acid at a dose of 6.3 mg. Placebo contained dehydrocholic acid at a dose of 6.3 mg
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Presentation of placebo described as identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Centrally generated randomisation code

WV15708

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multicentre study carried out in elderly persons in residential homes. Participants were randomised to treatment when a local outbreak was detected. Stratification factors were vaccine status and presence or absence of COPD Location, number of centres: Australia, New Zealand, South Africa, Brazil (14 centres) Duration of study: 8 weeks
Participants	Number screened: not described Number randomised: 372 (oseltamivir: 190; placebo: 182) Number completed: 335 M = 41% F = 59% Mean age: 79 years Baseline details: 99% Caucasian; 69% vaccinated against influenza; 12% had COPD. 90% participants had other pre-existing diseases, of which diabetes was more common in oseltamivir than placebo (17.4% versus 8.8% respectively) Inclusion criteria: Resident in care home Exclusion criteria: Not listed Definition of patient populations for analysis ITT population Not described. Incidence of influenza was low
Interventions	Intervention: oseltamivir 75 mg od (total daily dose: 75 mg) Control: matching placebo Treatment period: 6 weeks Follow-up period: 2 weeks post-treatment Co-interventions: not specified

WV15708 (Continued)

Outcomes

Primary outcome: laboratory-confirmed clinical influenza, defined as: fever (temperature > 99 °F) plus 1 respiratory symptom (cough, sore throat, nasal symptoms) and 1 constitutional symptom (headache, myalgia, sweats/chills, fatigue). Laboratory confirmation by either virus shedding within 2 days of symptom onset or 4-fold increase in influenza antibody

Secondary outcomes:

1. Adverse events
2. Mortality

Notes

Study period not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation numbers generated by Roche but more details of method and randomisation schedule not available
Allocation concealment (selection bias)	High risk	Insufficient details given
Incomplete outcome data (attrition bias) Symptoms	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups. Low rates of attrition from treatment groups were noted
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Patient-reported outcomes
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	Postdate changes to protocol after closure of enrolment. Outcome changes should be consistent with data collected
Other bias	High risk	Placebo contents and colour and similarity to active drug not described; very low rates of influenza or ILI in trial, so could not analyse for primary outcome of efficacy
Blinding of participants and personnel (performance bias) All outcomes	High risk	Information on appearance of placebo capsules not available
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Centrally generated randomisation code

WV15730

Methods	Randomised, double-blind, placebo-controlled, parallel-group study. Participants were stratified by current smoking behaviour (smoker/non-smoker). Centres activated to recruit participants during an influenza outbreak in the locality, detected using standardised surveillance techniques Location, number of centres: Australia and South Africa, 12 centres Duration of study: 21 +/- 4 days
Participants	Number screened: not described Number randomised: 58 (oseltamivir: 31; placebo: 27) Number completed: 56 M = 52% F = 48% Mean age: 35 years Baseline details: 93% Caucasian; 21% smoking history Inclusion criteria: 1. Fever $\geq 38^{\circ}\text{C}$ 2. 1 or more respiratory symptom (cough, sore throat, nasal symptoms) 3. 1 or more constitutional symptom (headache, myalgia, (aches and pains), sweat/chills (feeling feverish), prostration (fatigue)) 4. ≤ 36 hours post onset of feeling unwell 5. Between 18 and 65 years of age 6. Willing and able to comprehend and give written informed consent 7. Participants were to utilise an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study drug 8. Females of childbearing potential had to have negative urine pregnancy test prior to drug dosing Exclusion criteria: 1. Active clinically significant renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorder, adrenal disease) disease, immunodeficiency disorders, cancer, hepatitis or cirrhosis 2. Receipt of transplant 3. Steroids or immuno-suppressant therapy 4. Pregnant or breast-feeding females 5. Known HIV infection 6. Allergy to any excipients in capsule or paracetamol 7. Chronic therapy for asthma 8. Previous episode of acute upper respiratory tract infection (URTI): otitis, bronchitis or sinusitis; or received antibiotics for URTI, otitis, sinusitis or bronchitis, or antiviral therapy for influenza within 2 weeks prior to study entry 9. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry 10. Administrations of influenza vaccine less than 12 months prior to study entry 11. The use of the antiviral drugs for influenza such as rimantadine, ribavirin, zanamivir and amantadine was not permitted during this study 12. A clinically relevant history of abuse of alcohol or other drugs 13. Presentation > 36 hours post the onset of feeling unwell Definition of patient populations for analysis ITTI population (N = 38)

WV15730 (Continued)

Participants analysed according to groups to which they were randomised providing they had received at least 1 dose of study treatment and had laboratory-confirmed influenza virus infection

ITT population (N = 58)

The ITT population consisted of the same participants as the ITTI population; also included participants who did not have laboratory-confirmed influenza but took at least 1 dose of study medication. Participants analysed by groups to which they were randomised

Safety population (N = 58)

All participants randomised, who received at least 1 dose of study medication and at least 1 safety follow-up, whether or not they had withdrawn prematurely. Participants who received therapy other than intended were analysed according to therapy received

Standard population (N = 38)

All randomised participants without major protocol violations or deviations, with laboratory-confirmed influenza and who received at least the first 6 scheduled doses within 72 hours or who received the first 5 doses within 72 hours and went on to take 9 or 10 doses. Participants analysed according to treatment received

Interventions	Intervention: oseltamivir 75 mg bid (total daily dose: 150 mg), given as size 2 capsule Control: placebo, given as size 2 capsule Treatment period: 5 days Follow-up period: between 12 and 20 days post-treatment Co-interventions: rescue medication pack	
Outcomes	Primary outcome: time to alleviation of symptoms. Assessed as alleviation of nasal congestion, sore throat, cough, aches and pains, fatigue, headache and feeling feverish. Time to alleviation of symptoms calculated from study drug initiation to time at which all symptoms were alleviated. Participants withdrawing prior to alleviation of all symptoms were censored at the time of withdrawal Secondary outcomes: 1. Extent and severity of illness 2. Duration of viral shedding 3. Serology 4. Symptoms 5. Rescue medication consumption 6. Household contacts developing ILI 7. Viral resistance 8. Quality of life 9. Pharmacokinetics 10. Adverse events	
Notes	Study period not specified	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Original randomisation list not provided

WV15730 (Continued)

Allocation concealment (selection bias)	Low risk	Central randomisation service
Incomplete outcome data (attrition bias) Symptoms	High risk	Missing data imputed; number missing not reported
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Diagnosis of complication not standardised and based on objective criteria. Method of diagnosis was based on local centre definitions. Unknown what effect this could have on classification of outcome
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	70% under-recruitment
Other bias	High risk	Placebo capsule contained dehydrocholic acid. Unknown what effect this could have had on AEs Mentioned in protocol amendment that South American (SA) sites could not diagnose influenza by culture due to delays in processing, however there is no mention in M1 or rest of M2 that SA sites were included
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Certificates of analysis show identical colour and size
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available at the study centre, to the monitors, statistician or at Roche Headquarters. In the event of a medical emergency the blinding was to be broken if considered absolutely mandatory to properly manage the patient by contacting the randomisations centre. The blinding was not broken for any participant during the study."

WV15758

Methods	Randomised, double-blind, placebo-controlled study stratified for the presence of acute otitis media Location, number of centres: USA and Canada, 80 centres Duration of study: 28 +/-4 days
Participants	Number screened: not described Number randomised: 698 (oseltamivir: 342; placebo: 356) Number completed: 655 M = 50% F = 50% Mean age: 5.34 years Baseline details: 65% Caucasian; 18% otitis media Inclusion criteria:

WV15758 (Continued)

1. Temperature $\geq 100^{\circ}\text{F}$ or 37.8°C plus at least 1 respiratory symptom (either cough or coryza)
2. Between 1 and 12 years
3. Less than 48 hours between onset of feeling unwell and administration of first dose of study medication
4. Parent/guardian willing and able to comply with study requirements and give consent
5. Participant able to comply with study requirements and willing to give assent, if appropriate

Exclusion criteria:

1. RSV-positive, using a rapid diagnostic test
2. Steroids or immuno-suppressant therapy
3. HIV infection
4. Uncontrolled significant diseases (renal, vascular, neurologic or metabolic disease (diabetes, thyroid disorders, adrenal disease), hepatitis, cirrhosis or pulmonary disease (other than mild asthma), or participants with known chronic renal failure). Uncontrolled defined as requiring change of therapy (increased dose or change of medication) or hospitalisation 4 weeks or less before first dose of study drug
5. Active cancer
6. Hospitalised participants (participants hospitalised for less than 24 hours were not excluded)
7. Major transplant recipients
8. Allergy to study drug or paracetamol
9. Antiviral treatment for influenza in the previous 2 weeks
10. Females of childbearing potential
11. Participation in a clinical trial with an investigational drug within 4 weeks prior to study entry

Definition of patient populations for analysis

ITTI infected population (N = 452)

Participants analysed according assigned treatment provided they received at least 1 dose of study treatment with some follow-up efficacy data and had laboratory-confirmed influenza virus infection as determined post entry into the study

ITT population (N = 695)

All participants who took at least 1 dose of study medication with some follow-up efficacy data irrespective of influenza virus infection. Participants analysed according to the groups to which they were randomised

Safety population (N = 695)

Participants who received at least 1 dose of study medication and who received at least 1 safety follow-up, whether or not withdrawn prematurely. Participants analysed according to treatment received

Standard population (N = 396)

Used for summaries of efficacy parameters. All participants who had no major protocol violations or deviations, who had laboratory-confirmed influenza and who received at least the first 6 scheduled doses within 72 hours or who received the first 5 doses within 72 hours but went on to take 9/10 doses. Participants analysed according to the treatment received

Interventions

Intervention: oseltamivir 2 mg/kg (not exceeding a maximum of 100 mg/dose) bid

Control: placebo bid

Study drugs administered as dry powder to be reconstituted with water

Treatment period: 5 days

Follow-up period: 19 to 27 days post-treatment

WV15758 (Continued)

Co-interventions: relief medication was provided but details not specified

Outcomes	Primary outcome: Time to freedom from illness: defined as the length of time taken from the start of treatment to the point at which all of the following criteria were met 1. A score of '0' (no problem) or '1' (minor problem) for cough and nasal symptoms (items 14 and 15 of the CARIFS scale) 2. Return to normal activities 3. Return to afebrile state The duration of the event was calculated from 'time 0' (study drug initiation) to the time at which all the above 3 conditions were simultaneously met and remained true for a minimum of 24 hours Secondary outcomes: 1. Time to return to normal health and activity 2. Duration of symptoms 3. Extent and severity of symptoms 4. Secondary illnesses and associated antibiotic use 5. Symptom relief medication use 6. Medically attended visits and hospitalisation 7. Serology 8. Virology and viral resistance 9. Adverse events	
Notes	Protocol amendments 1. Eligibility: temperature at entry into the study from 101.3 °F to 100.0 °F (38.5 °C to 37.8 °C) so as not to exclude several febrile children who otherwise met the entry criteria at baseline since parents had administered antipyretic medication prior to the clinic (screening) visit 2. Composite outcome: normal health was based on combination of parental global assessment and the absence or alleviation of the key objective signs/symptoms including fever, cough and coryza which defined the illness for the purposes of inclusion into the protocol Study period: December 1998 to April 1999	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Original randomisations not provided in randomisation list
Allocation concealment (selection bias)	Low risk	"Randomization was conducted by a central randomisations service, ICTI (Interactive Clinical Technologies Inc., Princeton, NJ). The investigator telephoned the centre to report the participant's date of birth, sex and weight. The randomisations number was then supplied by the centre in the form of a message on an interactive voice response system (IVRS). The investigator entered the randomisations number in the appropriate place on the case report form. The participant randomisation numbers were allocated sequentially within a stratum in the order in which participants were enrolled."
Incomplete outcome data (attrition bias) Symptoms	High risk	Primary outcome changed during trial. Missing data imputed, number missing not reported

WV15758 (Continued)

Incomplete outcome data (attrition bias) Complications of influenza	High risk	Diagnosis of complications not standardised and based on objective criteria. Method of diagnosis was based on local centre definitions. Unknown what effect this may have had on classification of outcome
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	Original protocol missing
Other bias	High risk	Dehydrocholic acid in placebo. Unknown what impact this could have had on adverse events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Certificates of analysis available
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available (...) to the Roche monitors, statisticians or at Roche Headquarters."

WV15759/WV15871

Methods	Randomised, double-blind, stratified placebo-controlled study. Stratification by asthma severity Location, number of centres: not available Duration of study: not available
Participants	Number screened: not provided Number randomised: not provided (oseltamivir: NA; placebo: NA) Number completed: not provided M = NA F = NA Mean age: NA Baseline details: NA Inclusion criteria: 1. Chronic asthma 2. 6 to 12 years 3. Symptoms of influenza (as fever ($\geq 37.8^{\circ}\text{C}$ or $\geq 100.0^{\circ}\text{F}$), plus 1 respiratory symptom (cough or coryza) Exclusion criteria: None specified Definition of patient populations for analysis ITT population (N = NA)

WV15759/WV15871 (Continued)

Not specified

ITT population (N = NA)

Not specified

Interventions	Intervention: oseltamivir: 2.0 mg/kg bid Control: matching placebo bid Study drugs administered as dry powder Treatment period: 5 days Follow-up period: not specified Co-interventions: not specified
Outcomes	Primary outcome: Composite of all of the following: 1. First alleviation of cough and nasal congestion segment of the CARIFS score 2. First return to normal health and activity 3. First return to afebrile state (temperature < 37.2 °C or 98.9 °F) Secondary outcomes: 1. Return to normal health and activity 2. Duration of symptoms 3. Extent and severity of symptoms 4. Secondary illnesses 5. Lung function 6. Symptoms 7. Adverse events
Notes	Study period not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Only treatment received provided on randomisation lists
Allocation concealment (selection bias)	Low risk	Central randomisation service provided by telephone
Incomplete outcome data (attrition bias) Symptoms	High risk	Missing data imputed for primary outcome but numbers missing not provided
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Diagnosis of complications not standardised and based on objective criteria. Method of diagnosis was based on local centre definitions. Unknown what effect this may have had on classification of outcome
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories

WV15759/WV15871 (Continued)

Selective reporting (re-reporting bias)	High risk	Missing data for hospitalisations ITT population
Other bias	High risk	Placebo capsule contained dehydrocholic acid. Unknown what effect this may have had on adverse events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Certificates of analysis show identical colour and size
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available (...) to the Roche monitors, statisticians or at Roche Headquarters."

WV15799

Methods	Randomised, double-blind, placebo-controlled cluster trial recruiting families of 3 to 8 members. Households recruited if any member developed an influenza-like illness during an influenza outbreak within the community (index case) Location, number of centres: USA (35 centres); Canada (11 centres); Denmark (1 centre); Finland (6 centres); Germany (6 centres); Netherlands (3 centres); Norway (2 centres); Switzerland (1 centre); UK (8 centres) Duration of study: 21 +/- 4 days
Participants	Number screened: not described Number randomised: 962 (oseltamivir: 498; placebo: 464) Number completed: 944 M = not reported F = not reported Mean age: range from 1 to 76 years Baseline details: 13% contacts had received influenza vaccination in the same season. 40% contacts had pre-existing diseases (most frequently reported: asthma (3.0%), hypertension (5.7%), drug hypersensitivity (3.9%) and depression (2.9%)) Inclusion criteria: 1. Household contact of someone who developed ILI 2. Participants had to live in same home for at least 2 days before and 3 days after index case identification 3. Maintain daily contact with the index case Exclusion criteria: Not specified Definition of patient populations for analysis ITT (contacts: N = 550; index cases: 370) People residing in the same house as an index case (someone with ILI, irrespective of baseline infection status)

WV15799 (Continued)

ITTI (contacts: N = 405; index cases: 163)

People residing in the same house as a positive index case (somebody with confirmed influenza at baseline)

Standard population: N = unclear

Mentioned but not described

Interventions	Intervention: oseltamivir 75 mg od (total daily dose: 75 mg) Control: placebo Treatment period: 7 days Follow-up period: 10 to 18 days post-treatment Co-interventions: index case received paracetamol
Outcomes	Primary outcome: Incidence of laboratory-confirmed clinical influenza in contacts of the index case. Defined as fever plus at least 1 respiratory symptom (cough, sore throat, nasal congestion) and 1 constitutional symptom (fatigue, aches and pains, headache, feeling feverish), all recorded on the same day (either by the investigator as an illness visit report on the CRF, or by the participant on their diary card) plus laboratory confirmation of influenza infection Secondary outcomes: 1. Incidence of laboratory-confirmed non-clinical influenza 2. Laboratory-confirmed asymptomatic influenza 3. Laboratory-confirmed influenza infection 4. The incidence of viral shedding irrespective of whether participants had symptoms of influenza or not
Notes	Study period not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomised; procedure generating randomisation described
Allocation concealment (selection bias)	Low risk	Adequate information to ascertain concealment of allocation available
Incomplete outcome data (attrition bias) Symptoms	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the intervention groups. Only symptomatic participants were swabbed. Low rates of attrition from treatment groups were noted
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	Low risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories

WV15799 (Continued)

Selective reporting (reporting bias)	High risk	Original protocol missing
Other bias	High risk	Diagnosis breakdown by culture and/or antibody titre rises not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Certificates of analysis show identical colour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Centrally generated randomisation code. Randomisation key only available to the clinical trial supplies group for packaging purposes. Some participant numbers in M1 could not be found on the randomisation list (e.g. 3913 and 3921)

WV15812/WV15872

Methods	Randomised, double-blind, placebo-controlled, parallel-group design. Stratification performed by presence of chronic obstructive airways disease (COAD) Location, number of centres: northern hemisphere (80 centres) and southern hemisphere (20 centres) during influenza seasons Duration of study: 21 +/- 4 days
Participants	Number screened: not reported Number randomised: 404 (oseltamivir: 200; placebo: 204) Number completed: 393 M = 44% F = 56% Mean age: 52 years Baseline details: COAD 76%; vaccination: 28%; smoking: 22% Inclusion criteria: - Adults (≥ 13 years of age (Norway and Sweden ≥ 18 years of age) with chronic cardiac (excluding chronic idiopathic hypertension) or pulmonary disorders (including bronchopulmonary dysplasia and asthma but excluding cystic fibrosis) severe enough to require regular medical follow-up or hospital care. In study WV15872 the following clarification was also given: pulmonary disorders were defined as COAD, which permanently reduces the FEV1. Asymptomatic patients with a previous valve replacement or bypass surgery were also eligible - Symptoms consistent with influenza: fever $\geq 38^\circ\text{C}$ (100°F) if patients aged < 65 years or fever $\geq 37.5^\circ\text{C}$ (99.5°F) if patients aged ≥ 65 years plus 1 respiratory symptom (cough, sore throat, nasal symptoms) and 1 constitutional symptom (chills/sweats (feeling feverish), malaise (feeling unwell), headache, myalgia (aches and pains), prostration (fatigue)) - Presentation such that the first dose may be taken no later than 36 hours post onset of feeling unwell - Legally effective written informed consent available - Mental Status Questionnaire (MSQ) ≥ 7 - Not in need of or awaiting residential care - Women of childbearing potential provided they had a negative urine pregnancy test prior to drug dosing and they agreed to utilise an effective method of contraception throughout the study period and for 1 reproductive cycle following cessation of study therapy. (Male patients whose partners were of

WV15812/WV15872 (Continued)

childbearing potential were to agree to use an effective method of contraception throughout the study and for 3 months after completing the trial – added by amendment to protocol WV15872)

Exclusion criteria:

1. Uncontrolled disease (renal, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease), hepatitis or cirrhosis, defined as disease requiring change of therapy or hospitalisation within 4 weeks preceding the first dose of study drug)
2. Creatinine clearance (measured or estimated) ≤ 30 mL/min
3. Frank jaundice or with transaminase values within or greater than grade III of the WHO scale
4. New York Heart Association (NYHA) class IV
5. COAD stage III
6. Major transplant recipients
7. Immuno-suppressant therapy (inhaled steroids or systemic steroids less than or equivalent to 5 mg/day prednisolone were allowed)
8. Pregnant or breast-feeding females
9. Active cancer (basal cell carcinoma, squamous cell carcinoma of the skin or a previous history of cancer in remission and not requiring therapy were permitted)
10. HIV infection
11. Allergy to any excipients in capsule or paracetamol
12. Previous episode of acute upper respiratory tract infection (URTI), otitis, bronchitis or sinusitis or received antibiotics for URTI, otitis, sinusitis or bronchitis or antiviral therapy for influenza within 2 weeks prior to study day 1
13. Participation in a clinical study with an investigational drug within 4 weeks prior to study entry
14. A clinically relevant history of abuse of alcohol or other drugs
15. Presentation > 36 hours post the onset of feeling unwell

Definition of patient populations for analysis

ITTI population (N = 231)

All patients who had at least 1 dose of study medication and who had a laboratory-confirmed influenza virus infection. Data were analysed according to treatment assignment at randomisation

ITT population (N = 402)

All randomised patients who received at least 1 dose of study medication

Safety population (N = 401)

Randomised participants who received at least 1 dose of study medication and had at least 1 post-baseline safety assessment

Standard population (N = 236)

Participants from ITTI population without major protocol violations and who received at least the first 6 scheduled doses within 72 hours, or received the first 5 doses within 72 hours and went on to take 9 out of the 10 doses

Interventions	Intervention: oseltamivir 75 mg bid (total daily dose 150 mg) Control: placebo bid Treatment period: 10 days Follow-up period: 7 to 15 days Co-interventions: pack of paracetamol (500 mg)
Outcomes	Primary outcome: time to alleviation of illness (derived from a patient-rated symptom questionnaire). The 7 symptoms assessed in the questionnaire were:

WV15812/WV15872 (Continued)

1. Nasal congestion
2. Sore throat
3. Cough
4. Aches and pains
5. Fatigue
6. Headache
7. Chills/sweats

Secondary outcomes:

1. Extent and severity of symptoms
2. AUC of individual symptoms
3. Use of symptom relief medication
4. Quality of life
5. Virology
6. Adverse events

Notes	Study period: WV15812: January to April 1999; WV15872: June to October 1999	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation service, block randomisation (block size = 4)
Allocation concealment (selection bias)	Low risk	Central randomisation service
Incomplete outcome data (attrition bias) Symptoms	High risk	Missing symptoms data not reported. Available data analysed by ITTI population and not ITT
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Missing symptoms data not reported. Available data analysed by ITTI population and not ITT
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	Original protocol for WV15812 missing
Other bias	High risk	Placebo contained dehydrocholic acid. Dosage not available. Active drug Ro 64-0796 batches GMZ 0124/03 and GMZ 0129/03; matching placebo GMZ 0136
Blinding of participants and personnel (performance bias) All outcomes	High risk	No certificate of analysis to confirm same shape/size/colour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	From Module 1: "No open key to the code was available at the Study Centre, to the Monitors, Statisticians or at Roche Headquarters. The blind was to be broken only in the event of a medical emergency if considered absolutely necessary to manage the patient."

WV15819/WV15876/WV15978

Methods	Randomised, double-blind, placebo-controlled, parallel-group design. Participants were stratified according to vaccination status (vaccinated in the current influenza season or not) and coexistence or not of chronic obstructive airways disease (COAD) Location, number of centres: France, the Netherlands, Belgium, Germany, Switzerland, United Kingdom, Norway, Sweden, Denmark, Israel, Lithuania, Estonia, Poland, Canada USA, Canada, South Africa, New Zealand, Australia; 169 centres Duration of study: 21 +/- 4 days
Participants	Number screened: not reported Number randomised: 726 (oseltamivir: 362; placebo: 374) Number completed: 715 M = 43% F = 57% Mean age: 73 years Baseline details: 98% Caucasian; COAD: 8%; vaccination: 43% Inclusion criteria: 1. Age $\geq$ 65 years 2. Symptoms consistent with influenza: fever $\geq$ 37.5 °C ($\geq$ 97.5 °F) plus 1 respiratory symptom (cough, sore throat, nasal symptoms), plus 1 constitutional symptom (headache, myalgia (aches and pains), sweats/chills (feeling feverish), fatigue) 3. No more than 36 hours since onset of feeling unwell 4. Willingness and ability to understand and give written informed consent 5. Mental Status Questionnaire (MSQ) score $\geq$ 7 6. Living independently, capable of self care, ambulant and not in need of or awaiting residential care (residents of retirement homes were eligible provided they fulfilled these criteria) 7. If male with a partner of childbearing potential, agreement to use an effective method of contraception throughout the study and for 3 months after completing the trial Exclusion criteria: 1. Unstable or uncontrolled disease (renal, cardiac, pulmonary, vascular, neurologic or metabolic disease, hepatitis or cirrhosis) 2. Creatinine clearance $<$ 30 mL/min 3. Known significant liver dysfunction associated with frank jaundice or transaminase 4. Concentrations of WHO grade 3 or greater 5. Significant cardiac failure resulting in limitation of physical activity and clinical signs of cardiac failure including pitting oedema, elevated jugular venous pressure and/or evidence of pulmonary oedema 6. Transplant recipient 7. Active cancer at any site 8. HIV infection 9. Allergy to any excipients in the capsules/paracetamol 10. Acute upper respiratory tract infection (URTI), otitis media, bronchitis or sinusitis, or antibiotic therapy for URTI, otitis media, bronchitis or sinusitis, or antiviral therapy for influenza, within 2 weeks before study entry 11. Use of the antiviral drugs rimantadine, ribavirin, zanamivir and amantadine 12. Previous or concomitant treatment with neuraminidase inhibitor (inhaled or oral) 13. Participation in a clinical study of an investigational drug within 4 weeks before study entry

WV15819/WV15876/WV15978 (Continued)

14. Clinically relevant history of abuse of alcohol or other drugs

Definition of patient populations for analysis

ITTI population (N = 477)

Primary analysis population for efficacy. Participants analysed according to the groups to which they were randomised, provided they received at least 1 dose of study treatment and had laboratory-confirmed influenza virus infection. Participants with protocol violations or deviations were retained in the ITTI population

ITT population (N = 735)

All participants who took at least 1 dose of study medication. Participants analysed according to the groups to which they were randomised

Safety population (N = 736)

All randomised participants who received at least 1 dose of study medication and who had at least 1 safety follow-up, whether or not withdrawn prematurely. Data from participants were analysed according to therapy they received

Standard population (N = 445)

All randomised participants who had no major protocol violations or deviations, laboratory-confirmed influenza virus infection and who received at least the first 6 scheduled doses within 72 hours or who received the first 5 doses within 72 hours but went on to take 9 out of 10 total doses. Participants were analysed according to treatment received

Interventions	Intervention: oseltamivir 75 mg bid (total daily dose 150 mg) given as size 2 capsules Control: matching placebo size 2 capsules Treatment period: 5 days Follow-up period: 12 to 20 days post-treatment Co-interventions: rescue pack of paracetamol
Outcomes	Primary outcome: Duration of illness given as summary measures from Kaplan-Meier survival curves Secondary outcomes: 1. Extent and severity of illness 2. Virus shedding 3. Serology 4. Symptoms 5. Temperature and fever 6. Rescue medication use 7. Secondary illness 8. Hospitalisation 9. Quality of life 10. Adverse events 11. Vital signs (blood pressure, heart rate, respiratory rate)
Notes	Protocol amendments 1. Protocol WV15819 amendment B and protocol WV15876 amendment B. Originally, symptoms, signs and common sequelae of influenza were to be reported as adverse events. After this protocol amendment, such symptoms, signs and common complications were excluded from reporting as adverse

WV15819/WV15876/WV15978 (Continued)

events, unless they fulfilled the criteria for reporting as serious adverse events or the criteria for secondary illness

2. Protocol WV15876 amendment B also added a requirement for male participants whose partners were of childbearing potential to use effective contraception during the study and for 3 months after completing the study, to follow Roche current standard operating procedures
3. Protocol WV15819 amendment D and protocol WV15876 amendment C made changes to the secondary efficacy parameters. The secondary efficacy parameter reflecting the antiviral effect of treatment was changed from the duration of viral shedding to the proportion of participants shedding virus on day 3. This change was made because the intermittent sampling schedule used in the study meant that the true duration of viral shedding could not be assessed exactly, whereas the proportion of participants shedding virus could be determined. The incidence of secondary illnesses requiring antibiotics was included as a new secondary endpoint and the secondary illnesses were defined as sinusitis, LRTI, otitis media, bronchitis and pneumonia. The method of analysis of the proportion of participants shedding virus and for the proportion of participants with predefined secondary illnesses (Fisher's 2-tailed exact test) was added to the statistical methods. Protocol WV15978 included an additional exclusion criterion around previous or concomitant treatment with a neuraminidase inhibitor

Study period: Northern Hemisphere centres recruited during flu seasons in 1998 and 1999; Southern Hemisphere centres recruited during flu seasons in 1999

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list provided
Allocation concealment (selection bias)	Low risk	Central randomisation service provided by telephone
Incomplete outcome data (attrition bias) Symptoms	High risk	Missing data imputed but number missing unknown
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups. Also diagnosis not based on standardised objective criteria but based on local centre definitions. Unknown what effect this may have had on classification of outcome
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	Selection of symptom reporting after major protocol amendment
Other bias	High risk	Module 1 implies active contains dehydrocholic acid but certificate of analysis suggests otherwise. Unknown what effect this may have had on adverse events
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Certificates of analysis show identical colour and size
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key to the code was available at the study centres, to the monitors, statisticians or at Roche headquarters. In the event of a medical emergency

WV15819/WV15876/WV15978 (Continued)

the blind could be broken, if considered absolutely mandatory to properly manage the subject, by contacting the randomisations centre."

WV15825

Methods	Randomised, double-blind, placebo-controlled trial in residential homes for elderly people. Participants were recruited when a local outbreak was detected, defined as 2 cases in immediate vicinity within 7 days or 1 case in the home itself Location, number of centres: USA (16 centres), UK (1 centre), France (4 centres), Belgium (2 centres) and the Netherlands (3 centres) Duration of study: 8 weeks
Participants	Number screened: not reported Number randomised: 548 (oseltamivir: 276; placebo: 272) Number completed: 493 M = 31% F = 69% Mean age: 82 years Baseline details: 92% Caucasian; 4% Black; 4% Hispanic. 80% vaccinated; 14% COAD Inclusion criteria: No inclusion criteria detailed. Study conducted in residential homes for the elderly Exclusion criteria: Not specified Definition of patient populations for analysis Prophylaxis study, differentiation between populations at baseline not undertaken
Interventions	Intervention: oseltamivir 75 mg (frequency of administration not specified) Control: placebo Treatment period: not specified Follow-up period: 8 weeks Co-interventions: not specified
Outcomes	Primary outcome: Laboratory-confirmed clinical influenza. Defined as fever (temperature > 99 °F) plus 1 respiratory symptom (cough, sore throat, nasal symptoms) plus 1 constitutional symptom (headache, myalgia, sweats/chills, fatigue) confirmed by either virus shedding within 2 days of symptom onset or 4-fold increase in influenza antibody Secondary outcomes: Adverse events
Notes	—

WV15825 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Centrally generated randomisation code. No details reported. Randomisation key only available to the clinical trial supplies group for packaging purposes. Some participant numbers in M1 could not be found on the randomisation list (e.g. #3913 and #3921)
Allocation concealment (selection bias)	High risk	In the Module 1 at page 21: "The subject randomisation numbers were generated by Roche and incorporated into double-blind labeling. No open key was available at any of the study sites or to any Roche personnel involved with the study". Roche generated the codes and stuck them on the packaging and ICTI allocated through phone-in system
Incomplete outcome data (attrition bias) Symptoms	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the intervention groups. Only symptomatic participants were swabbed. Low rates of attrition from treatment groups were noted
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Possible effect of oseltamivir on antibody production makes the assessment of influenza status and associated complications in the infected subpopulation non-comparable between the treatment groups
Incomplete outcome data (attrition bias) Safety data	High risk	Adverse events could be classified as either symptoms of influenza, complications of influenza or adverse events. Reporting is inconsistent and some trials reported the same outcome in the same patient in different categories
Selective reporting (reporting bias)	High risk	No definitions given – see pg 69 and protocol 367. Events after positive swab are 3 in placebo group and 1 in oseltamivir group (pg 70 also pg 330-1) Participants with ILI in adverse events table are not included in efficacy analysis
Other bias	High risk	Retrospective changes to protocol and reporting analysis plan
Blinding of participants and personnel (performance bias) All outcomes	High risk	Certificate of analysis available. Placebo contained dehydrocholic acid. Dosage not available. More information needed on whether patients and personnel could distinguish between the 2 treatments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"No open key will be available"

WV16277

Methods	Randomised, double-blind, placebo-controlled, parallel-group study. Patients were stratified by age, gender, vaccination status (vaccinated in current season or not) and coexistence of chronic obstructive airways disease (present/absent). The objectives of the study were: - To investigate the clinical efficacy of oseltamivir in patients with influenza - To investigate the safety and tolerability of oseltamivir in patients with influenza - To investigate the effect of oseltamivir on well being and daily disruption of patients with influenza

WV16277 (Continued)

- To investigate the antiviral efficacy of oseltamivir in patients with influenza (in selected patients)

Participants	Patients aged 13 or more years (or 18 or more in countries with local IRB requirements) presenting with symptoms of influenza (fever 37.8 °C or more with at least 2 of the following symptoms: cough, sore throat, nasal congestion, chills/sweats, headache, myalgia (aches and pains), fatigue)
Interventions	Oseltamivir was provided as size 2 capsules containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate Matching placebo was provided as size 2 capsules, containing dehydrocholic acid, dibasic calcium phosphate dihydrate, pregelatinised starch, povidone, talc and sodium stearyl fumarate The following batch numbers of drugs were used in all centres: Oseltamivir: 75 mg capsules, Ro 64-0796/V14, batch number PT2247C01 Matching placebo capsules: Ro 64-0796/V16, batch number GMZ 0163 The medication was to be taken within 36 hours of first symptom onset at the clinic
Outcomes	This study was designed to investigate whether oseltamivir suppressed the main clinical symptoms (fever and cough) of patients with laboratory-confirmed influenza. For all time-to-event analyses, time zero was defined as coinciding with the initiation of treatment. For all endpoints defined in this section that involve 'alleviation' of symptoms, alleviation occurred at the start of the 24-hour period in which the symptom was less than or equal to 1 (mild) and remained less than or equal to 1 for at least 24 hours Primary outcome: The primary efficacy parameter was the proportion of patients alleviated of cough (none or mild for at least 24 hours) and without fever (37.2 °C or less) at 36 hours after initiation of study medication Secondary outcomes: Symptoms 1. The efficacy parameter to reflect the duration of illness was the length of time until alleviation of all symptoms. This was calculated from Time 0 (study drug initiation) to the length of time over which the area under the curve (AUC) for symptoms was to be calculated. Participants withdrawing prior to alleviation of symptoms were censored at last assessment 2. The efficacy parameter to reflect the extent and severity of illness was the AUC for symptoms. This was calculated from Time 0 (study drug initiation) to the time at which all symptoms were alleviated. Scores were calculated twice daily by totaling the separate symptoms that form the symptom scale. The AUC of these scores was then calculated for each patient using the trapezoidal rule. The base-line for each symptom was defined as the assessment prior to first study drug intake even though this might be before Time 0 3. Proportion of participants who were afebrile (oral temperature 37.2 °C or less) at 24 hours, 36 hours and 48 hours 4. Proportion of patients with fever each day (fever was defined as an oral temperature of 37.8 °C or higher at any assessment during that day) 5. At 12-hourly intervals over the first 2 days, the proportion of patients with alleviation of cough and no fever (37.2 °C or less), with a reduction in ≥ 1 symptom score, with alleviation of cough, with alleviation of myalgia and with alleviation of cough and no fever (38 °C or less)
Notes	ECGs were collected for a subset of (intensive) patients only, on day 1, day 3 and day 5. Further measurements were to be taken at day 10 or day 21 if abnormal results were observed at the previous visit. ECG tests were not part of the protocol but are mentioned as part of a "sub-study" at PDF pg 63

WV16277 (Continued)

Blank CRFs, searches under bronchitis, secondary identified only cases of bronchitis classified as harms or pre-existing conditions. Modules 3 and 4 table of content pages (PDF pages 660 and 3011) do not report listings of complications. H&L meta-analysis shows confidence interval without recognisable point estimate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	ICTI-run central randomisation scheme
Allocation concealment (selection bias)	High risk	Different coloured caps in size 2 capsules. Content of capsules stated, certificate of analysis missing perhaps because the August 2000 certificates from WP16263 are sufficient, but are not referenced. Concentration of dehydrocholic acid and CaPO4 unreported
Incomplete outcome data (attrition bias) Symptoms	Low risk	No systematic differences in drop-out rates between intervention groups; outcomes reported as specified in the protocol
Incomplete outcome data (attrition bias) Complications of influenza	High risk	Great difficulty in reconciling rationale with focus on cardiac complications of influenza with design and reporting of trial
Incomplete outcome data (attrition bias) Safety data	Low risk	Narratives for serious adverse events and drop-outs are reported with centre ID redacted
Selective reporting (reporting bias)	High risk	Undated amendment to text indicates sub-study of selected "intensive" population on the basis of viral isolates at baseline reported in the CRF: PDF page 388 "In selected patients (qualified as intensive patients in the Case Report Form), ECG's will be taken at baseline, day 3 and day 5. In these intensive patients, nose and throat swabs will be taken for virus culture at screening and on study days 3 and 5. In these patients also, a blood sample for laboratory safety measurements will be taken on days 1, 3 and 5 (and day 10/21 if indicated by the day 5/10 results)." Reason for change: "The sampling for the virology at baseline has been restricted to the selected intensive patients and the collection of the pharmaceutical data in the questionnaire has been updated"
Other bias	High risk	Certificate of analysis missing. Grossly underpowered trial
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different coloured capsules (identified through batch numbers and certificates of analysis of other study reports)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different coloured capsules unknown concentration of content

AEs: adverse events
AUC: area under the curve
bid: twice daily
CSR: clinical study report
CARIF: severity score

CDC: US Centers for Disease Control and Prevention
 COAD: chronic obstructive airways disease
 CONSORT: Consolidated Standards of Reporting Trials
 COPD: chronic obstructive pulmonary disease
 CPK: inflammation marker
 CRF: clinical report form
 d: day
 DAP: data analysis plan
 ECG: electrocardiogram
 EMA: European Medicines Agency
 EMEA: formerly EMA
 f: female
 FAS: full analysis set
 FEV1: forced expiratory volume (at interval 1 in spirometry testing)
 FDA: US Food and Drug Administration
 GCP: good clinical practice
 h: hour
 HAI: anti-haemagglutinin antibody
 IH: inhaled
 ILI: influenza-like illness
 IN: intranasal
 IP: infection-positive
 IPD: individual participant data
 IRB: institutional review board
 ITT: intention-to-treat (population)
 ITTI: intention-to-treat (influenza)-infected (population)
 LRTI: lower respiratory tract infection
 m: male
 MEP: middle ear pressure
 MI: myocardial infarction
 N: number
 NA: not applicable
 od: once daily
 OTC: over-the-counter
 PCR: polymerase chain reaction
 PEF: peak expiratory flow rate
 P-R: 1 of the segments of the ECG trace
 QRS: 1 of the segments of the ECG trace
 QT: 1 of the segments of the ECG trace
 QTc: 1 of the segments of the ECG trace
 RAP: reporting analysis plans
 R-R: risk ratio
 RSV: respiratory syncytial virus
 RTI: respiratory tract infection
 SAE: serious adverse event
 SAP: statistical analysis plan
 URTI: upper respiratory tract infection
 WBC: white blood cell
 WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
105934	Post-marketing study
107485	Dose-ranging study
108127	Non-randomised study

Study	Reason for exclusion
112311	Pharmaco-availability study
112312	Pharmaco-availability study
113268	Pharmaco-availability study
113502	Non-comparative study
113625	Pharmacokinetics study
113678	Non-comparative study
114045	Survey
114373	Not placebo/do nothing controlled
167-02	Dose ranging phase 1 in volunteers, no influenza exposure
167-03	Dose ranging phase 1 in volunteers, no influenza exposure
167-04	Dose ranging phase 1 in volunteers, no influenza exposure
167-05	Dose ranging phase 1 in volunteers, no influenza exposure
167T3-11	An open-label trial of 20 mg CG167 (zanamivir) in the treatment of influenza viral infection in children aged ≤ 5 and < 15 years old (open-label study). Non-randomised; the intervention group was compared to a survey group. 18 page summary available with no title
ADS-TCAD-PO206	Not placebo/do nothing controlled
BP21288	Pharmacokinetics study
C94-009	Pharmacokinetics study
C94-085	Pharmacokinetics study
GCP/95/045	Pharmacokinetics study
JNAI-02	Unknown study. Only ID traced
JNAI-03	Unknown study. Only ID traced
JP15734	Pharmacokinetics non-comparative study
JP15735	Does not test treatment, prophylaxis or PEP and there was no exposure to influenza
JV16284	Open-label, no control
JV21490	No influenza circulation, phase IV study with unusual oseltamivir dosages
M76006	Not placebo/do nothing controlled
ML17279	CSR bears no title. Study of community pharmacist availability
ML17713	Non-comparative study

Study	Reason for exclusion
ML19340	Text in French. Community pharmacist availability study
ML20542	Not placebo/do nothing controlled
ML21954	Not placebo/do nothing controlled
ML22789	Not placebo/do nothing controlled
ML22872	Not placebo/do nothing controlled
ML22879	Not placebo/do nothing controlled
ML25018	Bioavailability study
ML25087	Not placebo/do nothing controlled
ML25094	Non-comparative study
ML25157	Pharmacokinetics study
ML25176	Pharmacokinetics study
ML25179	Not placebo/do nothing controlled
ML25265	Non-comparative observational study
ML25266	Pharmacokinetics study
MP20691	Pharmacokinetics study
MV20043	Transmission study
MV20050	Dose-ranging study
MV22926	Non-comparative study
MV22949	Pharmacokinetics study
MV22951	Pharmacokinetics study
MV22963	Pharmacokinetics study
MV22970	Pharmacokinetics study
NAI106784	Pharmacokinetics study
NAI108166	Pharmacokinetics study
NAI10901	Comparator is vaccine
NAI10902	Pharmacokinetics study
NAI40012	Instructional leaflet study
NAIA1009	Pharmacokinetics study

Study	Reason for exclusion
NAIA2010	Open-label, rimantadine-controlled, cluster-randomised trial
NAIB1001	Pharmacokinetics study
NAIB1002	Pharmacokinetics study
NAIB1007	Pharmacokinetics study
NCT00297050	Dose-ranging study
NCT00416962	Not placebo/do nothing controlled
NCT00867139	Not placebo/do nothing controlled in immunocompromised people
NCT00957996	Peramivir study - does not have placebo/do nothing comparator
NCT01063933	Pharmacokinetics study
Not applicable (registry)	Unknown study. Only ID traced. Identified from Reddy D. J Antimicrob Chemother 2010; 65 Suppl 2: ii35–40 (doi:10.1093/jac/dkq014) Table 2. http://jac.oxfordjournals.org/cgi/content/full/65/suppl_2/ii35/DKQ014TB2
NP15525	Pharmacokinetics study
NP15717	Pharmacokinetics study
NP15718	Pharmacokinetics study
NP15719	Pharmacokinetics study
NP15728	Pharmacokinetics study
NP15729	Pharmacokinetics study
NP15743	Palatability study, open-label
NP15757	Pharmacokinetics study
NP15810	Pharmacokinetics study
NP15826	Pharmacokinetics study
NP15827	Pharmacodynamics study
NP15881	Palatability study in children
NP15901	Pharmacokinetics study
NP15912	Palatability study in children
NP16472	Not placebo/do nothing controlled
NP22770	Pharmacokinetics study
NP25138	Not placebo/do nothing controlled

Study	Reason for exclusion
NP25139	Not placebo/do nothing controlled
NP25140	Pharmacokinetics study
NV20234	Immunocompromised participants
NV20235	Immunocompromised participants
NV20237	Resistance study
NV22155	Not placebo/do nothing controlled
NV22158	Registry study
NV25118	Pharmacokinetics study
NV25182	Not placebo/do nothing controlled
NV25655	Open-label pharmacokinetics study
PP15974	Pharmacokinetics study
PP16351	Pharmacokinetics study
PP16361	Pharmacokinetics study
PV15615	Viral challenge study
PV15616	Viral challenge study
WP15517	Pharmacokinetics study
WP15525	Pharmacokinetics study
WP15647	Pharmacokinetics study
WP15648	Pharmacokinetics study
WP15676	Pharmacokinetics study
WP15979	Bioavailability study
WP16094	Pharmacokinetics study
WP16134	Bioequivalence study
WP16137	Bioequivalence study
WP16225	Bioequivalence study
WP16226	Pharmacokinetics study
WP16254	Pharmacokinetics study
WP16263	No influenza circulation, phase IV study

Study	Reason for exclusion
WP16295	Open-label absorption study
WP17721	Pharmacokinetics study
WP18308	Pharmacokinetics study
WP20727	Pharmacokinetics study
WP20749	Not placebo/do nothing controlled
WP21272	Pharmacokinetics study
WP22849	Pharmacokinetics study
WV15731	No placebo arm
WV16139	Unknown study. Only ID traced. ID could be a typo
WV16193	Not placebo/do nothing controlled

CSR: clinical study report
ID: identity number
PEP: post-exposure prophylaxis

Characteristics of studies awaiting assessment *[ordered by study ID]*

JPRN-JapicCTI-111647

Methods	A randomised, double-blind, placebo-controlled study to confirm the efficacy in the prevention of influenza virus infection (Phase 3 study) Duration of the study 2011-10-1 to 2012-6-30 Sponsor: Daiichi Sankyo Co., Ltd
Participants	—
Interventions	Laninamivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

ML20589

Methods	Economic and social benefits of treating and preventing influenza in aged care facilities Sponsor: The University of Sydney, Australia anzctr.org.au number ACTRN12606000278538
Participants	—
Interventions	Oseltamivir, 3 different regimens

ML20589 (Continued)

Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

ML20910

Methods	A study of Tamiflu (oseltamivir) treatment in laboratory-confirmed influenza Sponsor: Hoffmann-La Roche NCT00436124
Participants	—
Interventions	Oseltamivir
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

ML21776

Methods	Study to evaluate nosocomial transmission of influenza Sponsor: University Hospitals, Leicester NCT00798421
Participants	—
Interventions	—
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

MV21118

Methods	Early oseltamivir treatment of influenza in children 1 to 3 years of age Sponsor: Hospital District of Southwestern Finland NCT00593502
Participants	—
Interventions	Oseltamivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

MV21737

Methods	Long-term influenza prophylaxis with inhaled zanamivir or oral oseltamivir Sponsor: University of Oxford NCT00980109
Participants	—
Interventions	Oseltamivir, zanamivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

MV21879

Methods	Oseltamivir randomised controlled efficacy trial Sponsor: International Centre for Diarrhoeal Disease Research, Bangladesh NCT00707941
Participants	—
Interventions	Oseltamivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

MV22841

Methods	An observational clinical trial of influenza A/H1N1 2009 resistance under standard duration oseltamivir treatment Sponsor: not known
Participants	—
Interventions	Oseltamivir
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

MV22940

Methods	A randomised controlled trial on the effect of post-exposure oseltamivir prophylaxis on influenza transmission in nursing homes

MV22940 (Continued)

Sponsor: National Institute for Public Health and the Environment (RIVM), The Netherlands

NCT01053377

Participants	—
Interventions	Oseltamivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT00419263

Methods	Evaluation of the efficacy and safety of peramivir in subjects with uncomplicated acute influenza Sponsor: BioCryst Pharmaceuticals
Participants	—
Interventions	Peramivir
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT00453999

Methods	Evaluation of the efficacy and safety of peramivir in adults with acute serious or potentially life-threatening influenza Sponsor: BioCryst Pharmaceuticals
Participants	—
Interventions	Peramivir
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT00486980

Methods	Intramuscular peramivir for the treatment of uncomplicated influenza Sponsor: BioCryst Pharmaceuticals
Participants	—
Interventions	Peramivir

NCT00486980 (Continued)

Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT00555893

Methods	Efficacy study of early versus late oseltamivir administration for treating and preventing influenza
Participants	—
Interventions	Oseltamivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT00610935

Methods	Intramuscular peramivir in subjects with uncomplicated acute influenza Sponsor: Marshfield Clinic Research Foundation
Participants	—
Interventions	Peramivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT00705406

Methods	A phase II, multicentre, randomised, placebo-controlled, study to evaluate the efficacy and safety of intramuscular peramivir 600 mg in subjects with uncomplicated acute influenza Sponsor: BioCryst Pharmaceuticals
Participants	—
Interventions	Peramivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT00958776

Methods	A study to evaluate the efficacy and safety of IV peramivir in addition to standard of care compared to standard of care alone in adults and adolescents who are hospitalised due to influenza

NCT00958776 *(Continued)*

Sponsor: BioCryst Pharmaceuticals

Participants	Peramivir
Interventions	—
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT00980109

Methods Long-term influenza prophylaxis with inhaled zanamivir or oral oseltamivir

Sponsor: University of Oxford

Participants	—
Interventions	Oseltamivir, zanamivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NCT01032837

Methods A study of Tamiflu (oseltamivir) for treatment of influenza with a focus on (H1N1) 2009 flu strain

Sponsor: Hoffmann-La Roche

Participants	—
Interventions	Oseltamivir, placebo
Outcomes	—
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study

NV20236

Methods A study of Tamiflu (oseltamivir) for seasonal prophylaxis of influenza in children

Sponsor: Hoffmann-La Roche

NCT00412555

Participants	—
Interventions	Oseltamivir
Outcomes	—

NV20236 (Continued)

Notes

Awaiting assessment as we do not yet have the clinical study reports for this study

DATA AND ANALYSES

Comparison 1. Oseltamivir versus placebo for treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to first alleviation of symptoms in adult treatment (ITT population)	8	3954	Mean Difference (IV, Random, 95% CI)	-16.76 [-25.10, -8.42]
2 Hospital admission in adult treatment (safety population)	7	4394	Risk Ratio (IV, Random, 95% CI)	0.92 [0.57, 1.50]
3 Defined as influenza-infected at baseline in adult treatment	8	4452	Risk Ratio (IV, Random, 95% CI)	0.95 [0.91, 0.99]
4 Antibody rise four-fold or greater in adult treatment	8	4025	Risk Ratio (IV, Random, 95% CI)	0.92 [0.86, 0.97]
5 Adverse events - nausea in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	1.57 [1.14, 2.15]
6 Adverse events - vomiting in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	2.43 [1.75, 3.38]
7 Adverse events - diarrhoea in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	0.67 [0.46, 0.98]
8 Withdrawal from adult treatment trial due to adverse events	8	4452	Risk Ratio (IV, Random, 95% CI)	0.91 [0.56, 1.48]
9 All withdrawals from adult treatment	8	4452	Risk Ratio (IV, Random, 95% CI)	1.02 [0.73, 1.41]
10 Adverse events - cough in adult treatment (on-treatment)	6	3943	Risk Ratio (IV, Random, 95% CI)	0.63 [0.41, 0.96]
11 Adverse events - abdominal pain in adult treatment (on-treatment)	6	4368	Risk Ratio (IV, Random, 95% CI)	1.00 [0.64, 1.55]
12 Adverse events: dizziness in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	0.77 [0.51, 1.18]
13 Adverse events: headache in adult treatment (on-treatment)	7	4426	Risk Ratio (IV, Random, 95% CI)	1.17 [0.72, 1.90]
14 Serious adverse events: overall in adult treatment (on-treatment)	7	4394	Risk Ratio (IV, Random, 95% CI)	0.96 [0.51, 1.80]
15 Serious adverse events: overall in adult treatment (off-treatment)	7	4394	Risk Ratio (IV, Random, 95% CI)	0.73 [0.39, 1.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Complications: bronchitis in adult treatment	8	4452	Risk Ratio (IV, Random, 95% CI)	0.75 [0.56, 1.01]
16.1 Trials which collected data on non-specific adverse event or secondary/intercurrent illness form	6	3316	Risk Ratio (IV, Random, 95% CI)	0.66 [0.42, 1.03]
16.2 Trials which collected data on specific "Diagnosis of secondary illness" form	2	1136	Risk Ratio (IV, Random, 95% CI)	0.87 [0.61, 1.26]
17 Complications: pneumonia in adult treatment	8	4452	Risk Ratio (IV, Random, 95% CI)	0.55 [0.33, 0.90]
17.1 Trials which collected data on non-specific adverse event or secondary/intercurrent illness form	6	3316	Risk Ratio (IV, Random, 95% CI)	0.44 [0.22, 0.88]
17.2 Trials which collected data on specific "Diagnosis of secondary illness" form	2	1136	Risk Ratio (IV, Random, 95% CI)	0.69 [0.33, 1.44]
18 Complications: sinusitis in adult treatment	8	4452	Risk Ratio (IV, Random, 95% CI)	1.03 [0.76, 1.40]
18.1 Trials which collected data on non-specific adverse event or secondary/intercurrent illness form	6	3316	Risk Ratio (IV, Random, 95% CI)	1.05 [0.74, 1.50]
18.2 Trials which collected data on specific "Diagnosis of secondary illness" form	2	1136	Risk Ratio (IV, Random, 95% CI)	0.97 [0.52, 1.80]
19 Complications: otitis media in adult treatment	6	4368	Risk Ratio (IV, Random, 95% CI)	1.11 [0.57, 2.15]
19.1 Trials which collected data on non-specific adverse event or secondary/intercurrent illness form	4	3232	Risk Ratio (IV, Random, 95% CI)	0.99 [0.46, 2.12]
19.2 Trials which collected data on specific "Diagnosis of secondary illness" form	2	1136	Risk Ratio (IV, Random, 95% CI)	1.57 [0.41, 6.02]
20 Complications in adult trials classified as serious or leading to study withdrawal	6	3675	Risk Ratio (IV, Random, 95% CI)	0.91 [0.40, 2.06]
21 Culture-positive at baseline in adult treatment	8	4452	Risk Ratio (IV, Random, 95% CI)	1.01 [0.95, 1.07]
22 Adverse events: general body system in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	0.88 [0.67, 1.17]
23 Adverse events: neurological body system in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	1.05 [0.80, 1.38]
24 Adverse events: respiratory body system in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	0.81 [0.65, 1.00]

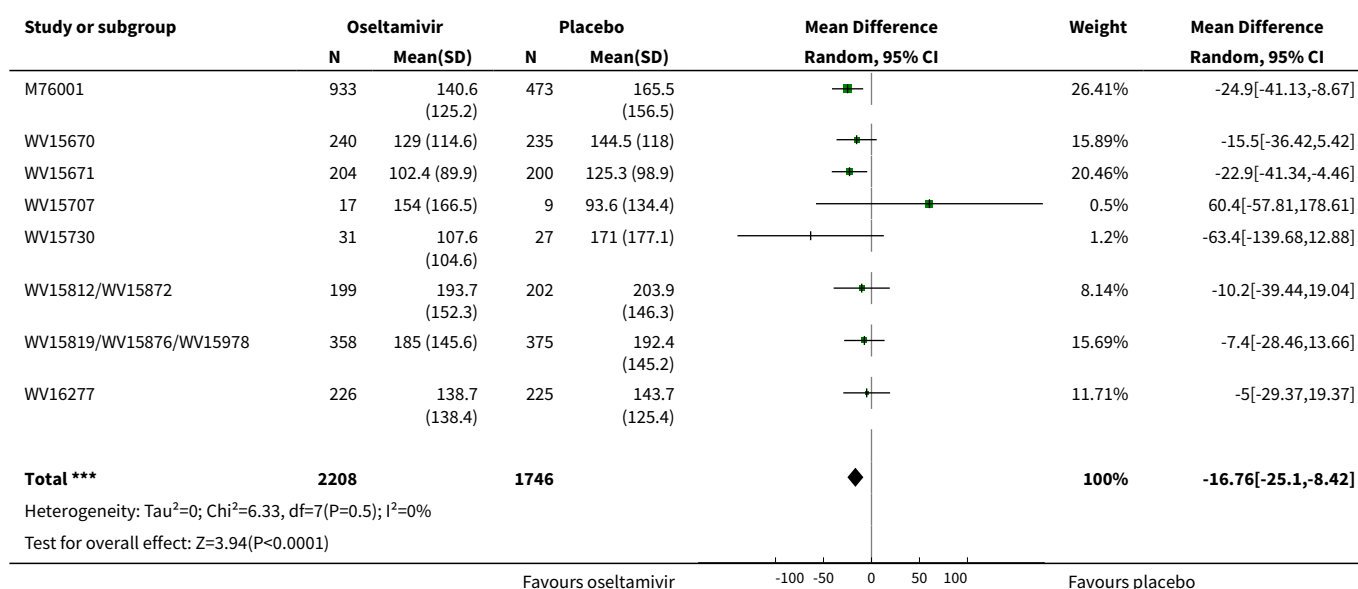
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 Adverse events: infection body system in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	0.85 [0.71, 1.01]
26 Adverse events: gastrointestinal body system in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	1.25 [1.08, 1.45]
27 Adverse events: cardiac body system in adult treatment (on-treatment)	6	3943	Risk Ratio (IV, Random, 95% CI)	0.49 [0.25, 0.97]
28 Adverse events: ear body system in adult treatment (on-treatment)	7	4426	Risk Ratio (IV, Random, 95% CI)	0.99 [0.61, 1.60]
29 Adverse events: eye body system in adult treatment (on-treatment)	7	4426	Risk Ratio (IV, Random, 95% CI)	1.00 [0.52, 1.92]
30 Adverse events: metabolism body system in adult treatment (on-treatment)	7	4394	Risk Ratio (IV, Random, 95% CI)	0.81 [0.46, 1.43]
31 Adverse events: musculoskeletal body system in adult treatment (on-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	1.01 [0.59, 1.73]
32 Adverse events: psychiatric body system in adult treatment (on-treatment)	7	4426	Risk Ratio (IV, Random, 95% CI)	0.93 [0.43, 2.03]
33 Adverse events: skin body system in adult treatment (on-treatment)	7	4426	Risk Ratio (IV, Random, 95% CI)	1.14 [0.63, 2.06]
34 Adverse events: cardiac body system in adult treatment (off-treatment)	7	4394	Risk Ratio (IV, Random, 95% CI)	1.21 [0.55, 2.64]
35 Adverse events: ear body system in adult treatment (off-treatment)	6	4368	Risk Ratio (IV, Random, 95% CI)	1.17 [0.57, 2.42]
36 Adverse events: gastrointestinal body system in adult treatment (off-treatment)	7	4394	Risk Ratio (IV, Random, 95% CI)	1.08 [0.74, 1.58]
37 Adverse events: general body system in adult treatment (off-treatment)	7	4394	Risk Ratio (IV, Random, 95% CI)	0.90 [0.50, 1.62]
38 Adverse events: infection body system in adult treatment (off-treatment)	7	4426	Risk Ratio (IV, Random, 95% CI)	0.80 [0.61, 1.03]
39 Adverse events: musculoskeletal body system in adult treatment (off-treatment)	7	4394	Risk Ratio (IV, Random, 95% CI)	0.84 [0.54, 1.30]
40 Adverse events: neurological body system in adult treatment (off-treatment)	6	4368	Risk Ratio (IV, Random, 95% CI)	1.29 [0.87, 1.91]
41 Adverse events: respiratory body system in adult treatment (off-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	0.94 [0.71, 1.24]
42 Adverse events: skin body system in adult treatment (off-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	0.81 [0.42, 1.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43 Adverse events: cough in adult treatment (off-treatment)	8	4452	Risk Ratio (IV, Random, 95% CI)	1.01 [0.55, 1.85]
44 Adverse events: headache in adult treatment (off-treatment)	6	4368	Risk Ratio (IV, Random, 95% CI)	1.34 [0.83, 2.15]
45 Adverse events: nausea in adult treatment (off-treatment)	6	4368	Risk Ratio (IV, Random, 95% CI)	1.05 [0.50, 2.23]
46 Time to first alleviation of symptoms in child treatment [hours]	3	1329	Mean Difference (IV, Random, 95% CI)	-8.04 [-33.34, 17.26]
46.1 Otherwise healthy children	1	669	Mean Difference (IV, Random, 95% CI)	-29.40 [-47.04, -11.76]
46.2 Children with chronic asthma	2	660	Mean Difference (IV, Random, 95% CI)	5.18 [-11.06, 21.41]
47 Hospital admission in child treatment (safety population)	3	1359	Risk Ratio (IV, Random, 95% CI)	1.92 [0.70, 5.23]
48 Defined as influenza-infected at baseline in child treatment	3	1359	Risk Ratio (IV, Random, 95% CI)	0.92 [0.84, 1.01]
49 Antibody rise four-fold or greater in child treatment	2	909	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.00]
50 Complications: bronchitis in child treatment	3	1359	Risk Ratio (IV, Random, 95% CI)	0.65 [0.27, 1.55]
51 Complications: otitis media in child treatment	3	1359	Risk Ratio (IV, Random, 95% CI)	0.80 [0.62, 1.02]
52 Complications: pneumonia in child treatment	3	1359	Risk Ratio (IV, Random, 95% CI)	1.06 [0.62, 1.83]
53 Complications: sinusitis in child treatment	3	1359	Risk Ratio (IV, Random, 95% CI)	1.00 [0.58, 1.72]
54 Complications: pneumonia in child treatment by on- and off-treatment	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
54.1 On-treatment	3	1359	Risk Ratio (IV, Random, 95% CI)	0.87 [0.48, 1.60]
54.2 Off-treatment	3	1359	Risk Ratio (IV, Random, 95% CI)	2.83 [0.52, 15.31]
55 Complications in trials of children classified as serious or leading to study withdrawal	3	1359	Risk Ratio (IV, Random, 95% CI)	1.98 [0.58, 6.72]
56 Withdrawal from child treatment trial due to adverse events	2	1029	Risk Ratio (IV, Random, 95% CI)	0.99 [0.33, 3.01]

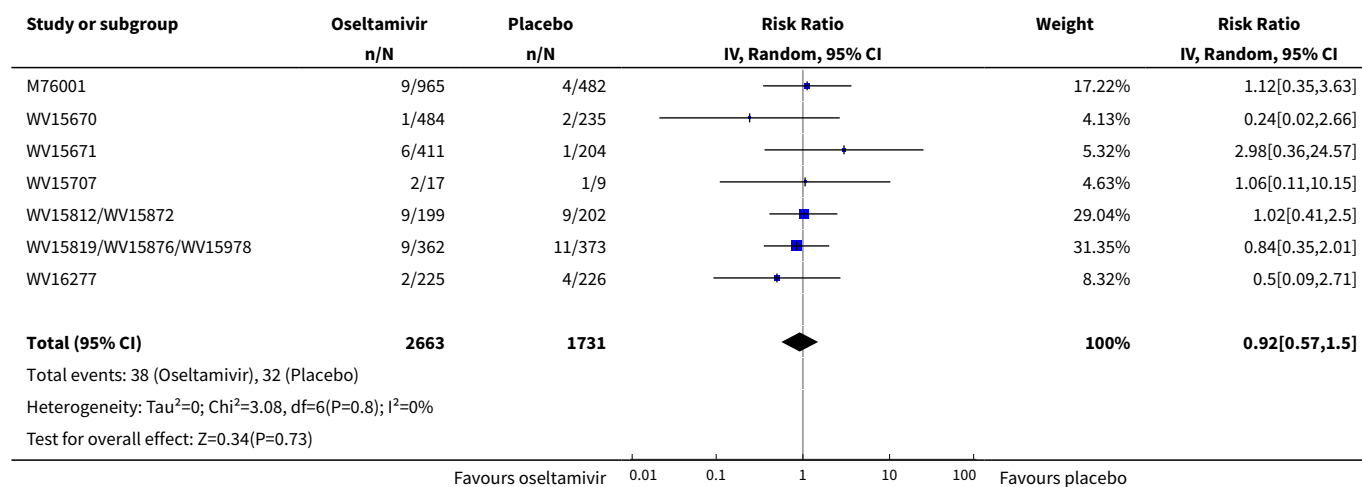
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
57 All withdrawals from child treatment	2	1029	Risk Ratio (IV, Random, 95% CI)	0.94 [0.56, 1.60]
58 Serious adverse events: overall in child treatment (on-treatment)	2	1029	Risk Ratio (IV, Random, 95% CI)	1.97 [0.59, 6.56]
59 Serious adverse events: overall in child treatment (off-treatment)	3	1358	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.38, 8.46]
60 Adverse events: abdominal pain in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.10 [0.62, 1.95]
61 Adverse events: diarrhoea in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	0.87 [0.58, 1.28]
62 Adverse events: nausea in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	0.87 [0.50, 1.51]
63 Adverse events: vomiting in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.70 [1.23, 2.35]
64 Adverse events: abdominal pain in child treatment (off-treatment)	3	1358	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.39, 2.11]
65 Adverse events: cough in child treatment (off-treatment)	2	1029	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.27, 1.85]
66 Adverse events: diarrhoea in child treatment (off-treatment)	3	1358	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.36, 1.40]
67 Adverse events: headache in child treatment (off-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.13 [0.55, 2.34]
68 Adverse events: vomiting in child treatment (off-treatment)	3	1358	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.57, 2.02]
69 Adverse events: ear body system in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.18 [0.30, 4.56]
70 Adverse events: gastrointestinal body system in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.18 [0.96, 1.44]
71 Adverse events: general body system in child treatment (on-treatment)	3	1358	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.47, 1.92]
72 Adverse events: infection body system in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	0.75 [0.59, 0.95]
73 Adverse events: neurological body system in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	0.66 [0.17, 2.62]
74 Adverse events: respiratory body system in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.02 [0.73, 1.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
75 Adverse events: skin body system in child treatment (on-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.26 [0.71, 2.22]
76 Adverse events: ear body system in child treatment (off-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.10 [0.52, 2.32]
77 Adverse events: gastrointestinal body system in child treatment (off-treatment)	2	1029	Risk Ratio (IV, Random, 95% CI)	1.15 [0.69, 1.91]
78 Adverse events: general body system in child treatment (off-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.00 [0.54, 1.86]
79 Adverse events: infection body system in child treatment (off-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.14 [0.82, 1.58]
80 Adverse events: neurological body system in child treatment (off-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	1.07 [0.51, 2.26]
81 Adverse events: respiratory body system in child treatment (off-treatment)	3	1358	Risk Ratio (IV, Random, 95% CI)	0.94 [0.65, 1.35]
82 Culture-positive at baseline in child treatment	3	1359	Risk Ratio (IV, Random, 95% CI)	0.93 [0.83, 1.04]

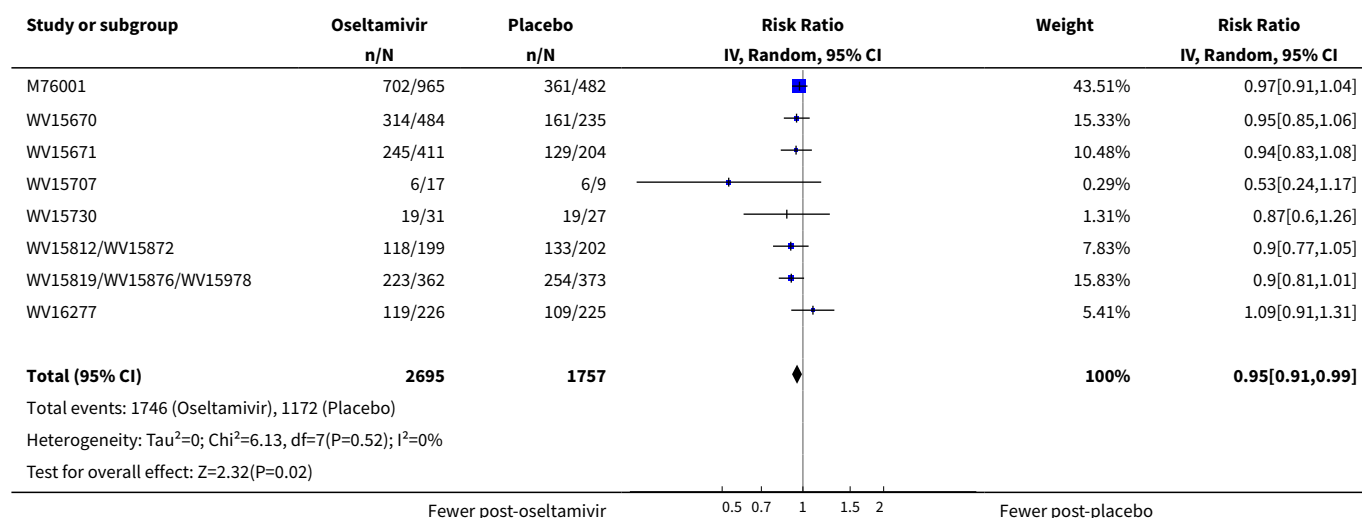
Analysis 1.1. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 1 Time to first alleviation of symptoms in adult treatment (ITT population).



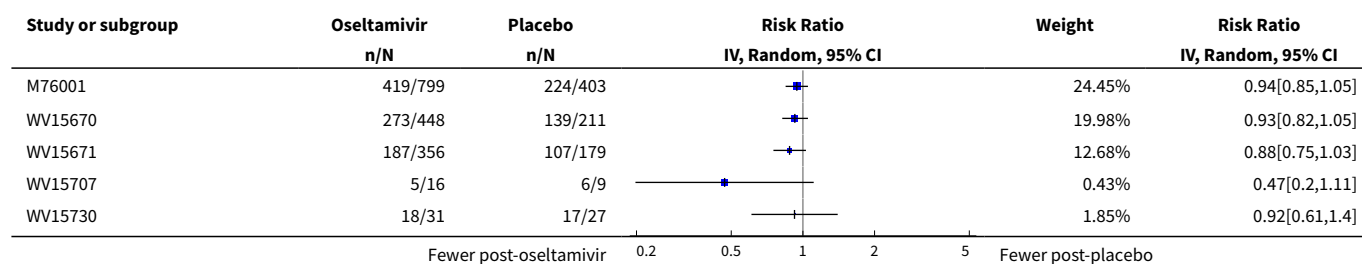
Analysis 1.2. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 2 Hospital admission in adult treatment (safety population).

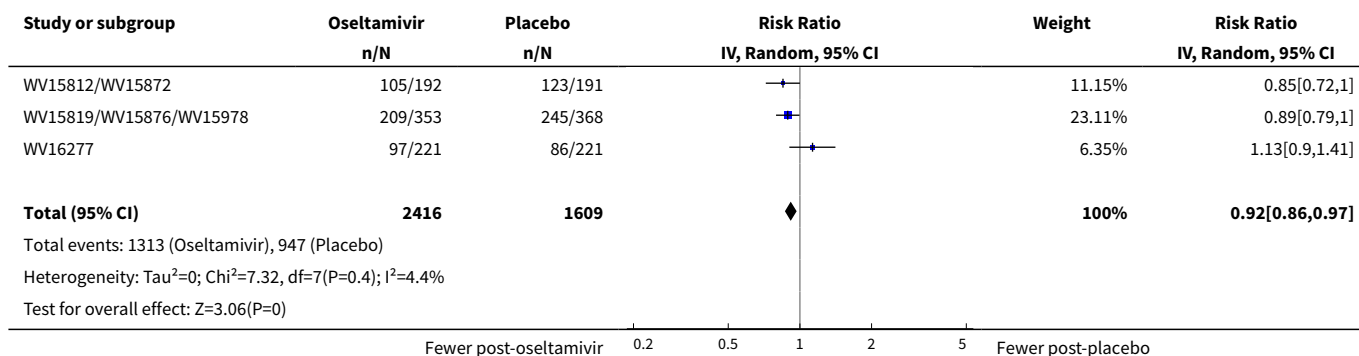


Analysis 1.3. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 3 Defined as influenza-infected at baseline in adult treatment.

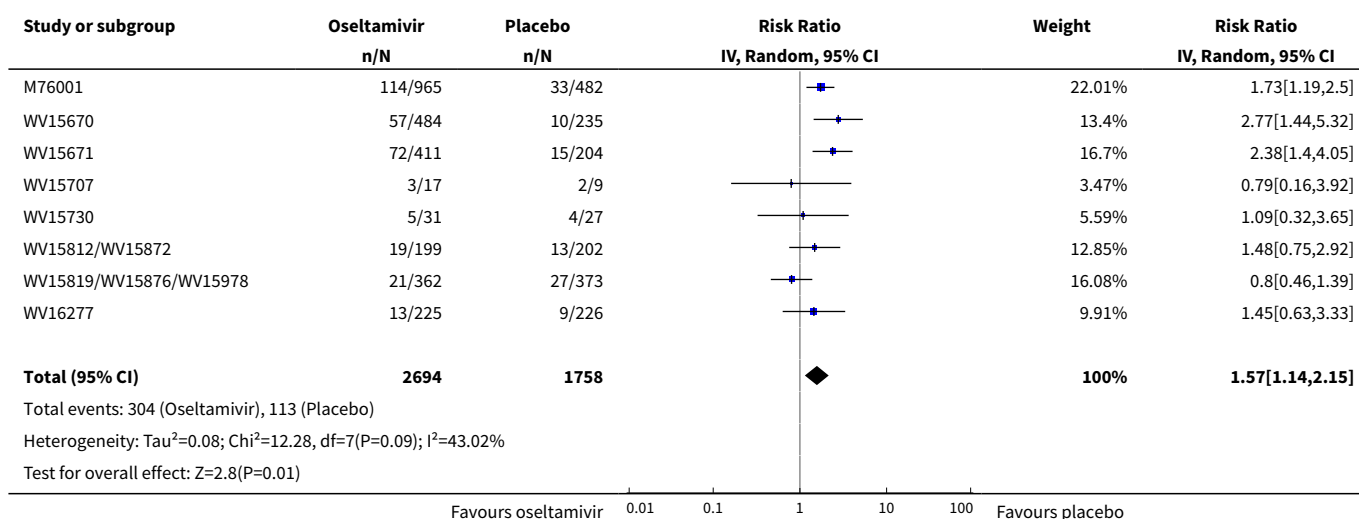


Analysis 1.4. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 4 Antibody rise four-fold or greater in adult treatment.

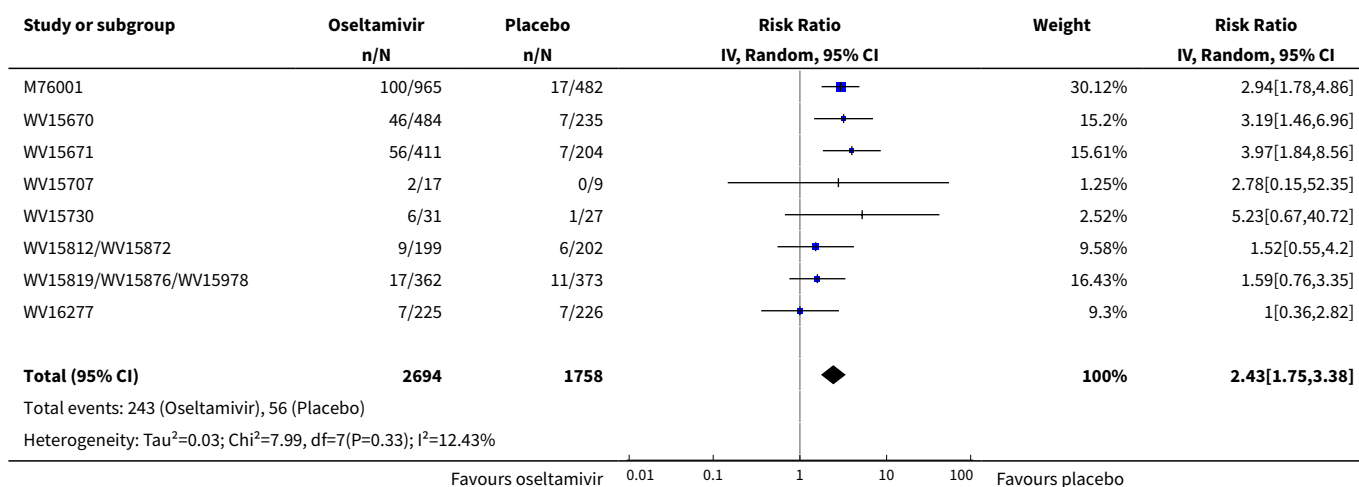


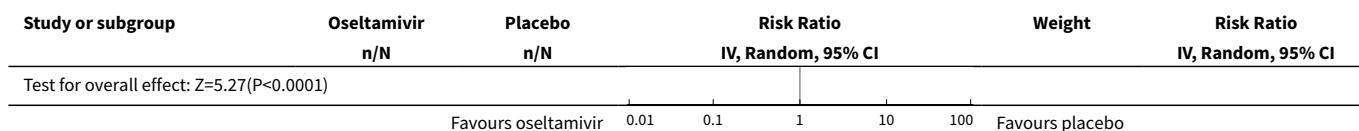


Analysis 1.5. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 5 Adverse events - nausea in adult treatment (on-treatment).

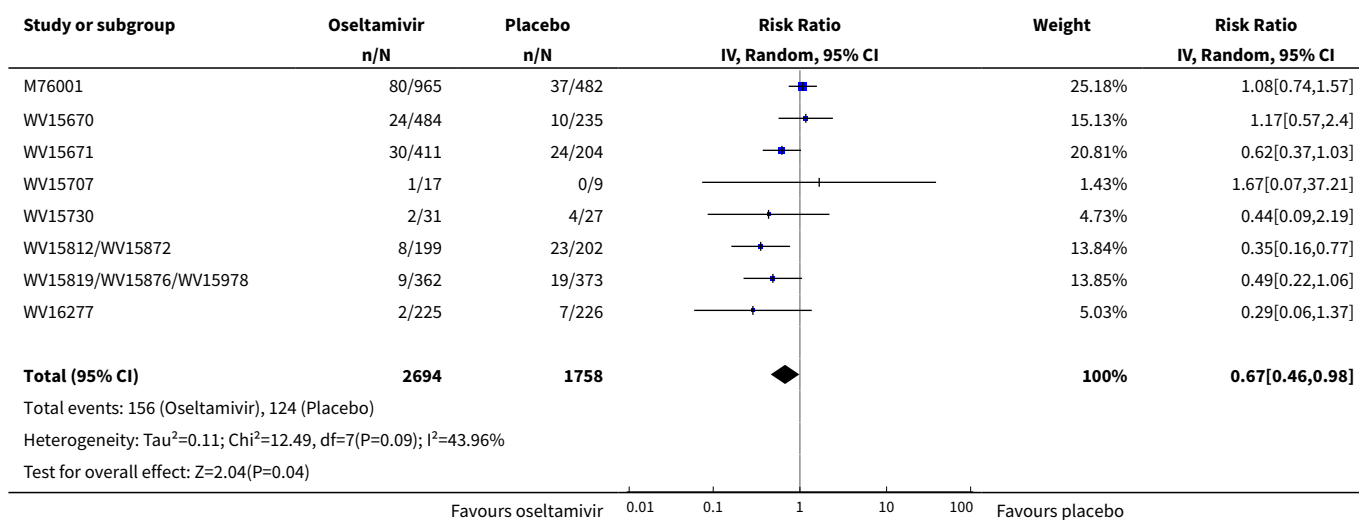


Analysis 1.6. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 6 Adverse events - vomiting in adult treatment (on-treatment).

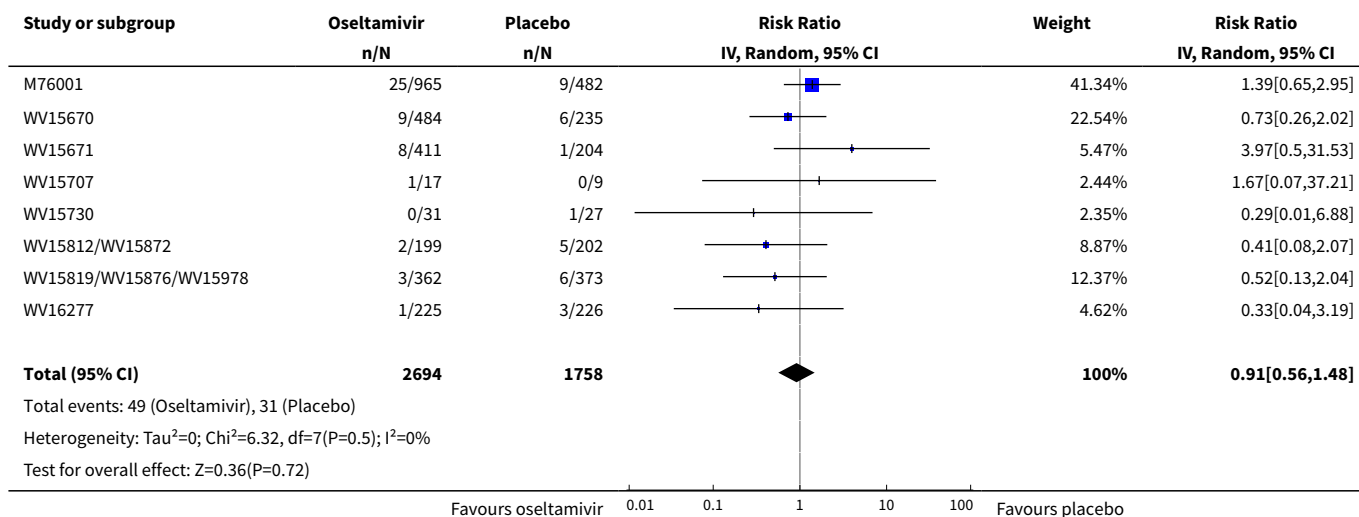




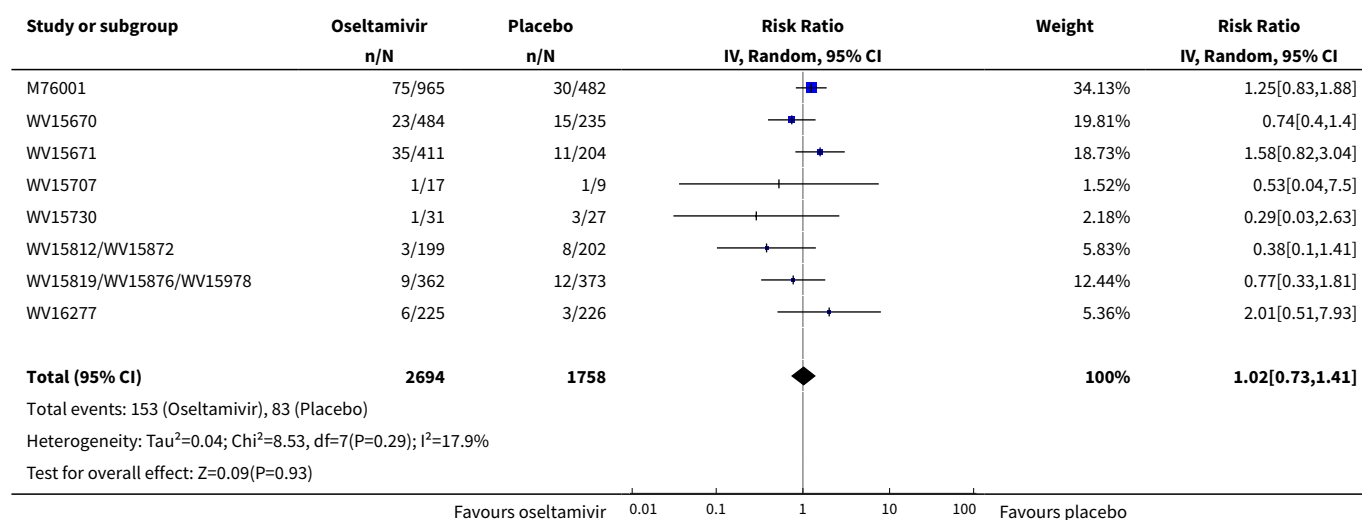
Analysis 1.7. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 7 Adverse events - diarrhoea in adult treatment (on-treatment).



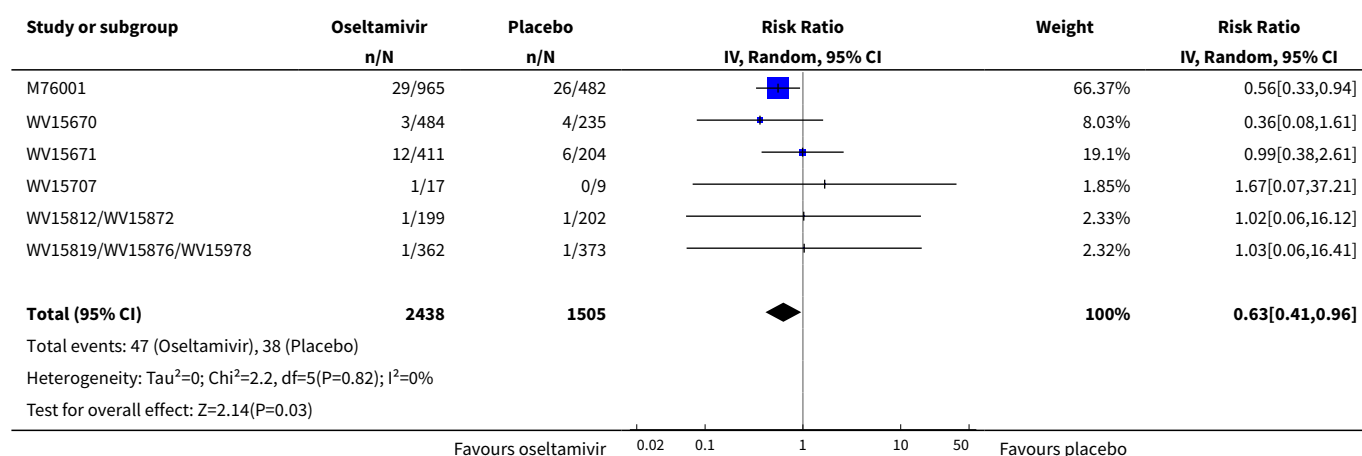
Analysis 1.8. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 8 Withdrawal from adult treatment trial due to adverse events.



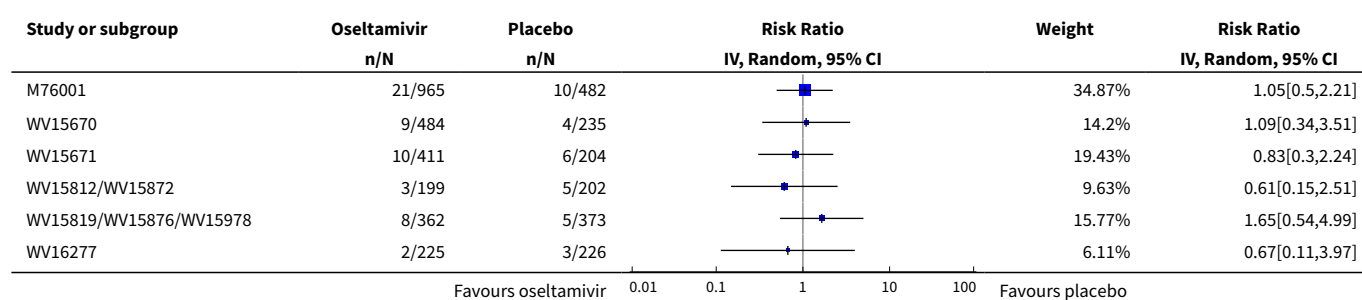
Analysis 1.9. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 9 All withdrawals from adult treatment.

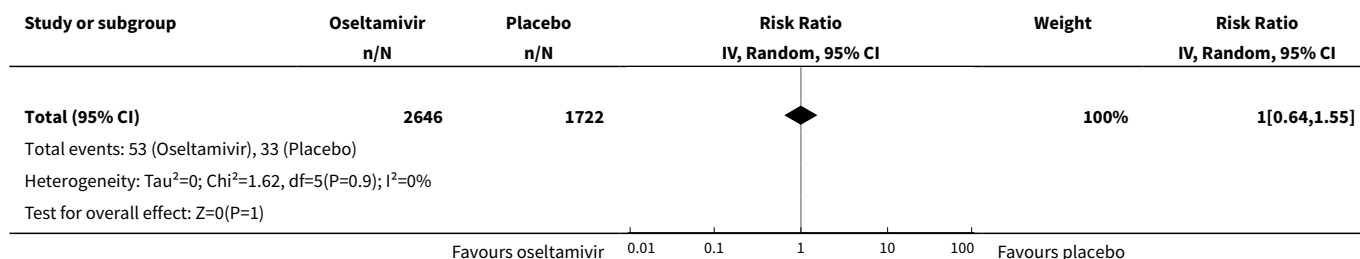


Analysis 1.10. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 10 Adverse events - cough in adult treatment (on-treatment).

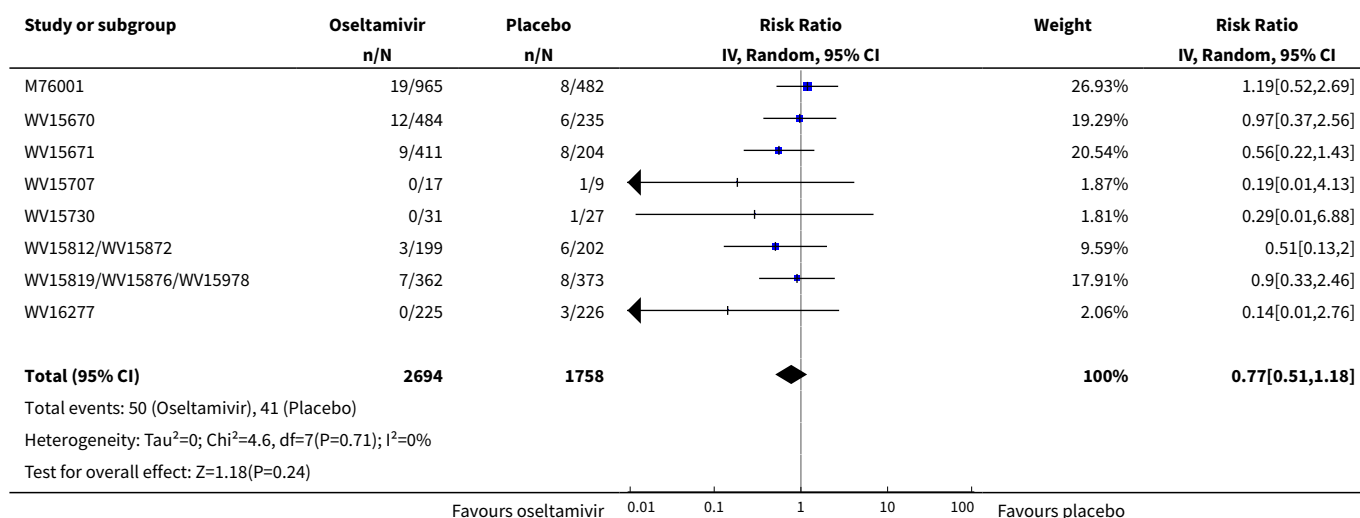


Analysis 1.11. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 11 Adverse events - abdominal pain in adult treatment (on-treatment).

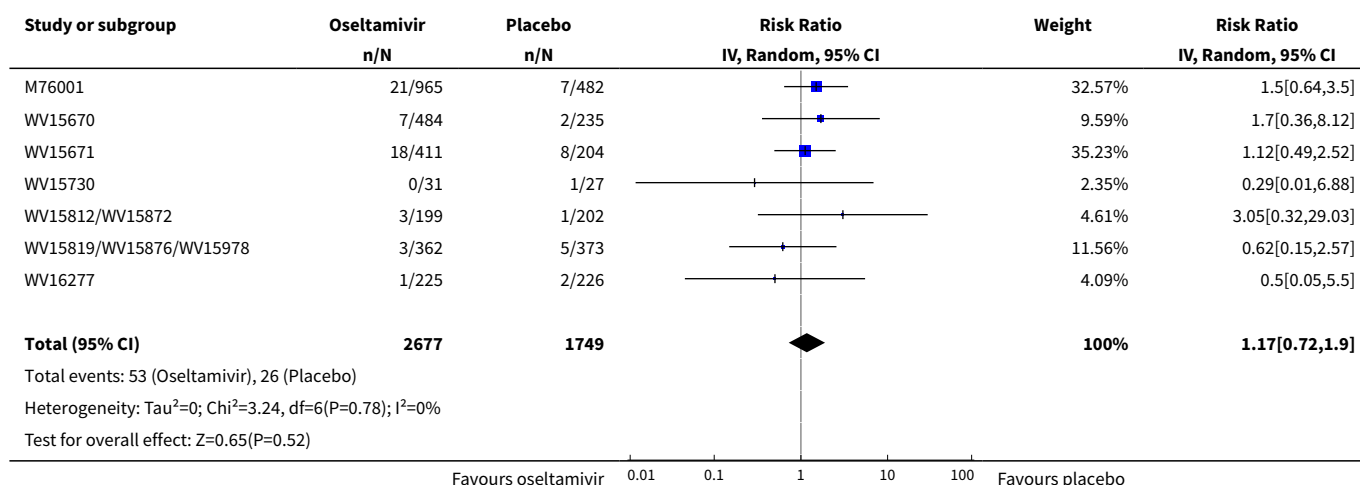




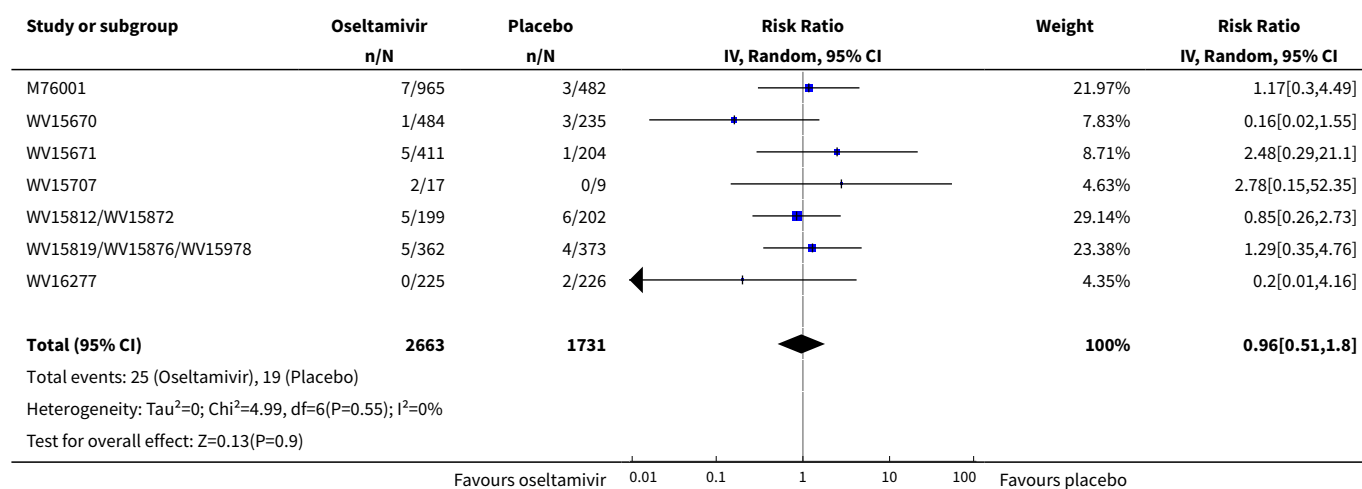
Analysis 1.12. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 12 Adverse events: dizziness in adult treatment (on-treatment).



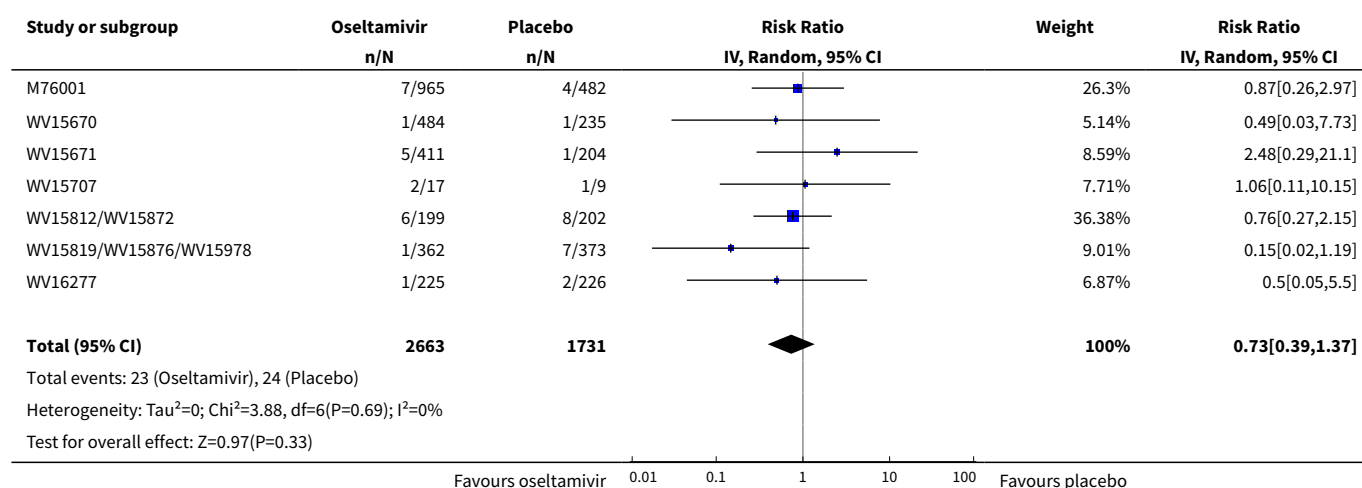
Analysis 1.13. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 13 Adverse events: headache in adult treatment (on-treatment).



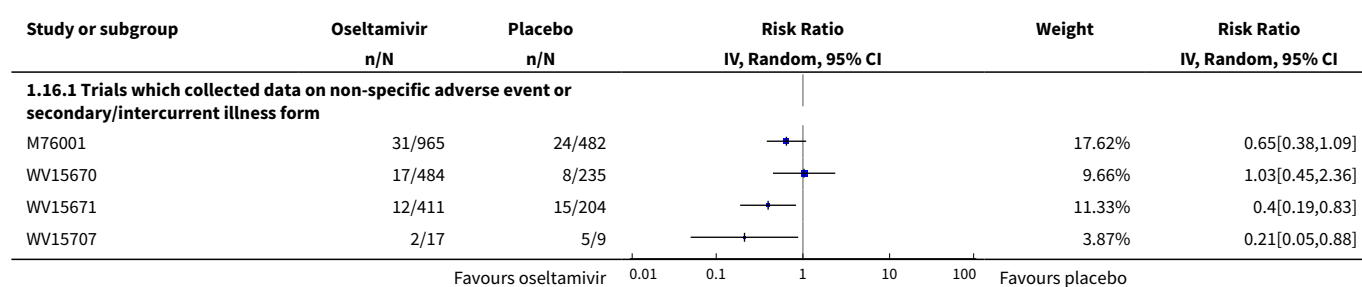
Analysis 1.14. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 14 Serious adverse events: overall in adult treatment (on-treatment).

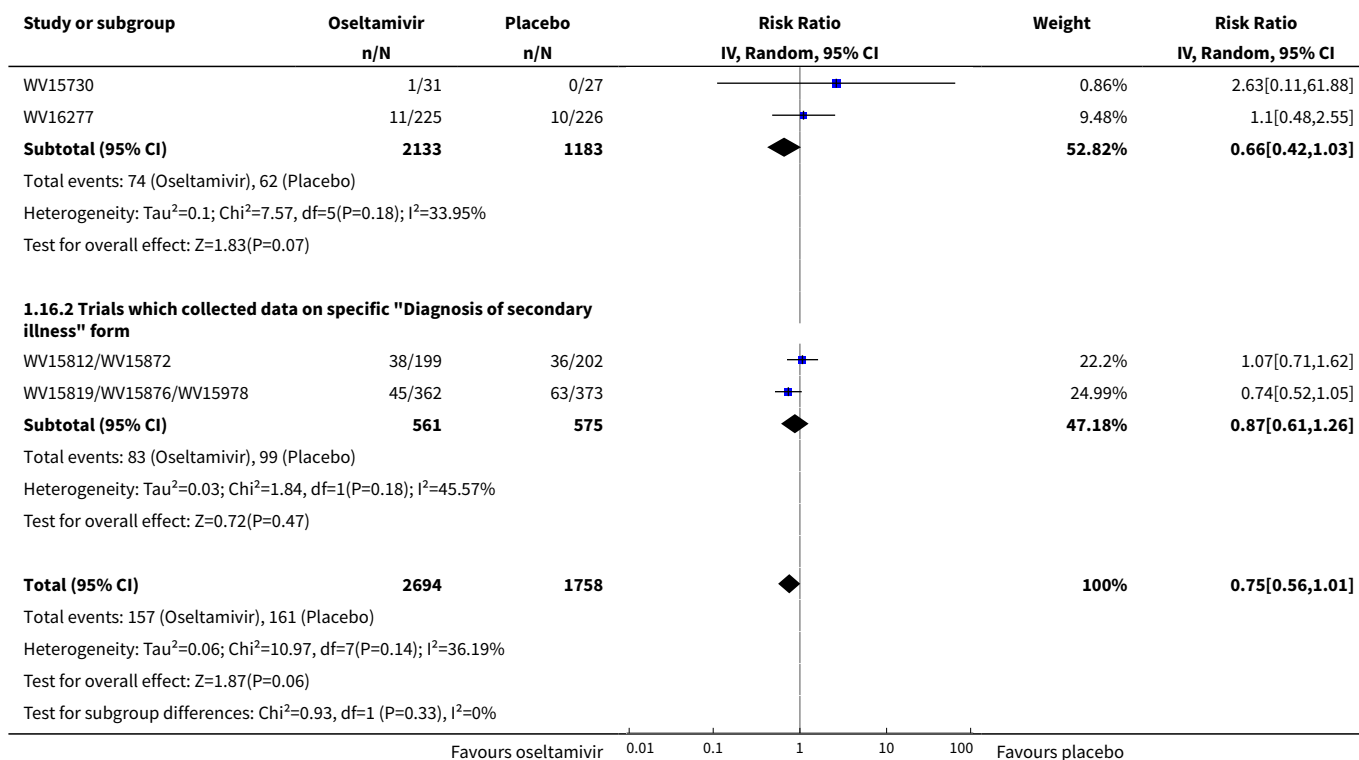


Analysis 1.15. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 15 Serious adverse events: overall in adult treatment (off-treatment).

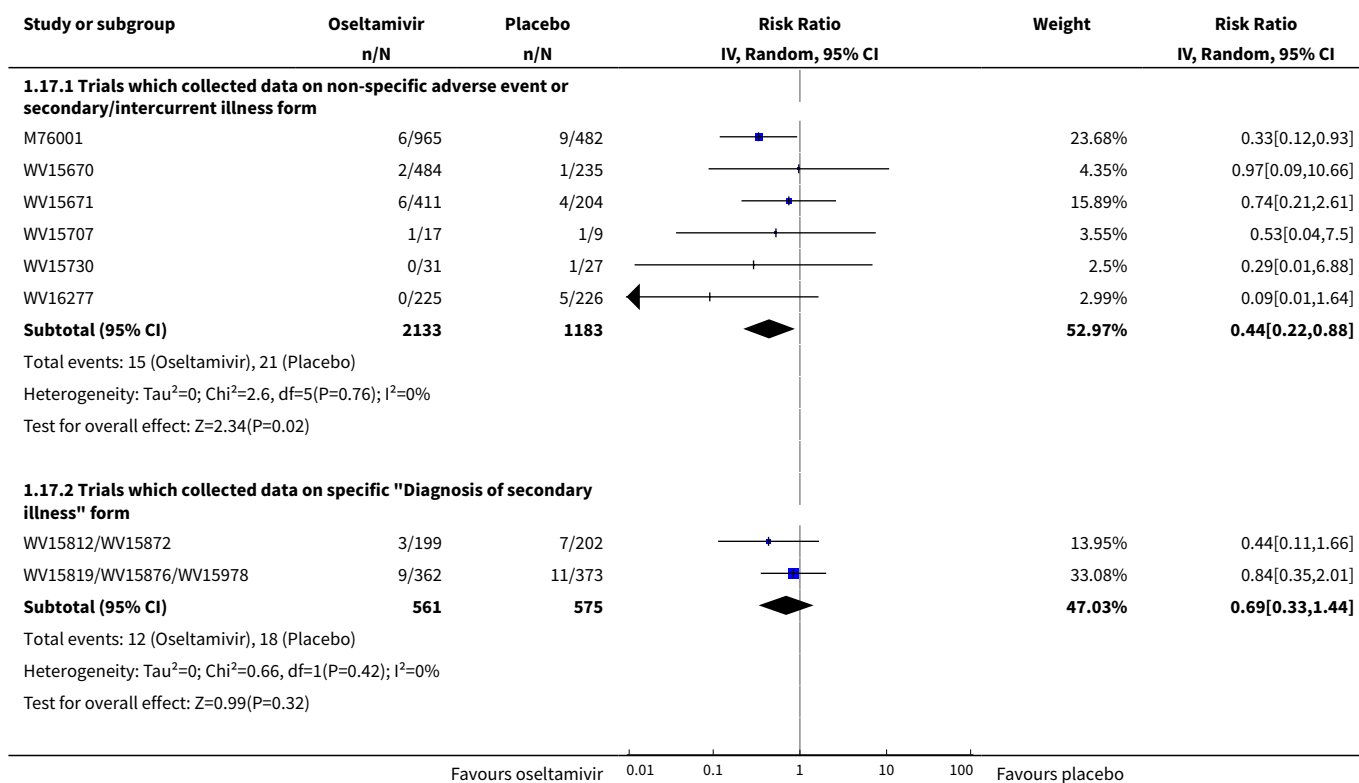


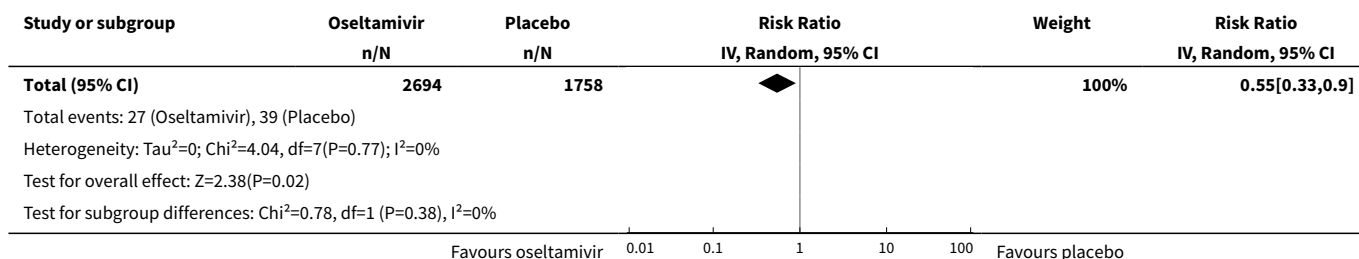
Analysis 1.16. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 16 Complications: bronchitis in adult treatment.



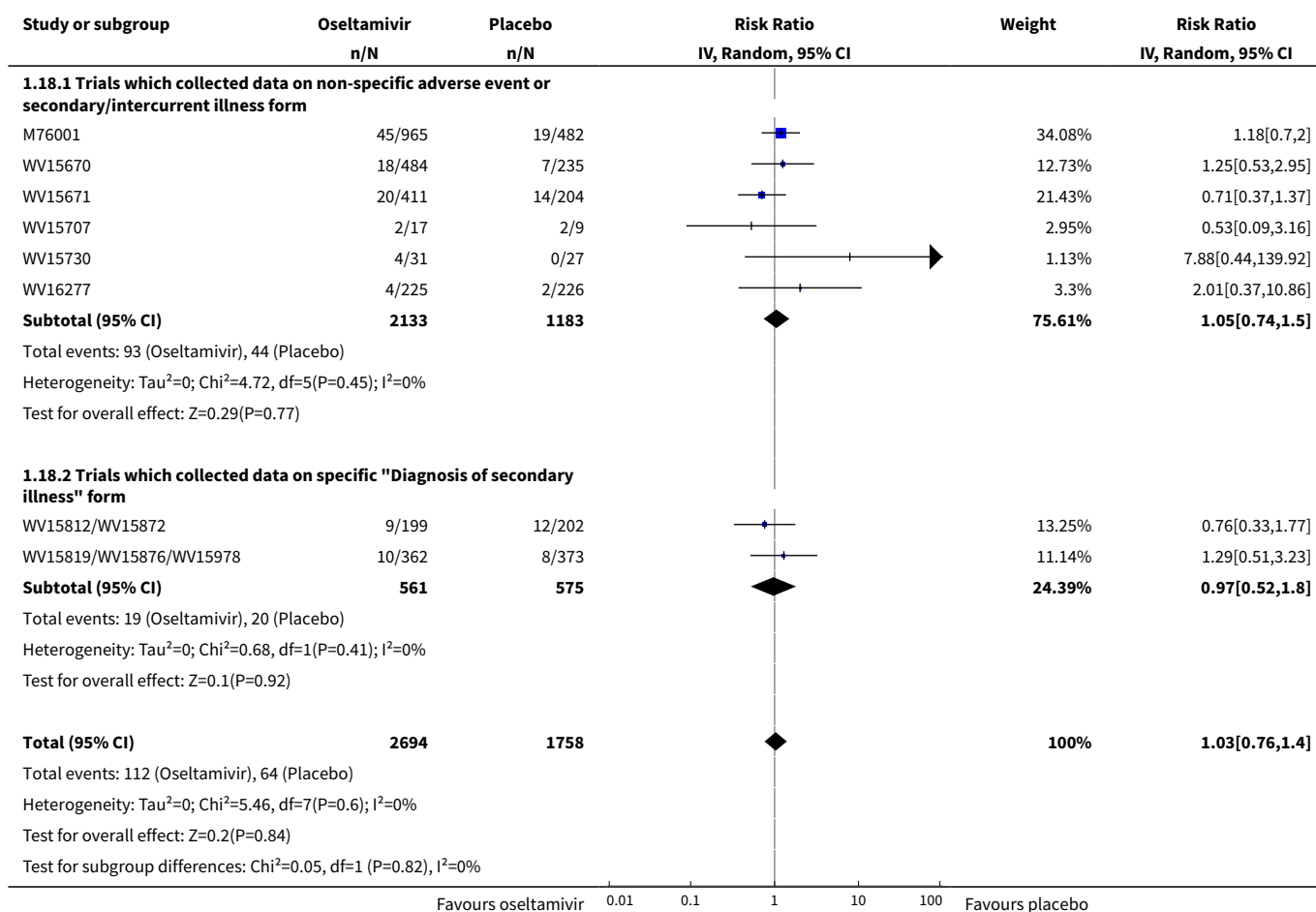


Analysis 1.17. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 17 Complications: pneumonia in adult treatment.

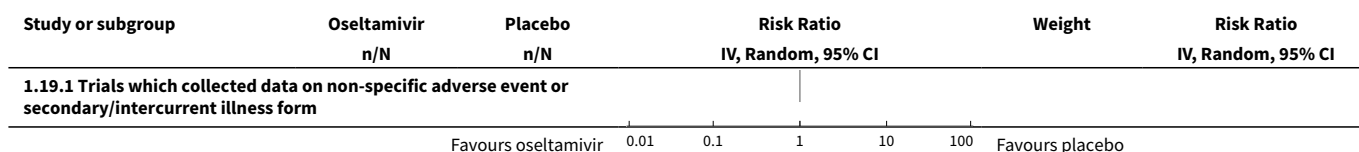


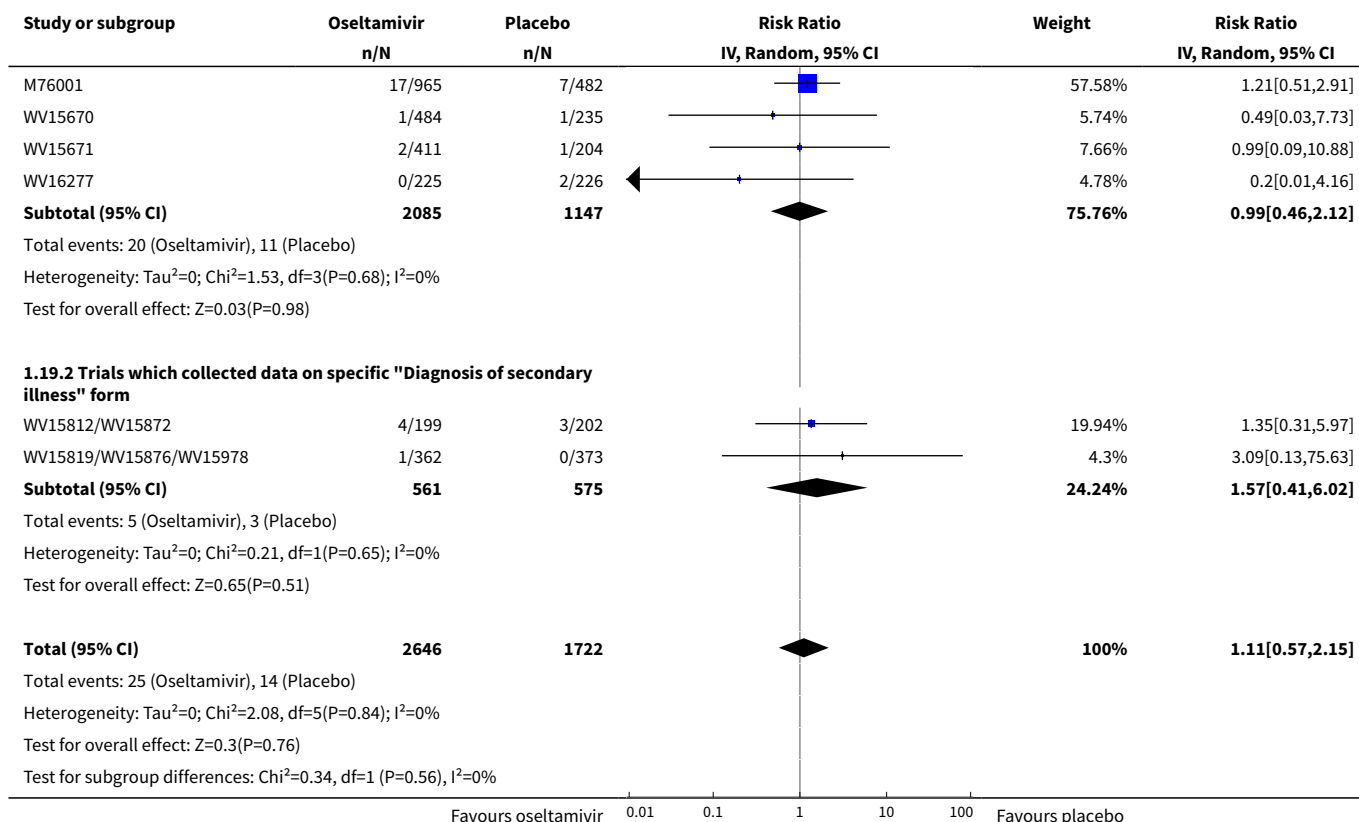


Analysis 1.18. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 18 Complications: sinusitis in adult treatment.

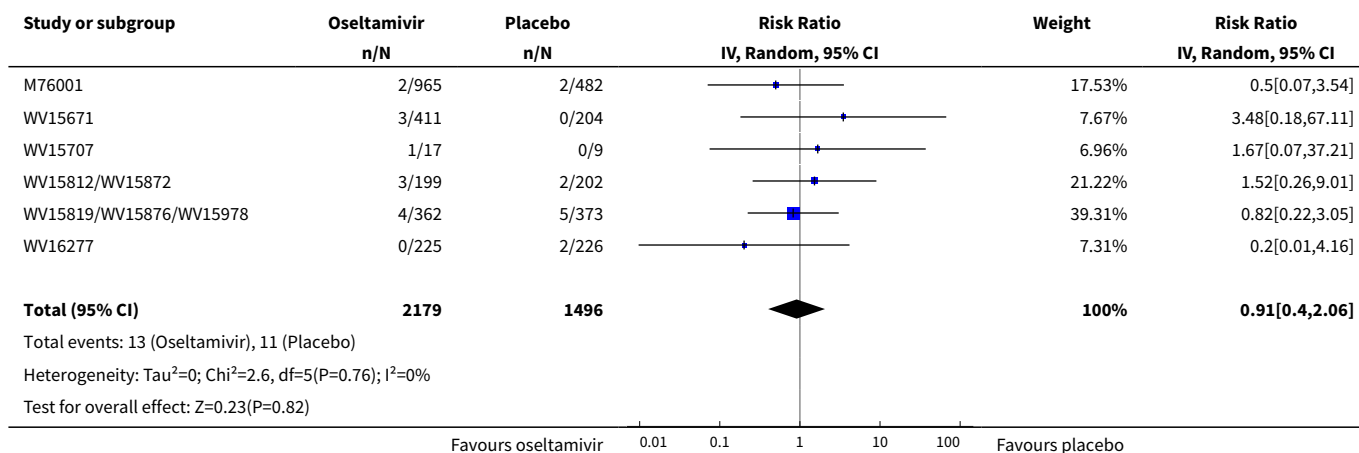


Analysis 1.19. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 19 Complications: otitis media in adult treatment.

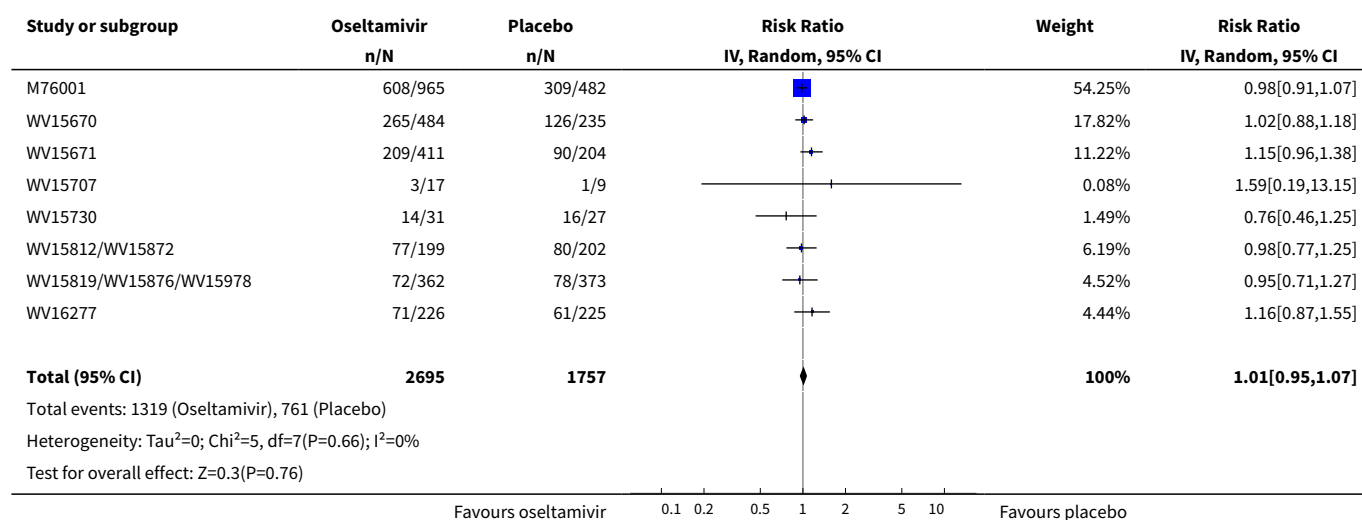




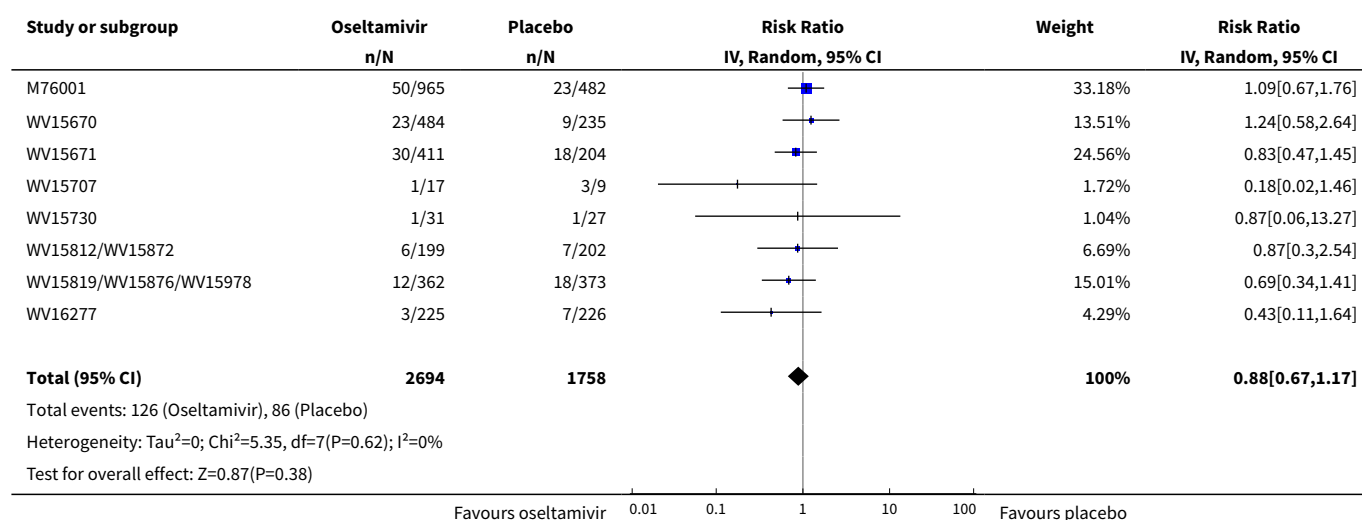
Analysis 1.20. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 20 Complications in adult trials classified as serious or leading to study withdrawal.



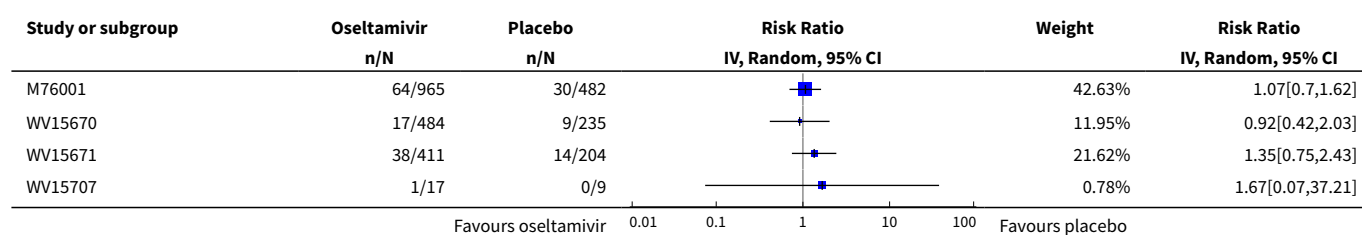
Analysis 1.21. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 21 Culture-positive at baseline in adult treatment.

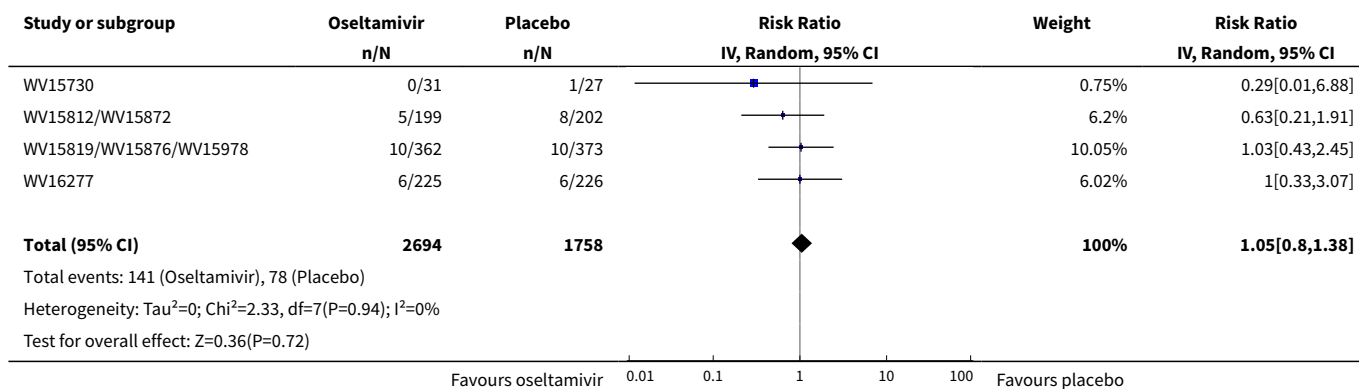


Analysis 1.22. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 22 Adverse events: general body system in adult treatment (on-treatment).

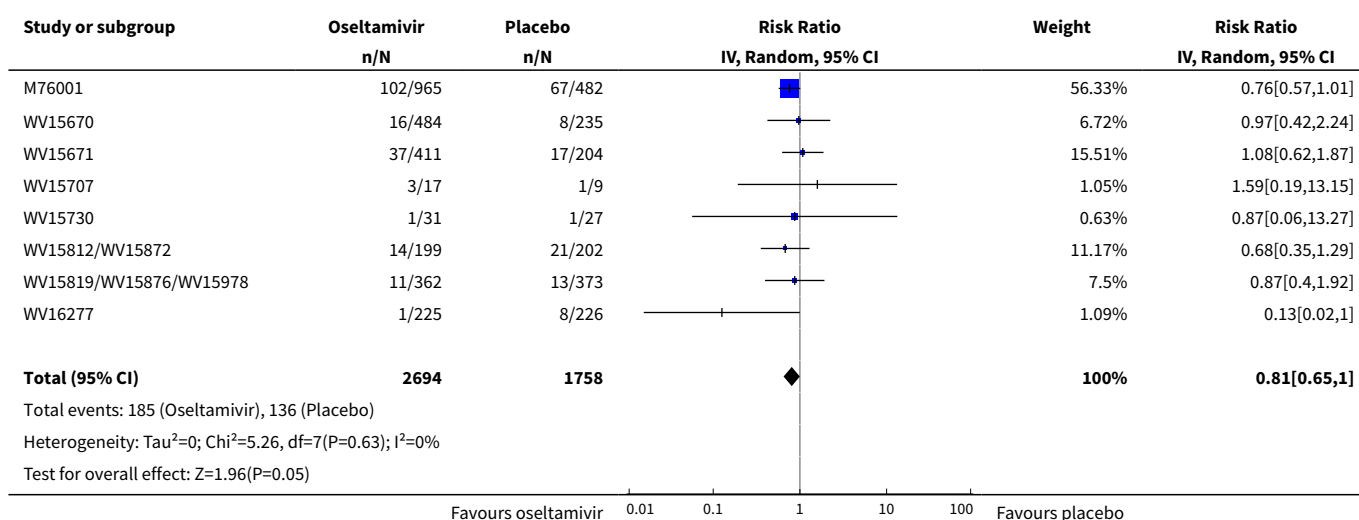


Analysis 1.23. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 23 Adverse events: neurological body system in adult treatment (on-treatment).

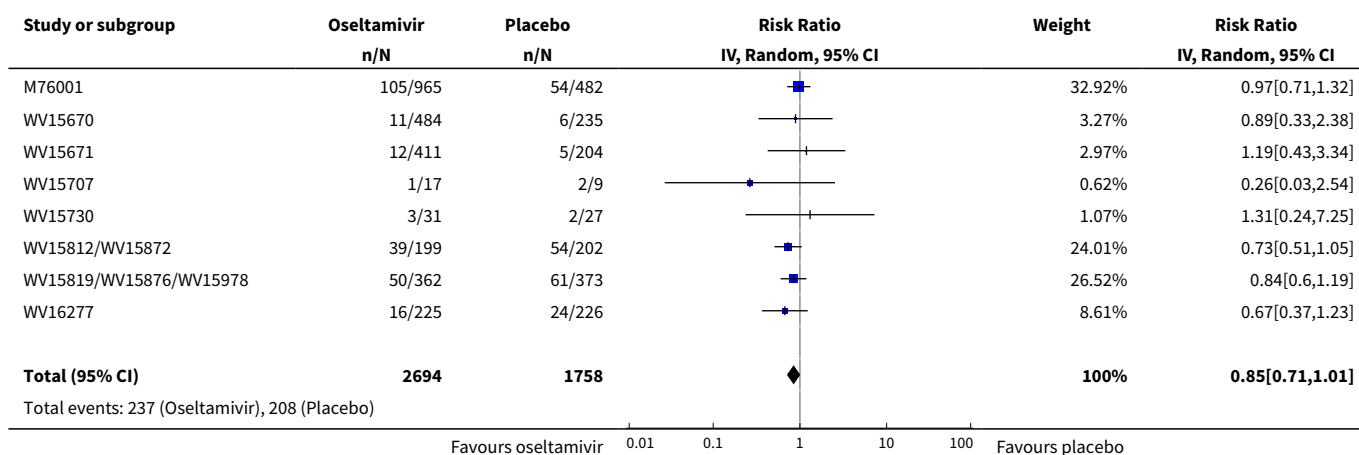


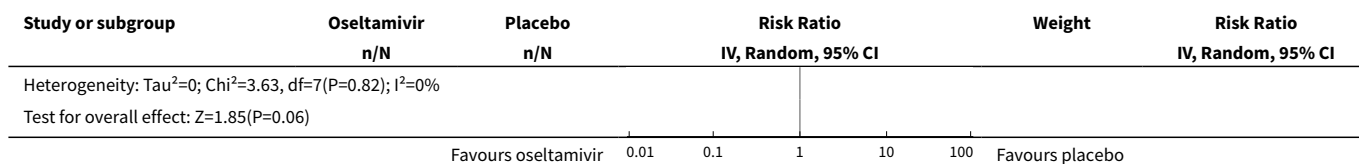


Analysis 1.24. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 24 Adverse events: respiratory body system in adult treatment (on-treatment).

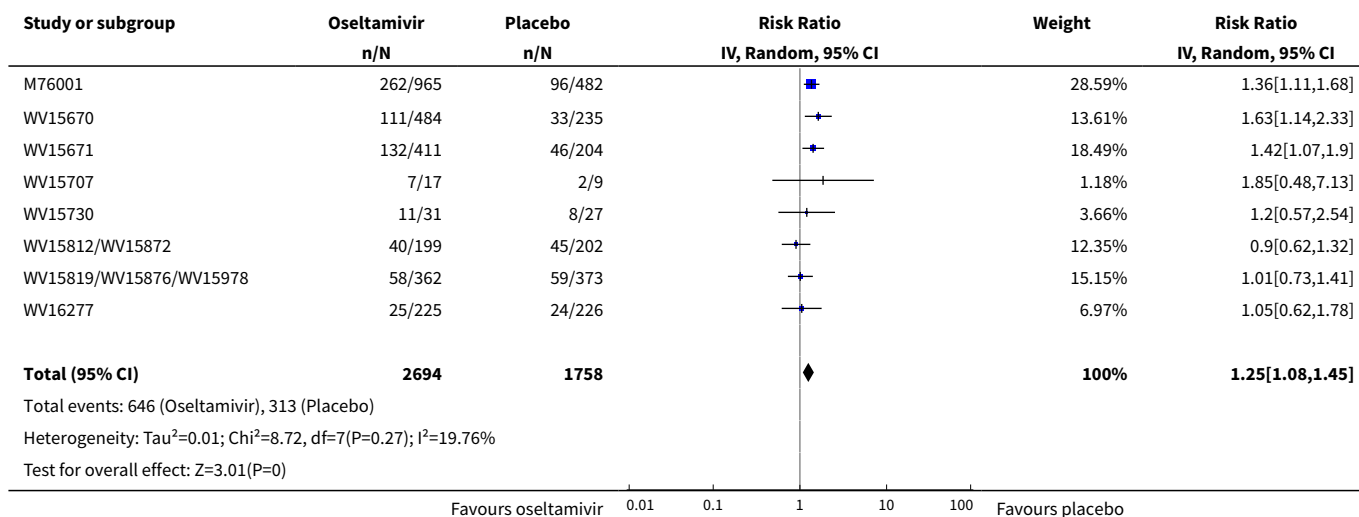


Analysis 1.25. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 25 Adverse events: infection body system in adult treatment (on-treatment).

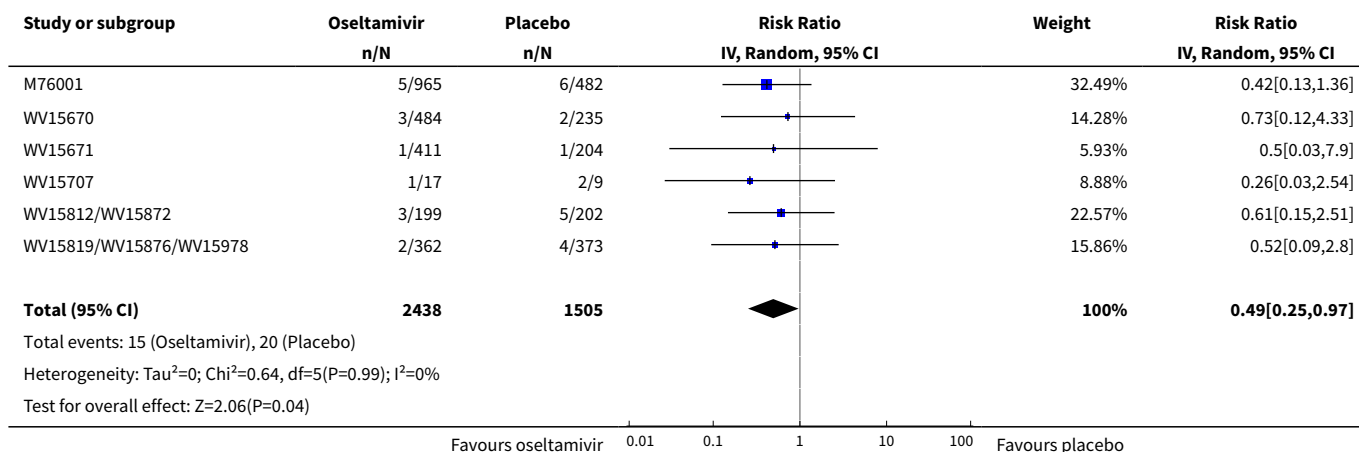




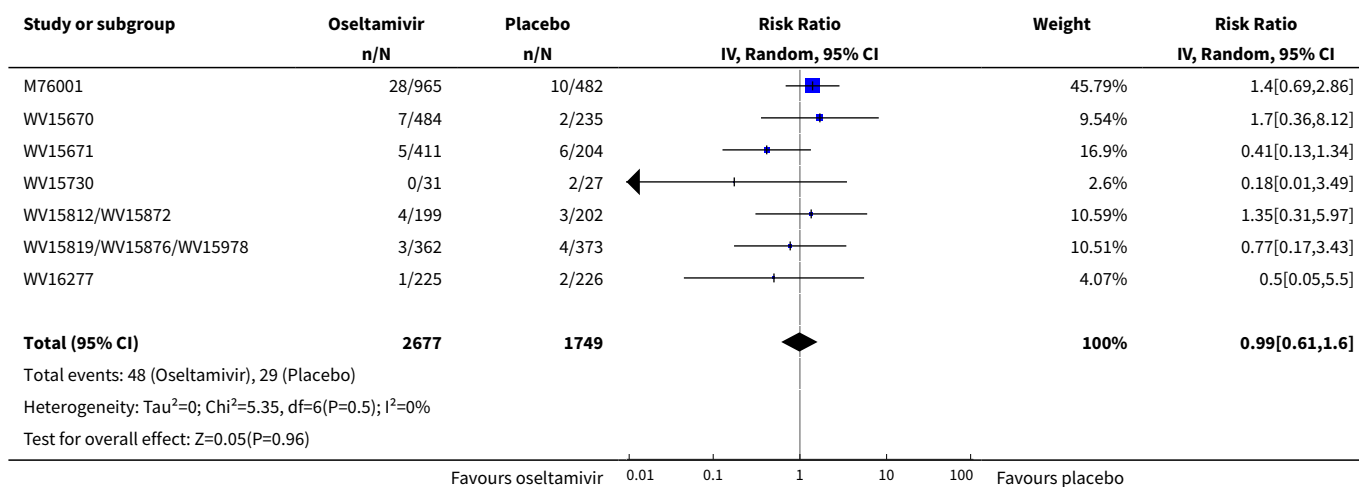
Analysis 1.26. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 26 Adverse events: gastrointestinal body system in adult treatment (on-treatment).



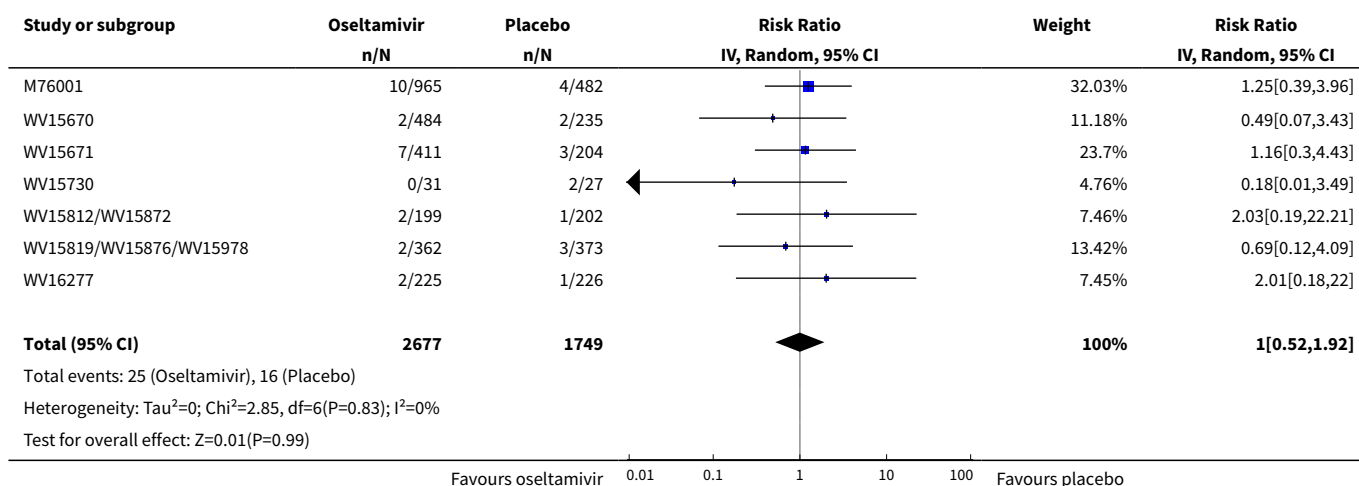
Analysis 1.27. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 27 Adverse events: cardiac body system in adult treatment (on-treatment).



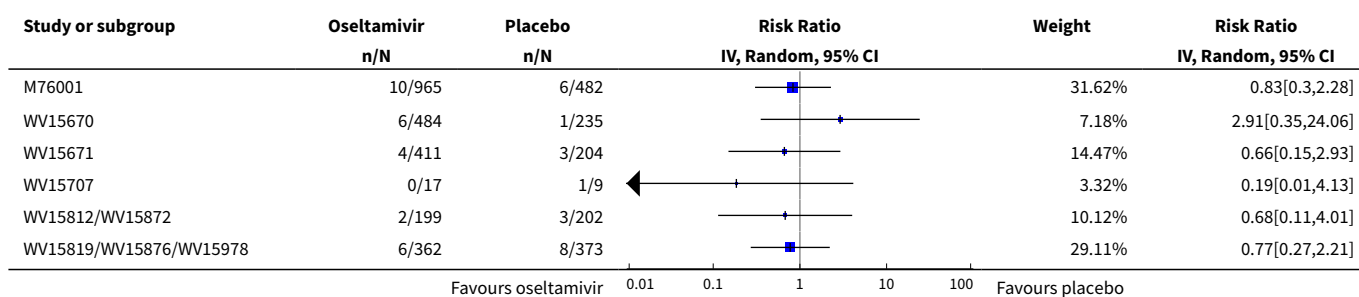
Analysis 1.28. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 28 Adverse events: ear body system in adult treatment (on-treatment).

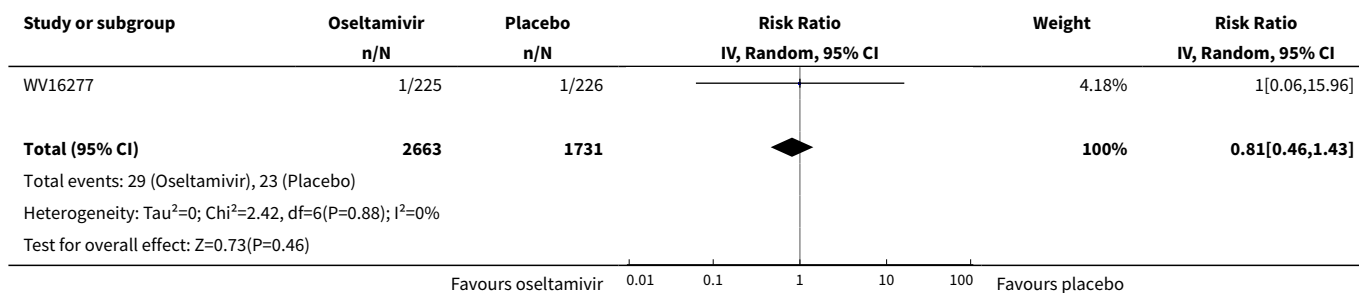


Analysis 1.29. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 29 Adverse events: eye body system in adult treatment (on-treatment).

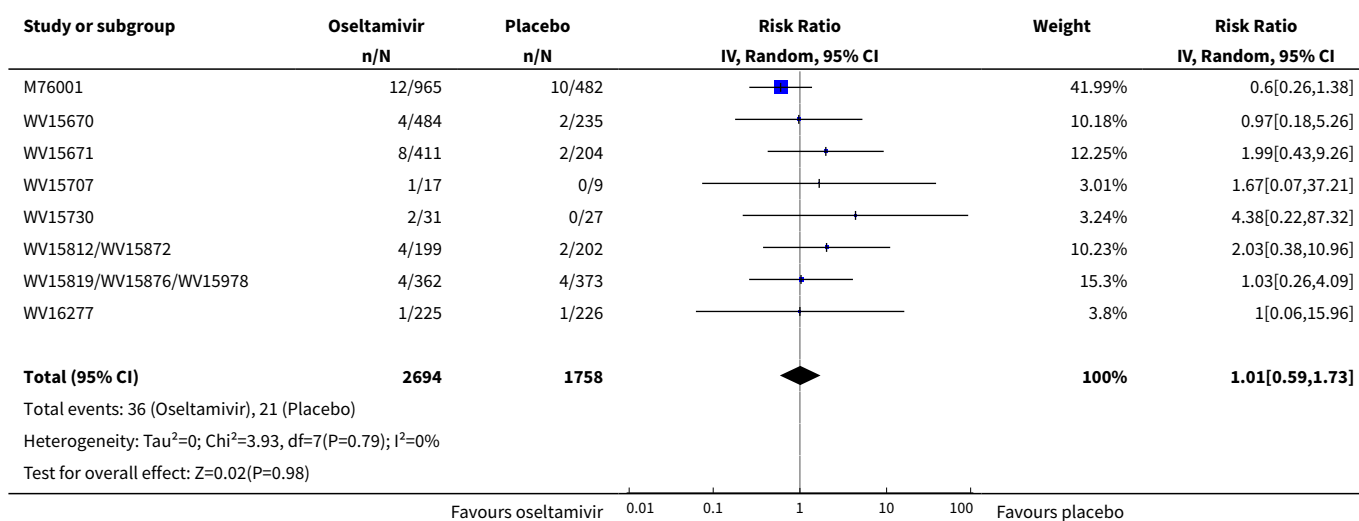


Analysis 1.30. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 30 Adverse events: metabolism body system in adult treatment (on-treatment).

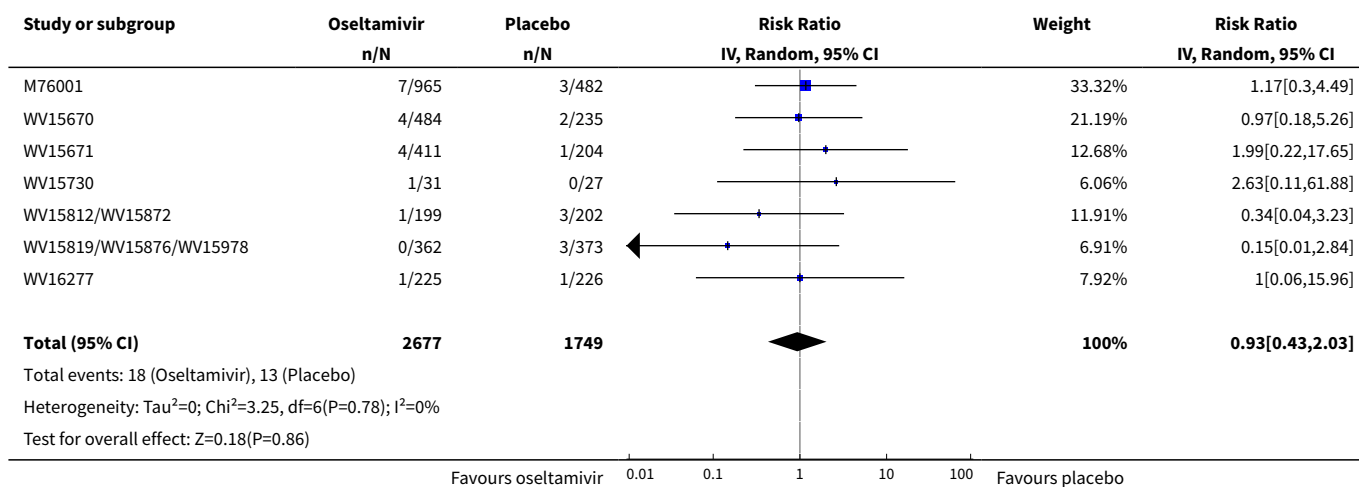




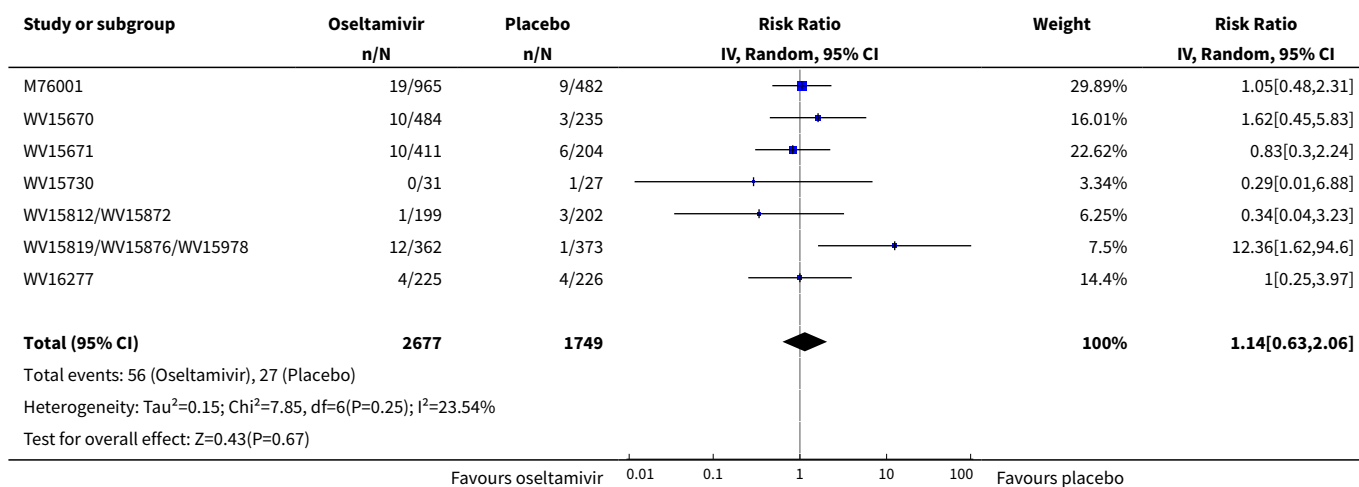
Analysis 1.31. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 31 Adverse events: musculoskeletal body system in adult treatment (on-treatment).



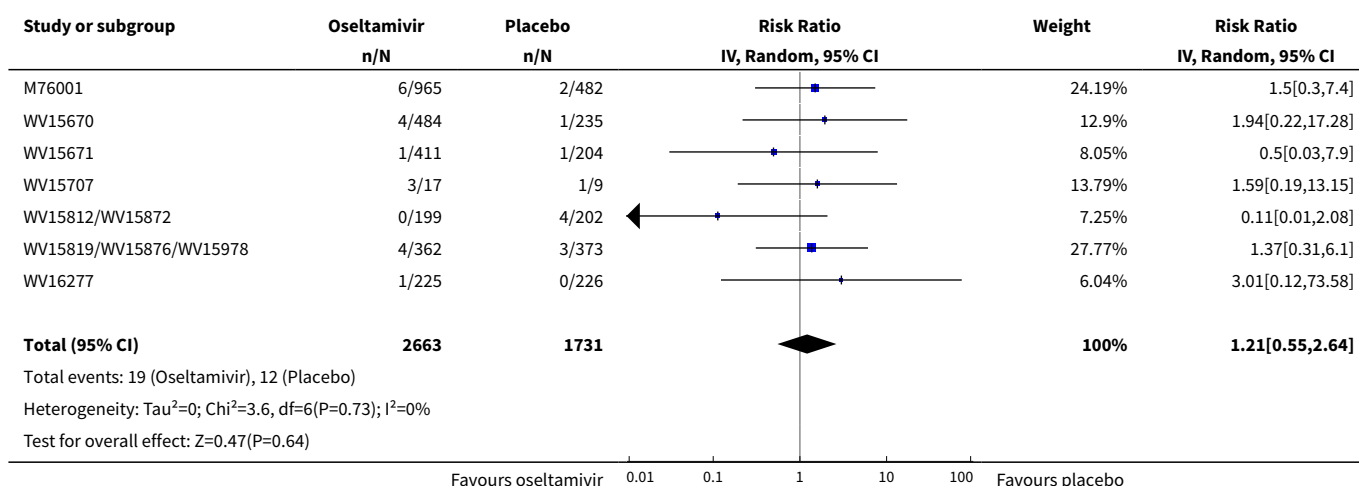
Analysis 1.32. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 32 Adverse events: psychiatric body system in adult treatment (on-treatment).



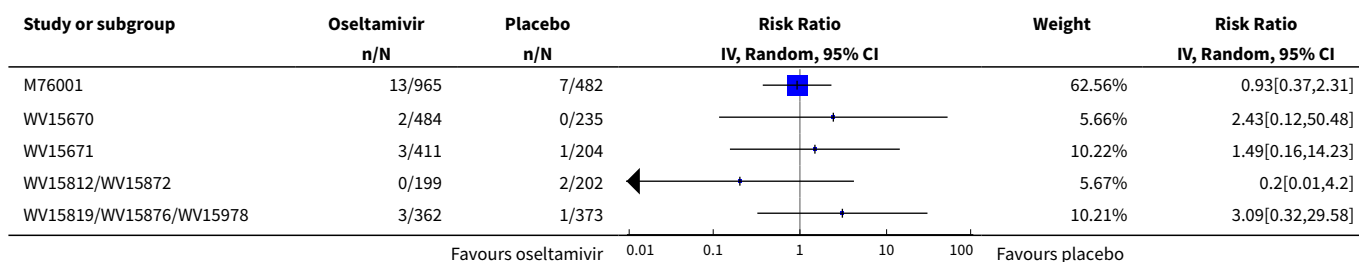
Analysis 1.33. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 33 Adverse events: skin body system in adult treatment (on-treatment).

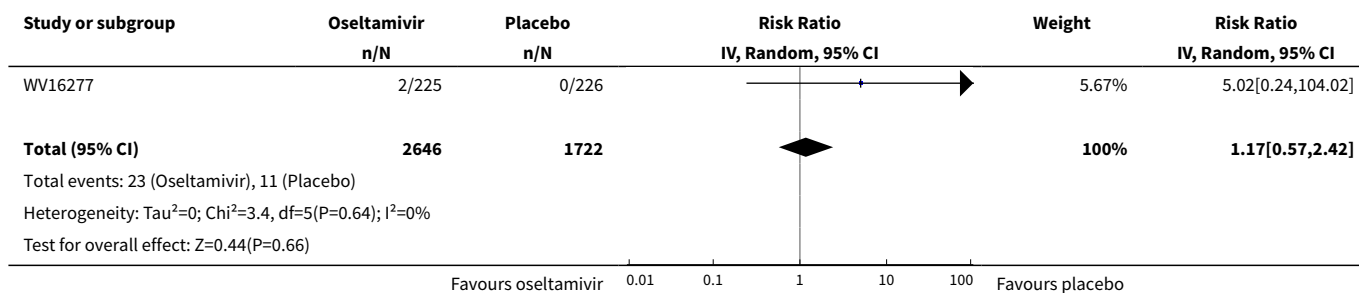


Analysis 1.34. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 34 Adverse events: cardiac body system in adult treatment (off-treatment).

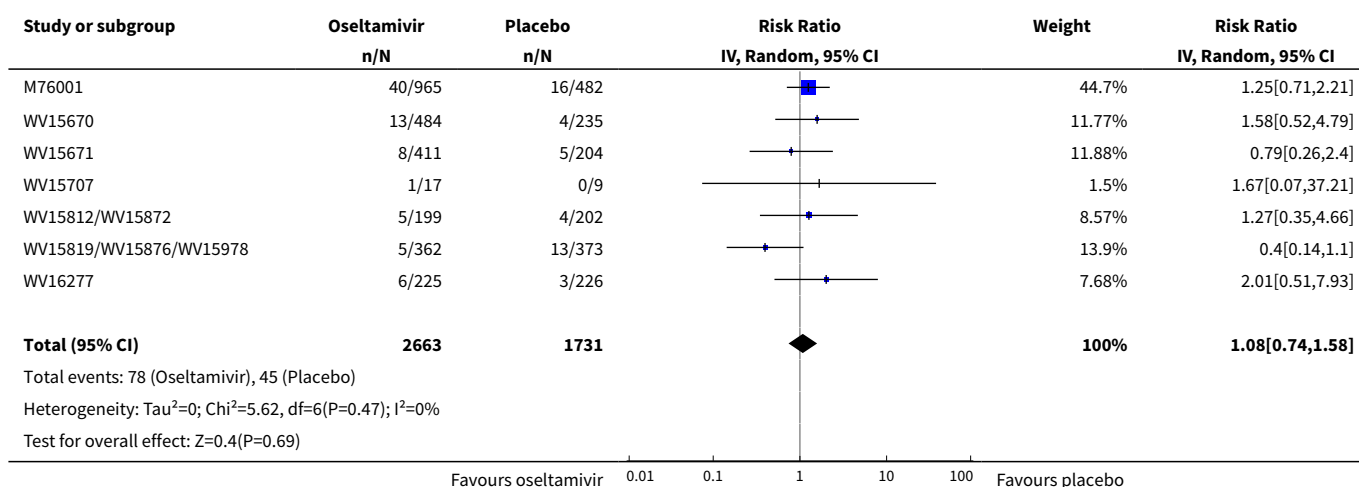


Analysis 1.35. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 35 Adverse events: ear body system in adult treatment (off-treatment).

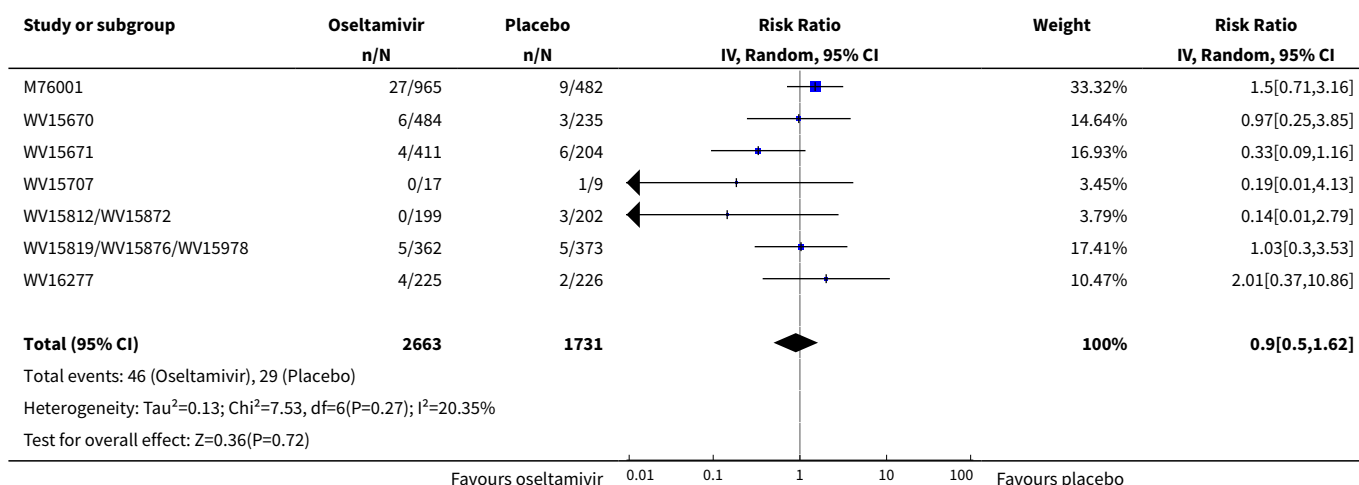


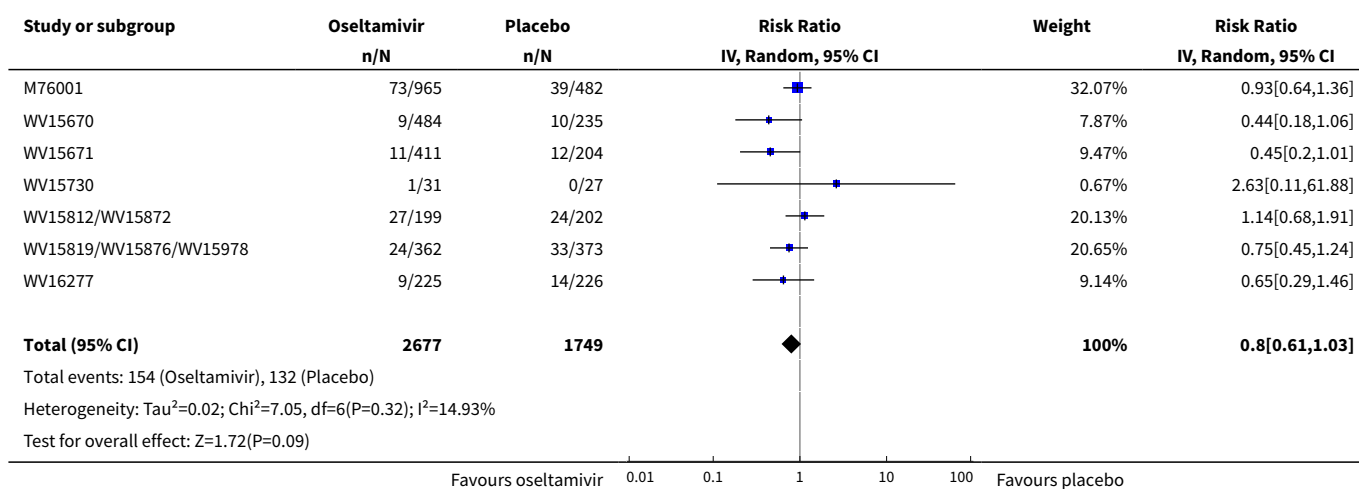
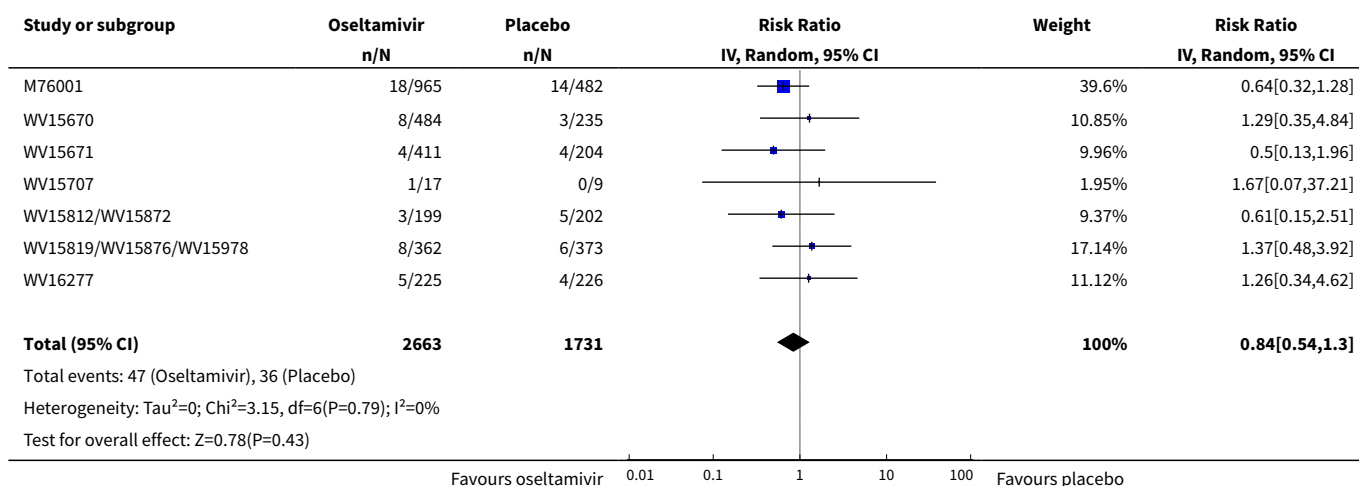
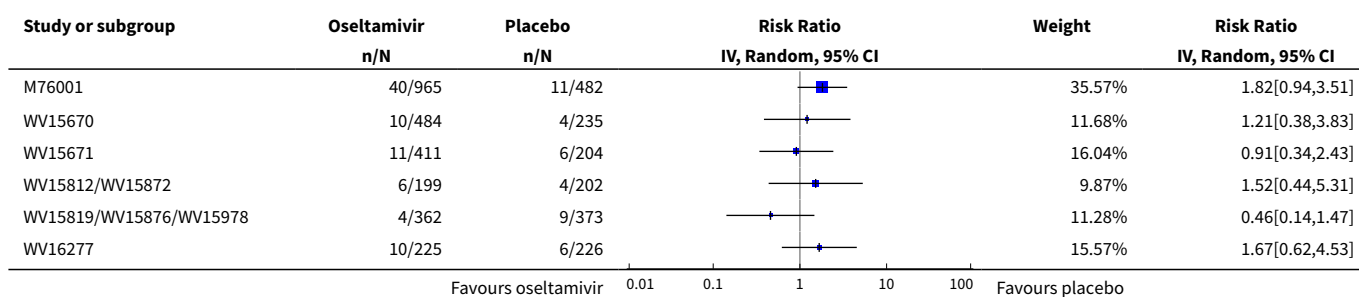


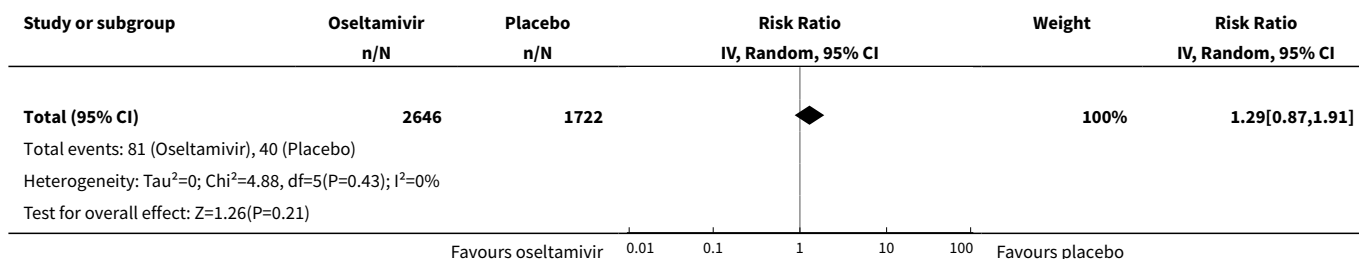
Analysis 1.36. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 36 Adverse events: gastrointestinal body system in adult treatment (off-treatment).



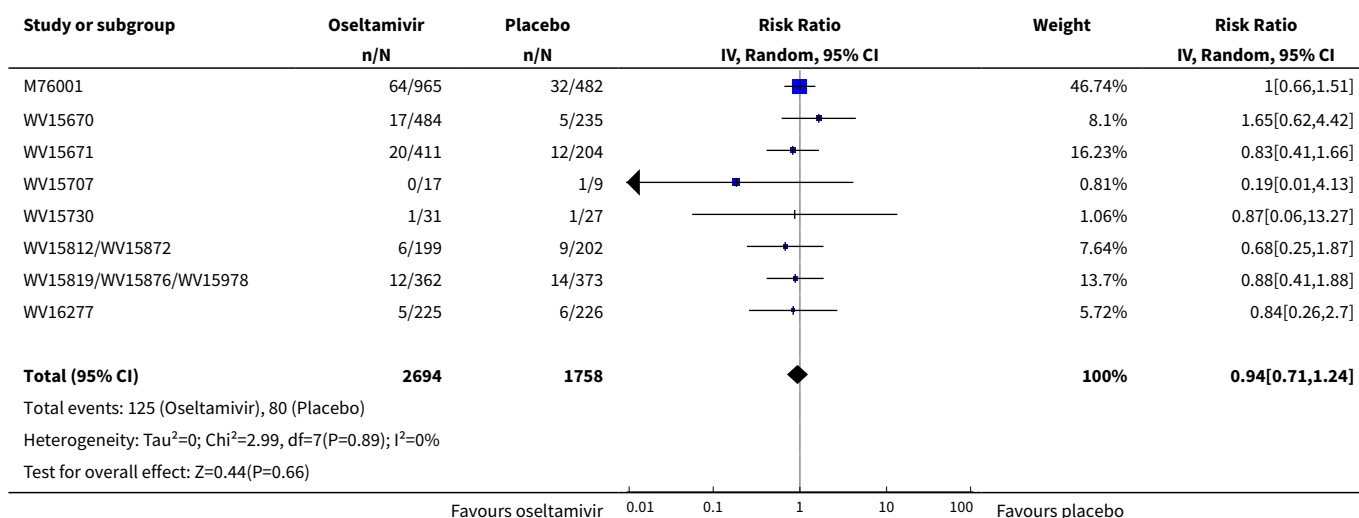
Analysis 1.37. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 37 Adverse events: general body system in adult treatment (off-treatment).



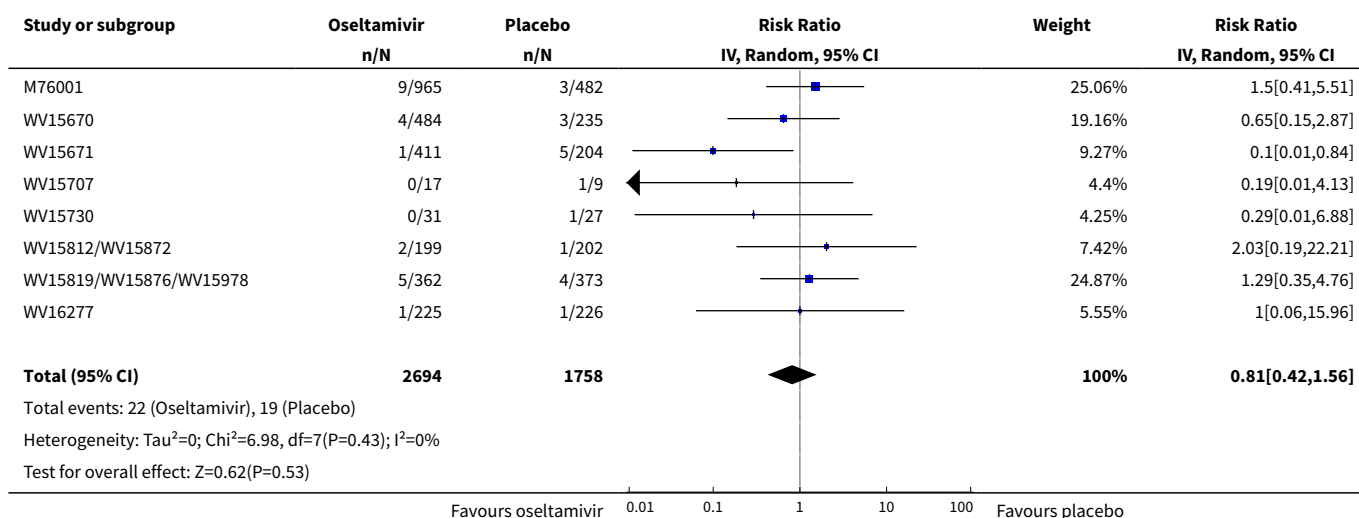
Analysis 1.38. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 38 Adverse events: infection body system in adult treatment (off-treatment).**Analysis 1.39. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 39 Adverse events: musculoskeletal body system in adult treatment (off-treatment).****Analysis 1.40. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 40 Adverse events: neurological body system in adult treatment (off-treatment).**

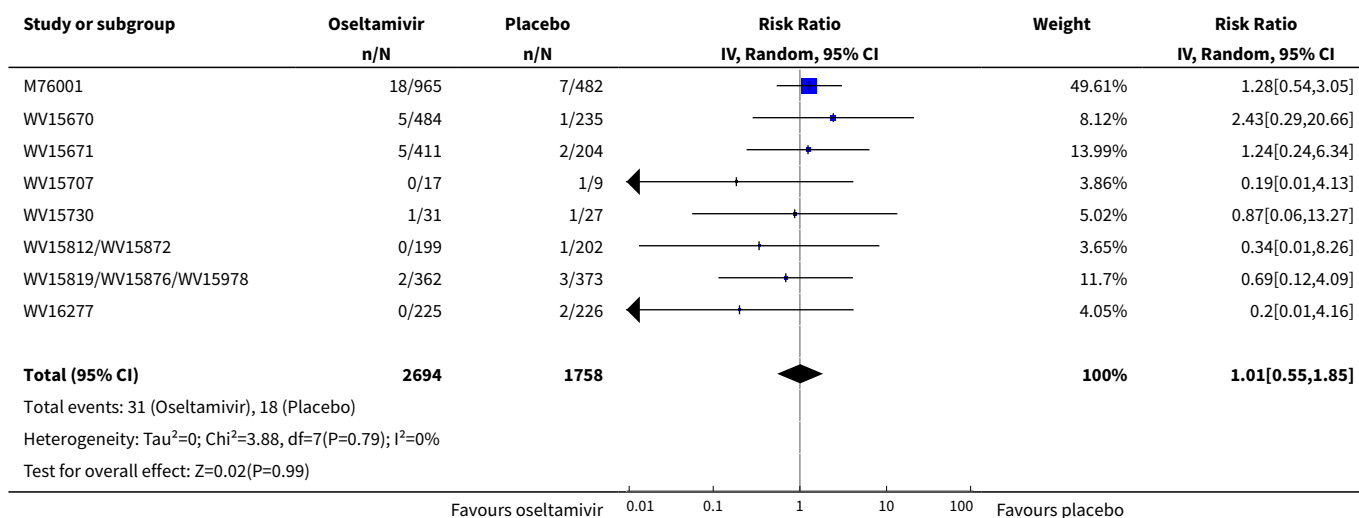
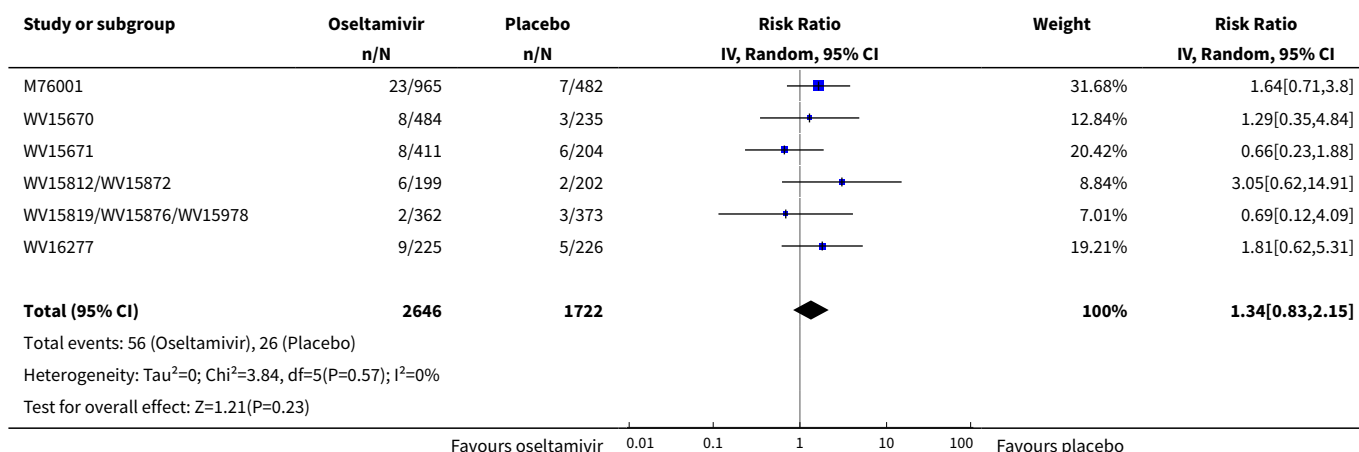
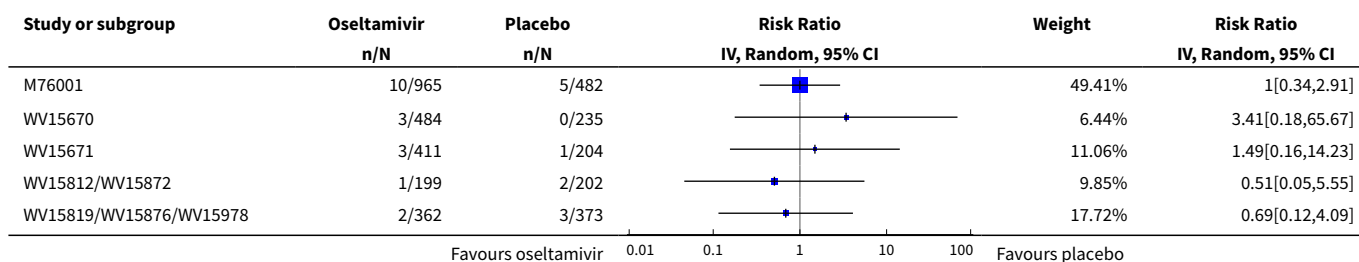


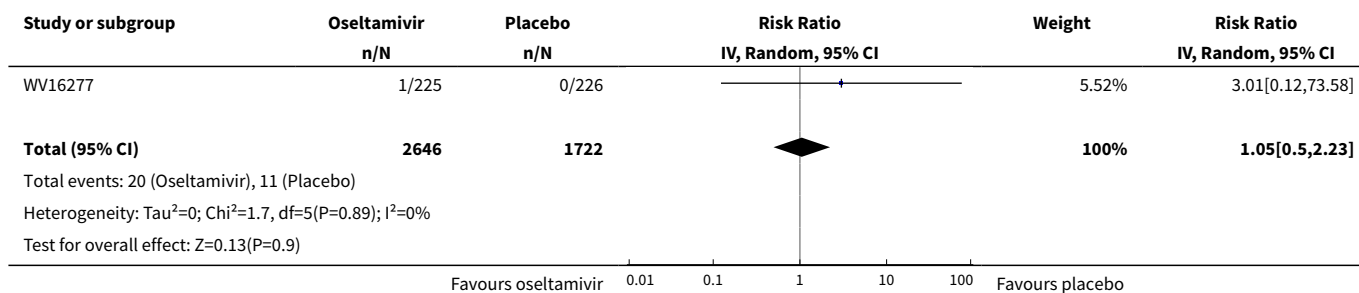
Analysis 1.41. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 41 Adverse events: respiratory body system in adult treatment (off-treatment).



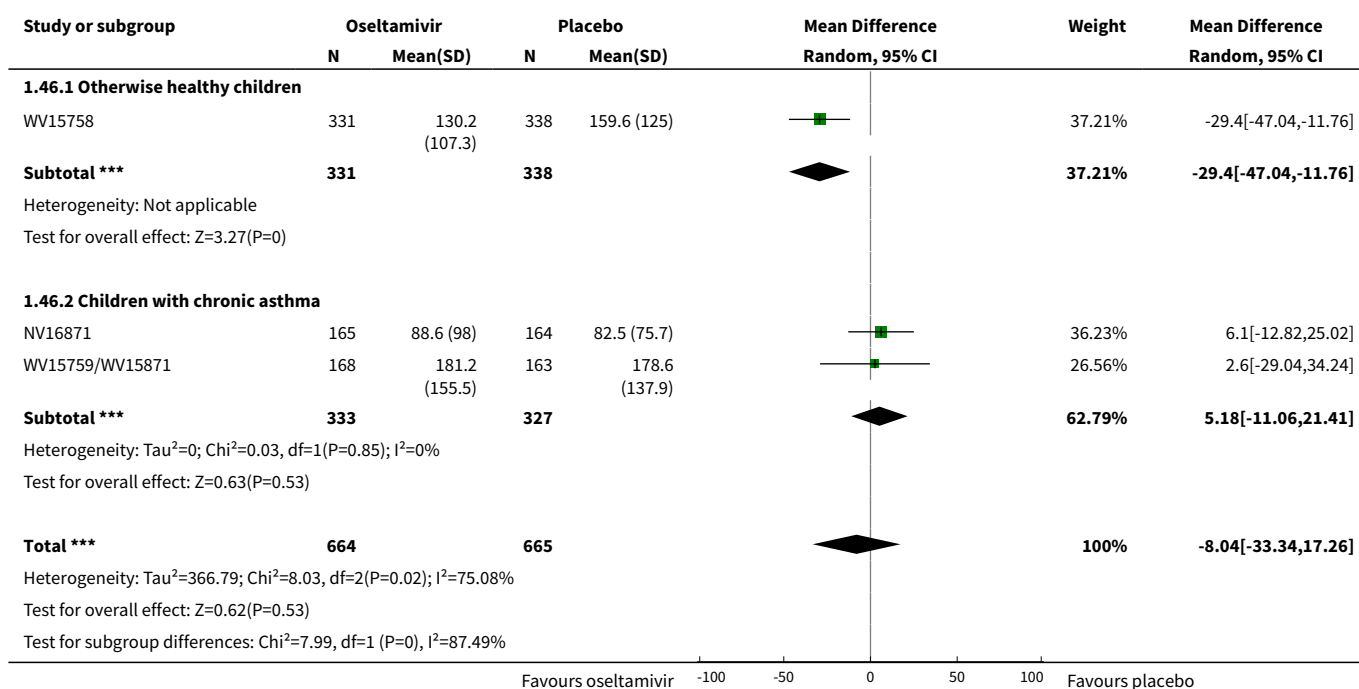
Analysis 1.42. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 42 Adverse events: skin body system in adult treatment (off-treatment).



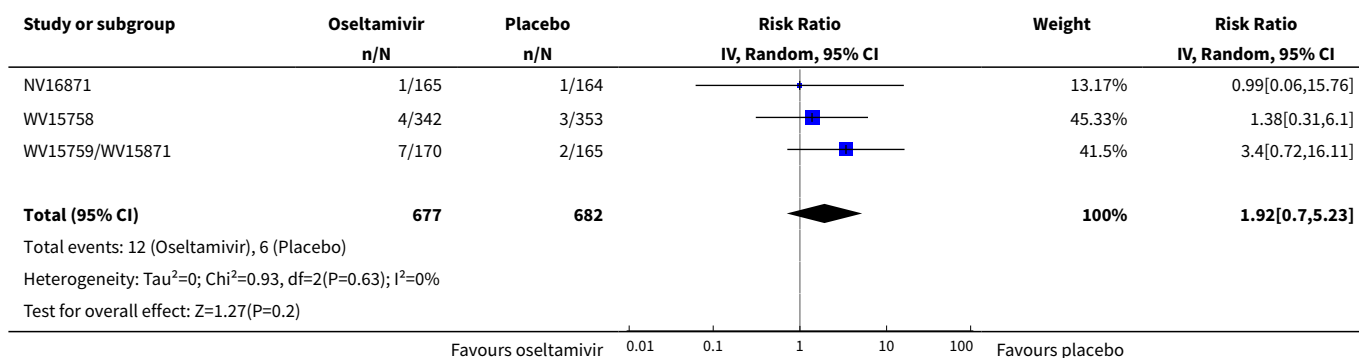
**Analysis 1.43. Comparison 1 Oseltamivir versus placebo for treatment,
Outcome 43 Adverse events: cough in adult treatment (off-treatment).****Analysis 1.44. Comparison 1 Oseltamivir versus placebo for treatment,
Outcome 44 Adverse events: headache in adult treatment (off-treatment).****Analysis 1.45. Comparison 1 Oseltamivir versus placebo for treatment,
Outcome 45 Adverse events: nausea in adult treatment (off-treatment).**



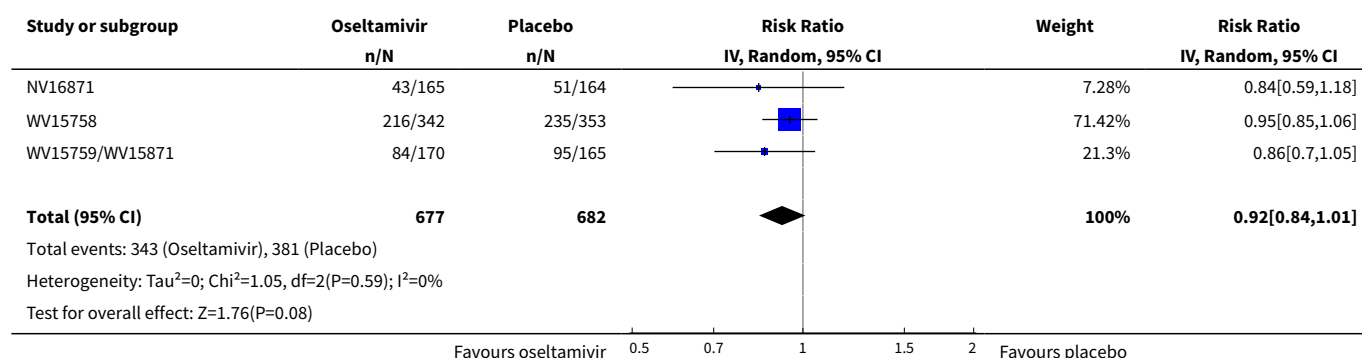
Analysis 1.46. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 46 Time to first alleviation of symptoms in child treatment [hours].



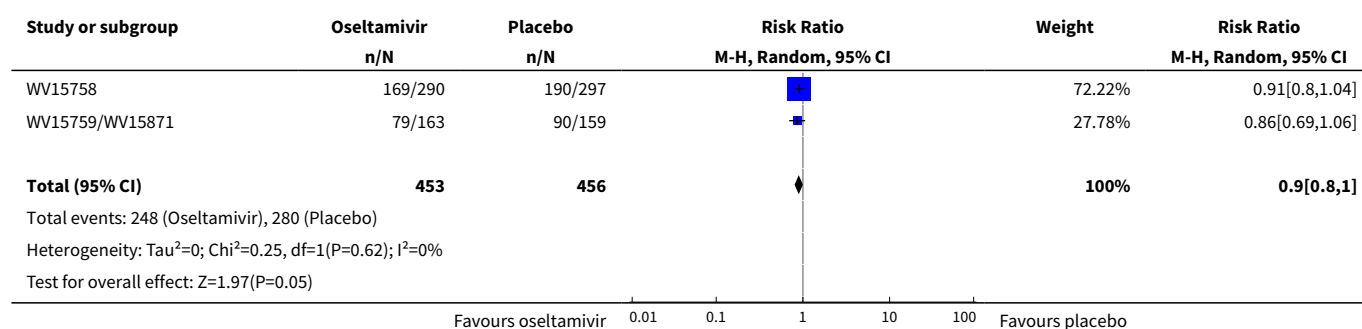
Analysis 1.47. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 47 Hospital admission in child treatment (safety population).



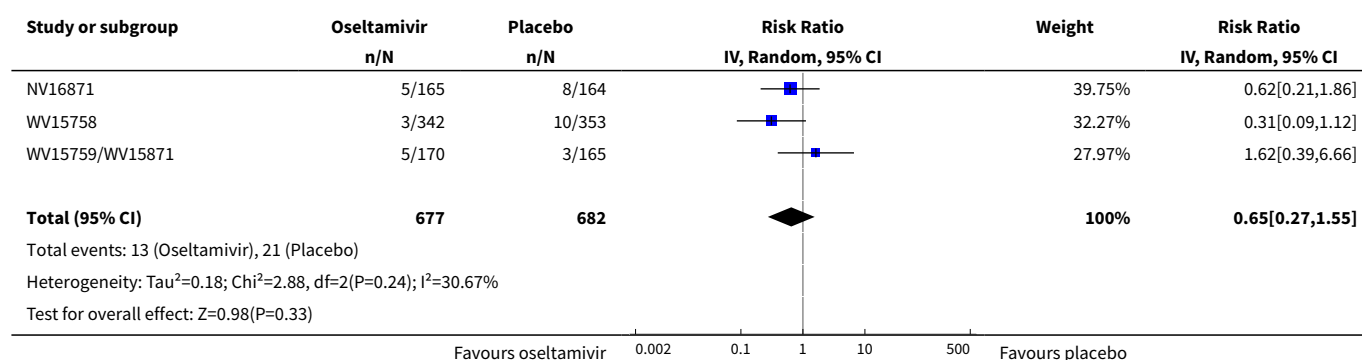
Analysis 1.48. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 48 Defined as influenza-infected at baseline in child treatment.



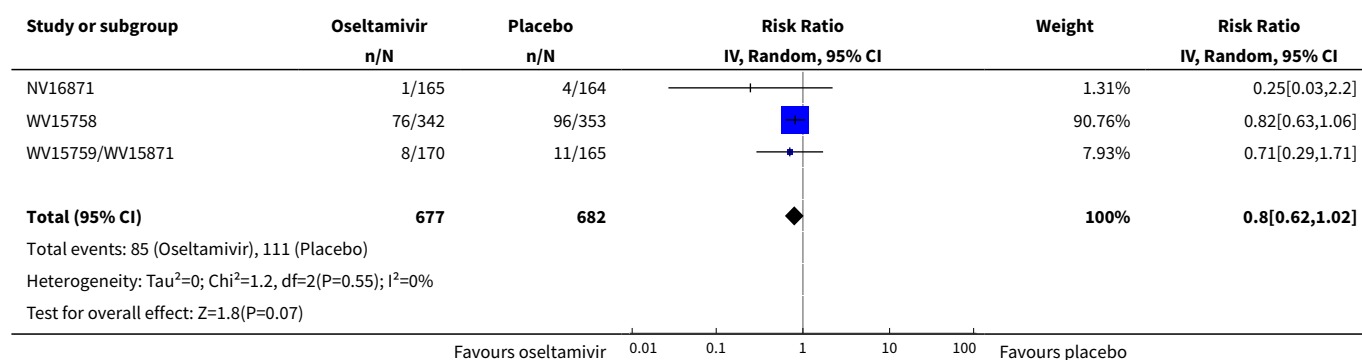
Analysis 1.49. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 49 Antibody rise four-fold or greater in child treatment.



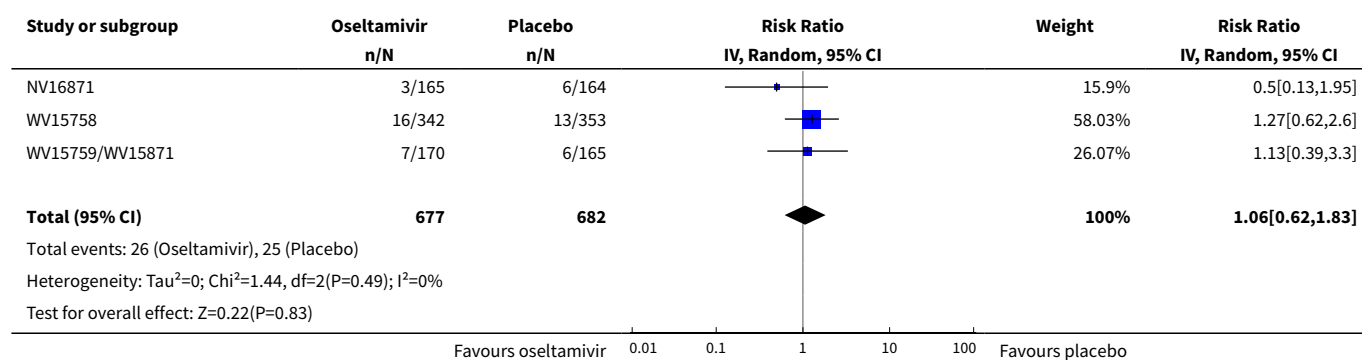
Analysis 1.50. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 50 Complications: bronchitis in child treatment.



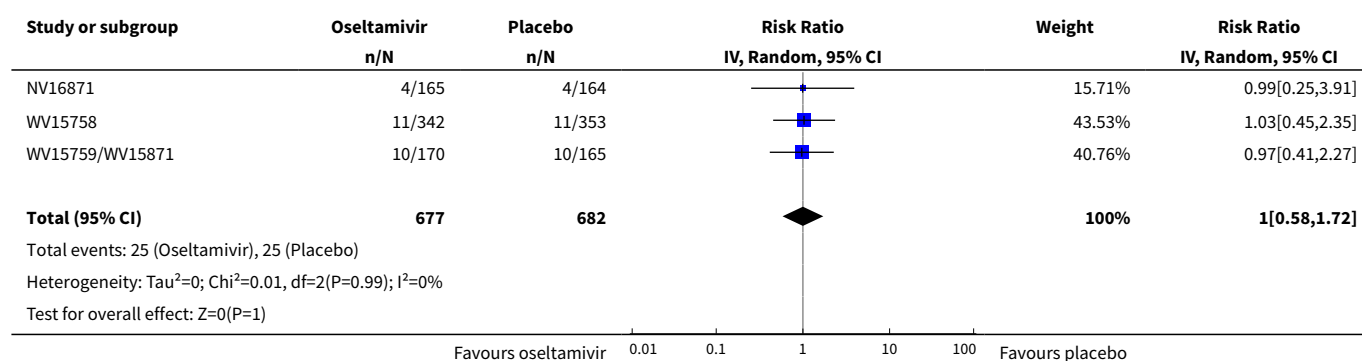
Analysis 1.51. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 51 Complications: otitis media in child treatment.



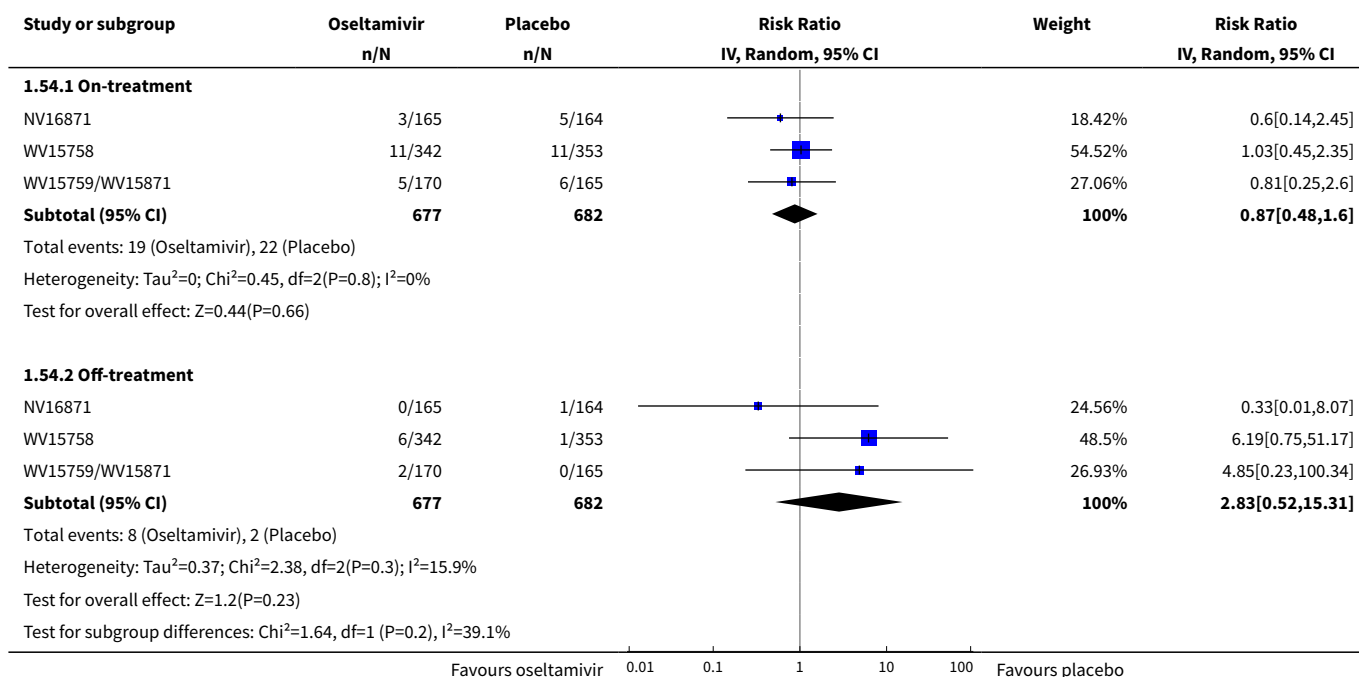
Analysis 1.52. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 52 Complications: pneumonia in child treatment.



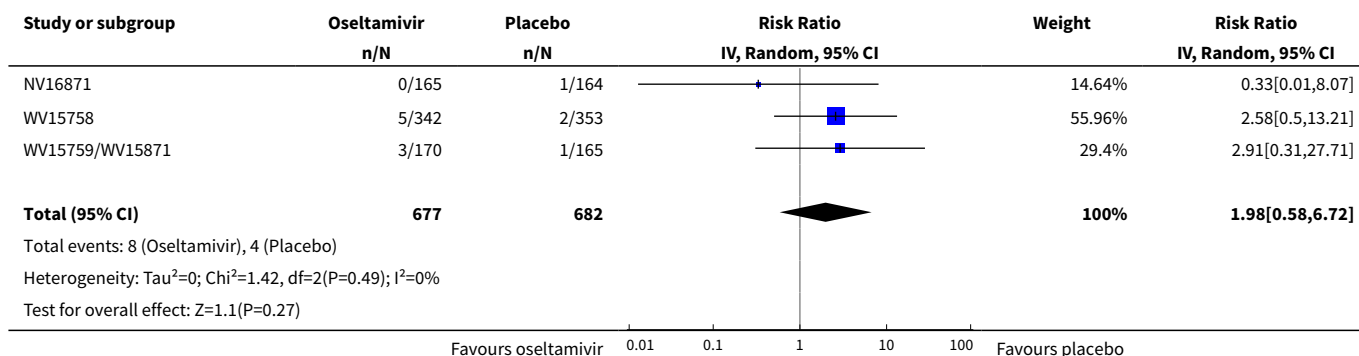
Analysis 1.53. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 53 Complications: sinusitis in child treatment.



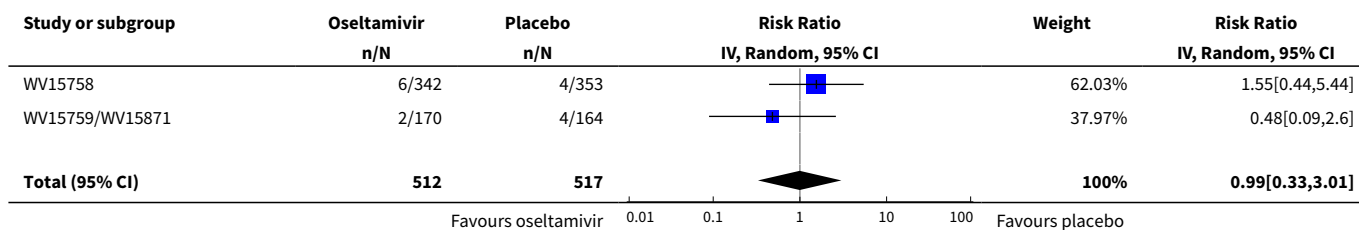
Analysis 1.54. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 54 Complications: pneumonia in child treatment by on- and off-treatment.

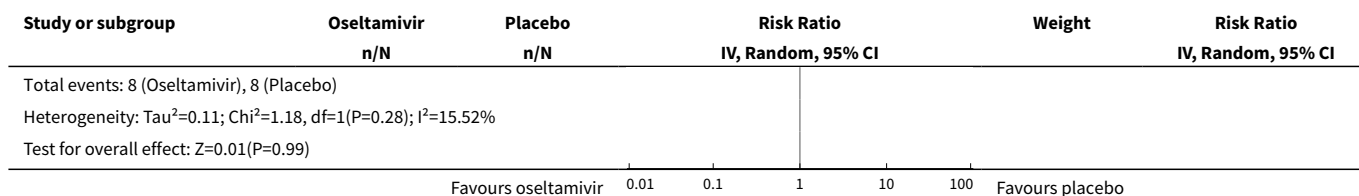


Analysis 1.55. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 55 Complications in trials of children classified as serious or leading to study withdrawal.

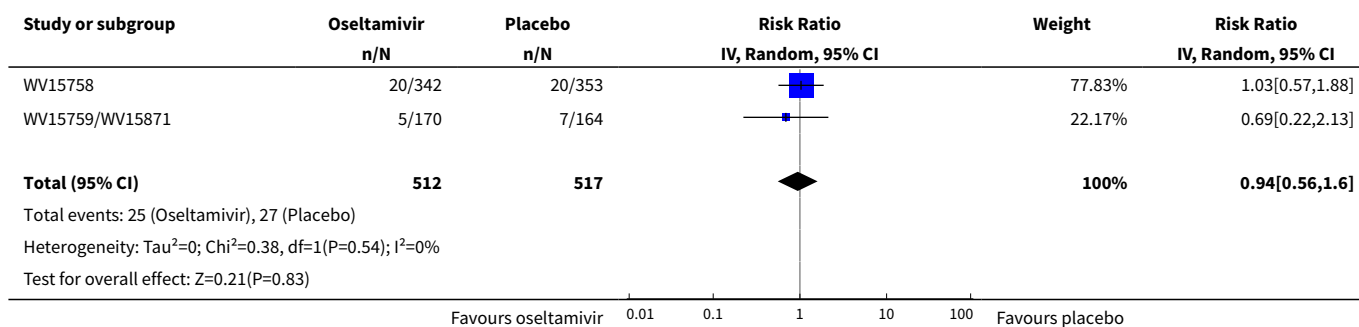


Analysis 1.56. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 56 Withdrawal from child treatment trial due to adverse events.

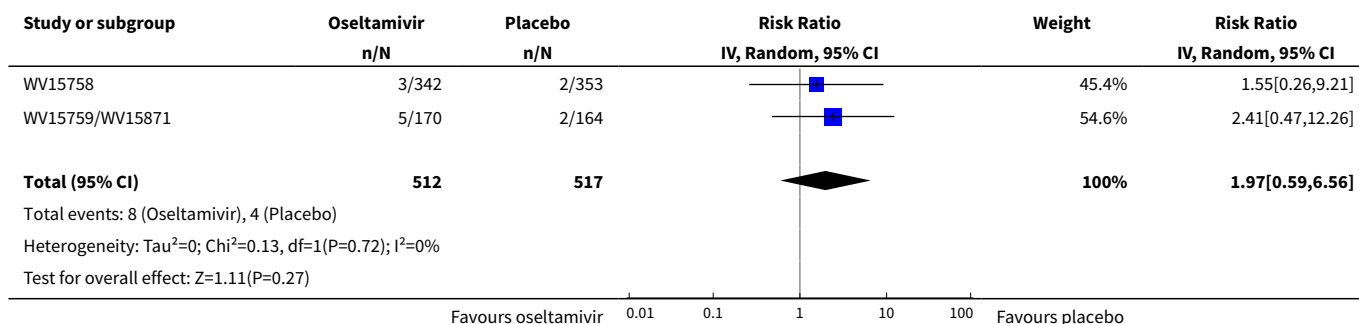




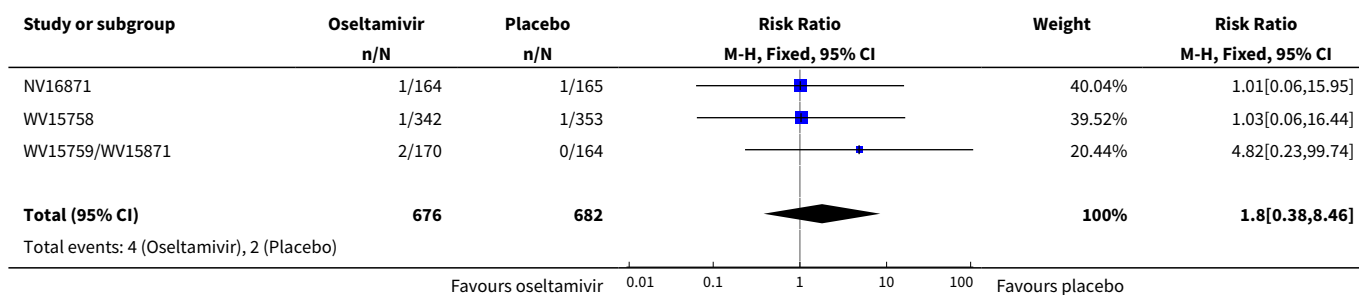
Analysis 1.57. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 57 All withdrawals from child treatment.

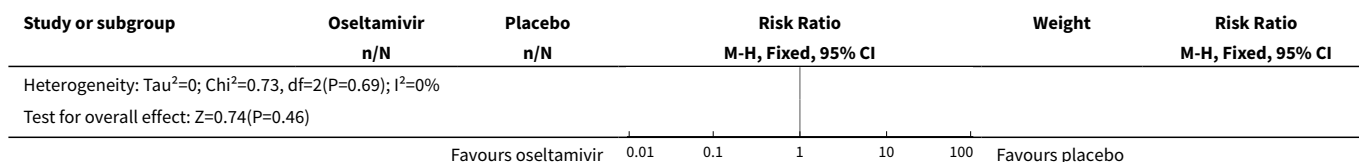


Analysis 1.58. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 58 Serious adverse events: overall in child treatment (on-treatment).

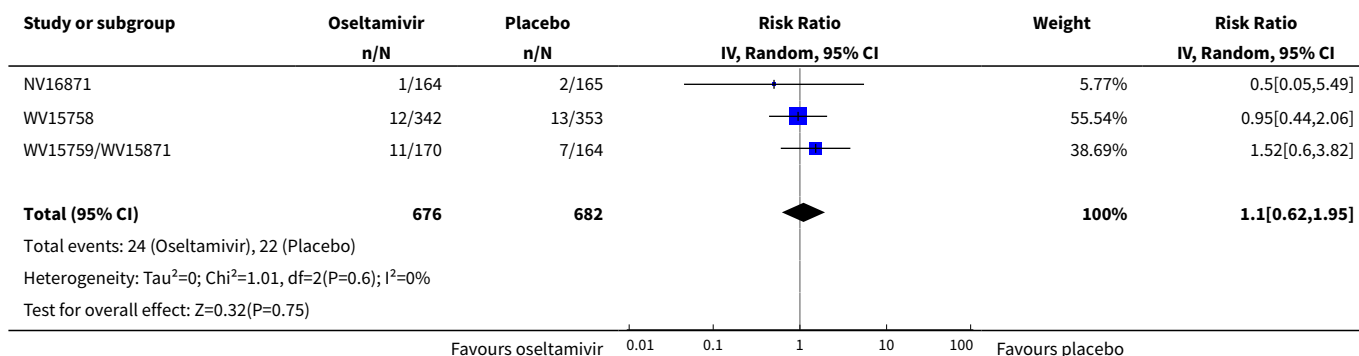


Analysis 1.59. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 59 Serious adverse events: overall in child treatment (off-treatment).

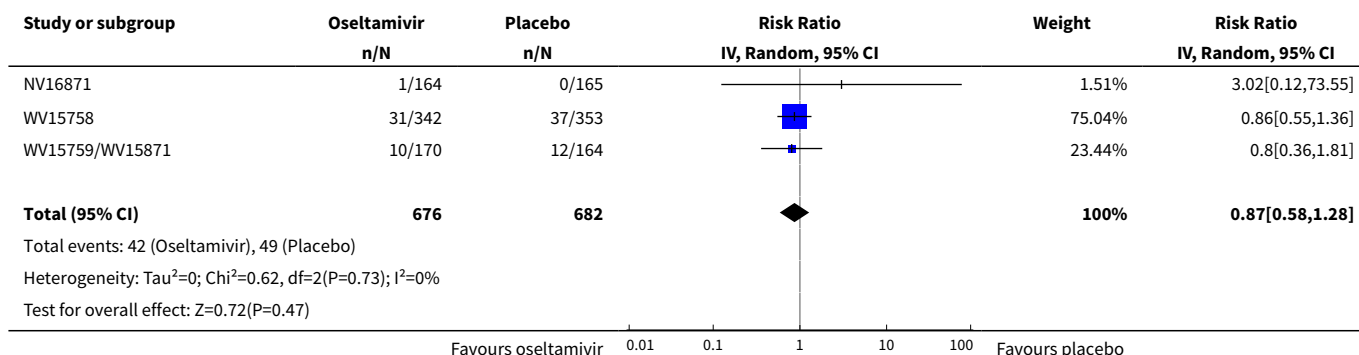




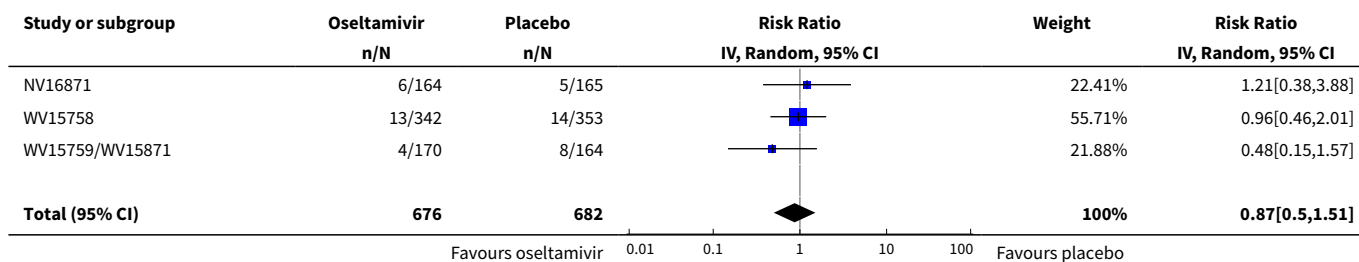
Analysis 1.60. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 60 Adverse events: abdominal pain in child treatment (on-treatment).

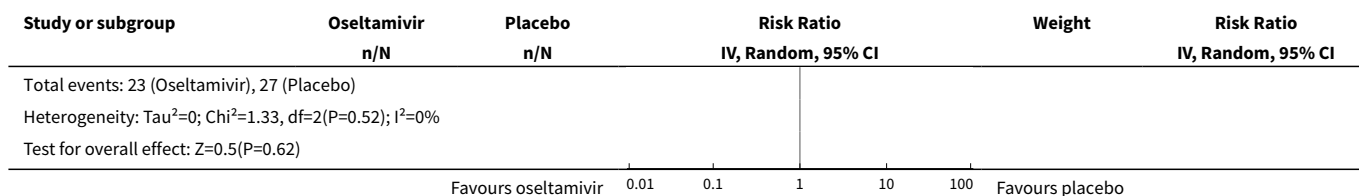


Analysis 1.61. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 61 Adverse events: diarrhoea in child treatment (on-treatment).

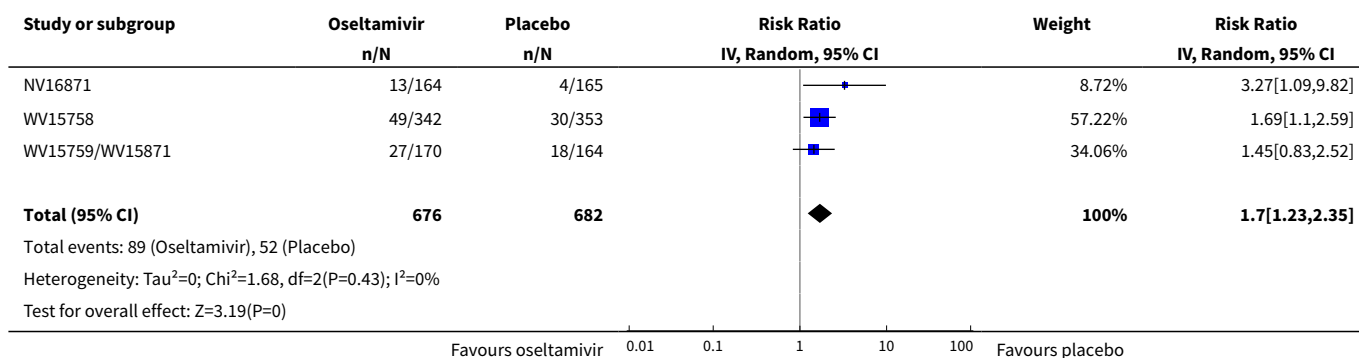


Analysis 1.62. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 62 Adverse events: nausea in child treatment (on-treatment).

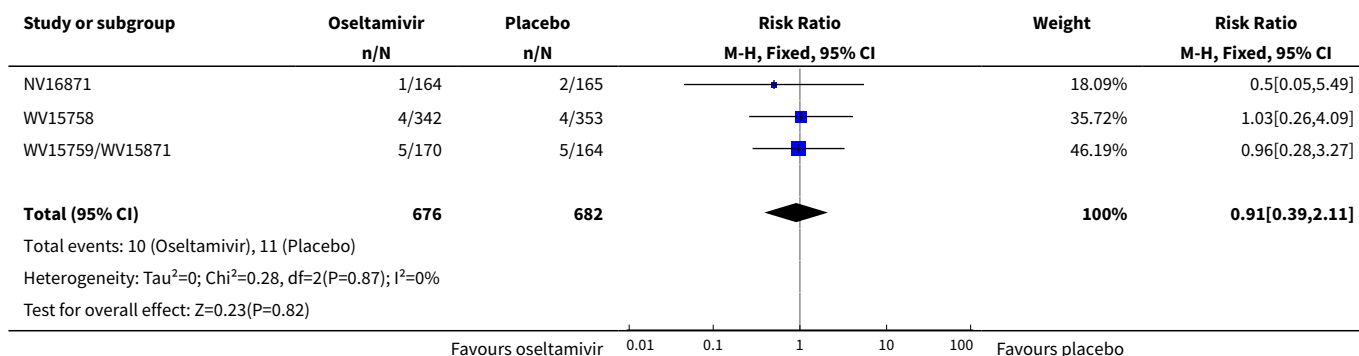




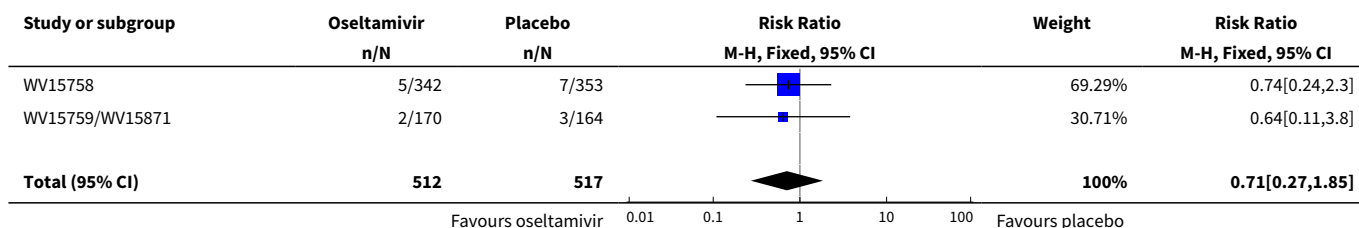
Analysis 1.63. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 63 Adverse events: vomiting in child treatment (on-treatment).

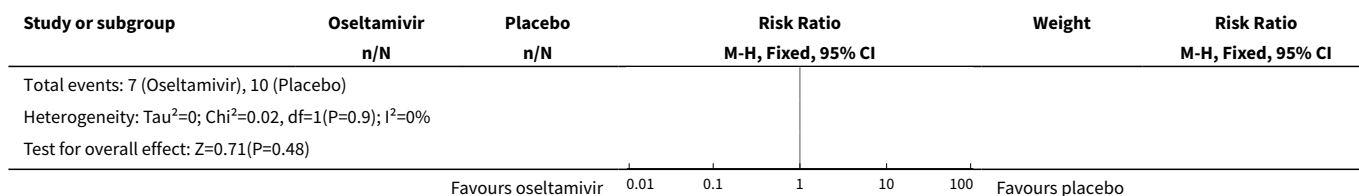


Analysis 1.64. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 64 Adverse events: abdominal pain in child treatment (off-treatment).

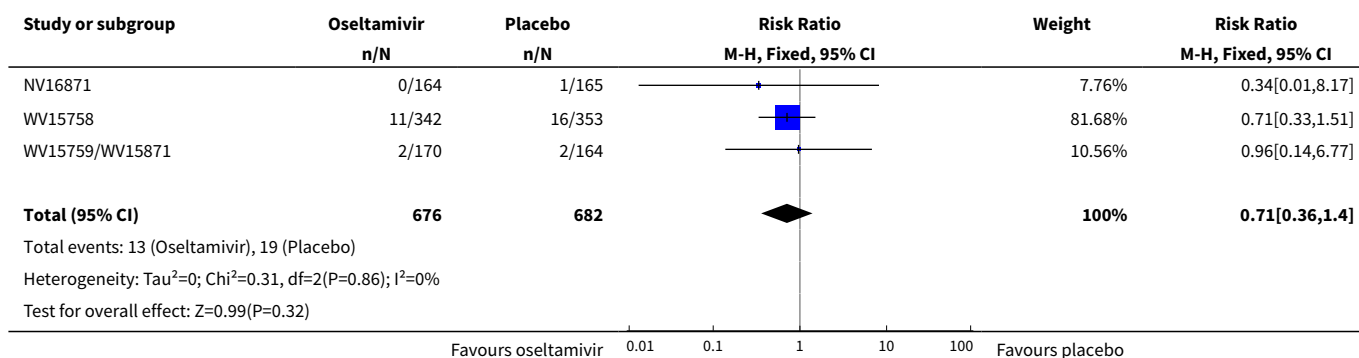


Analysis 1.65. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 65 Adverse events: cough in child treatment (off-treatment).

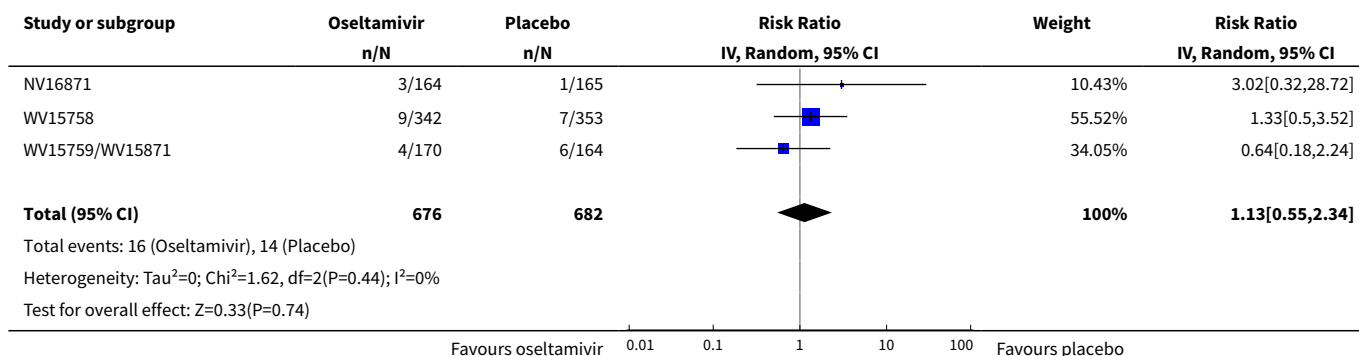




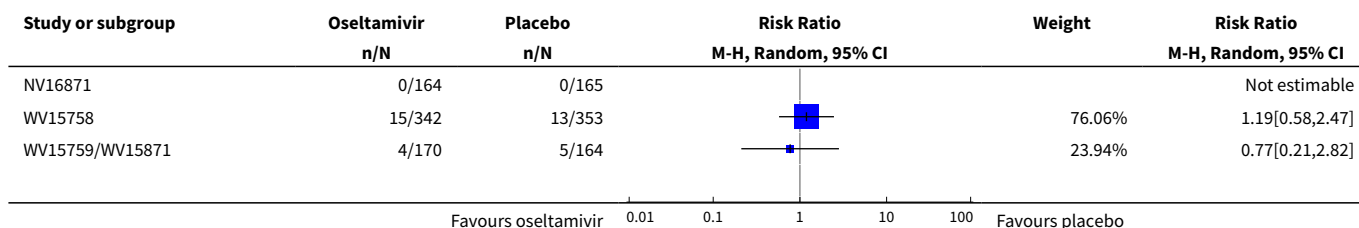
Analysis 1.66. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 66 Adverse events: diarrhoea in child treatment (off-treatment).

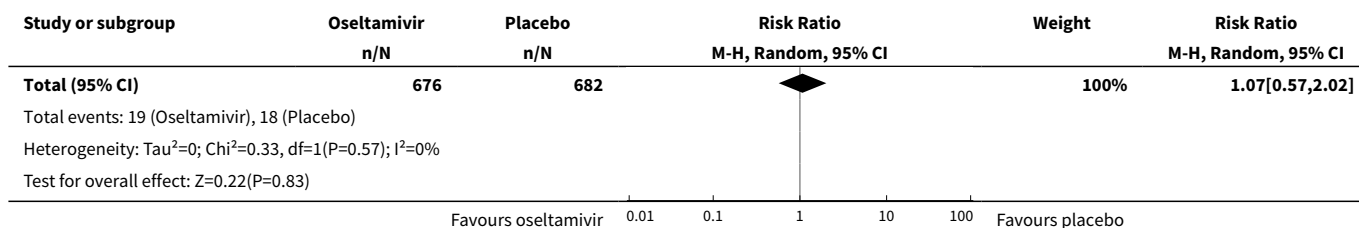


Analysis 1.67. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 67 Adverse events: headache in child treatment (off-treatment).

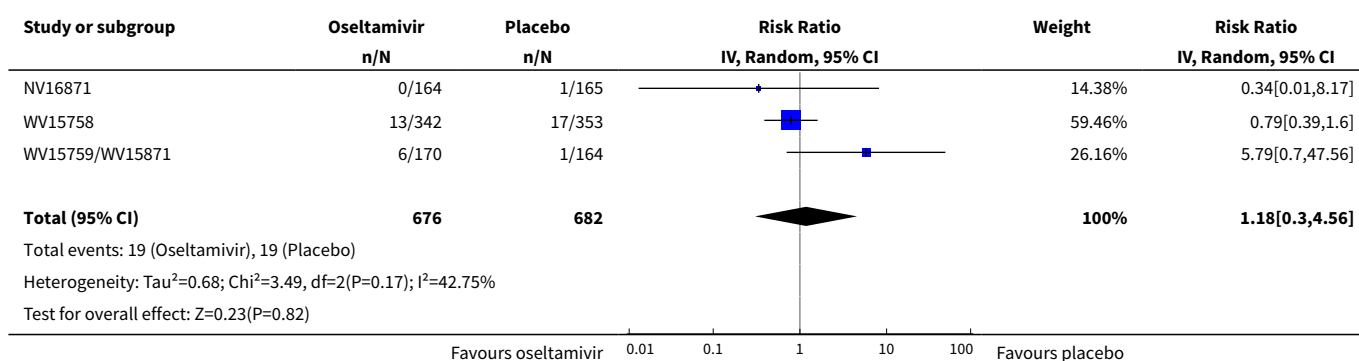


Analysis 1.68. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 68 Adverse events: vomiting in child treatment (off-treatment).

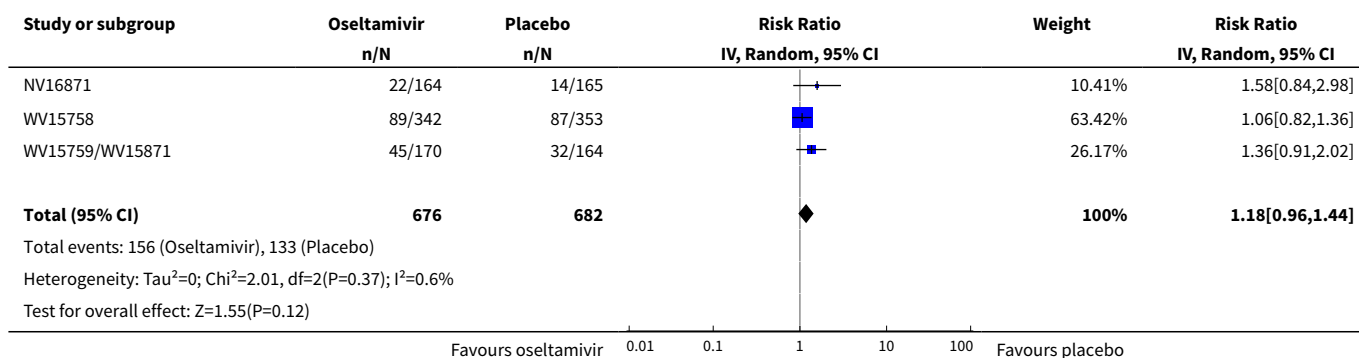




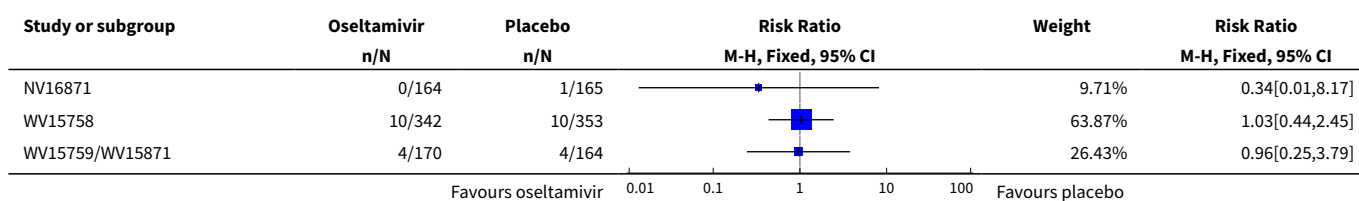
Analysis 1.69. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 69 Adverse events: ear body system in child treatment (on-treatment).

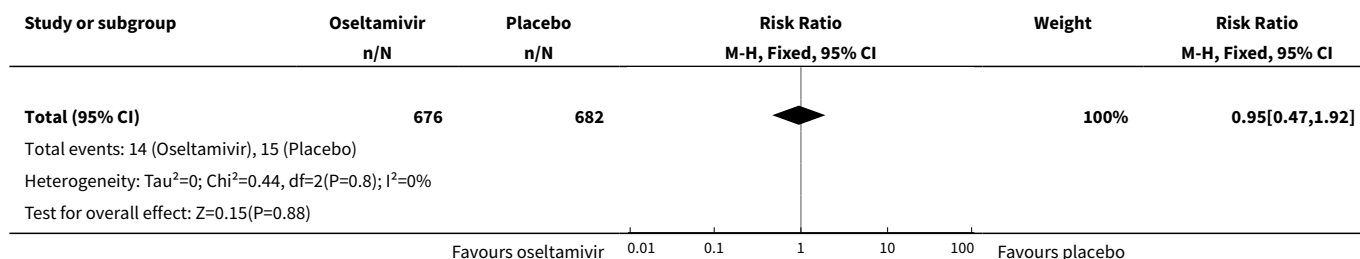


Analysis 1.70. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 70 Adverse events: gastrointestinal body system in child treatment (on-treatment).

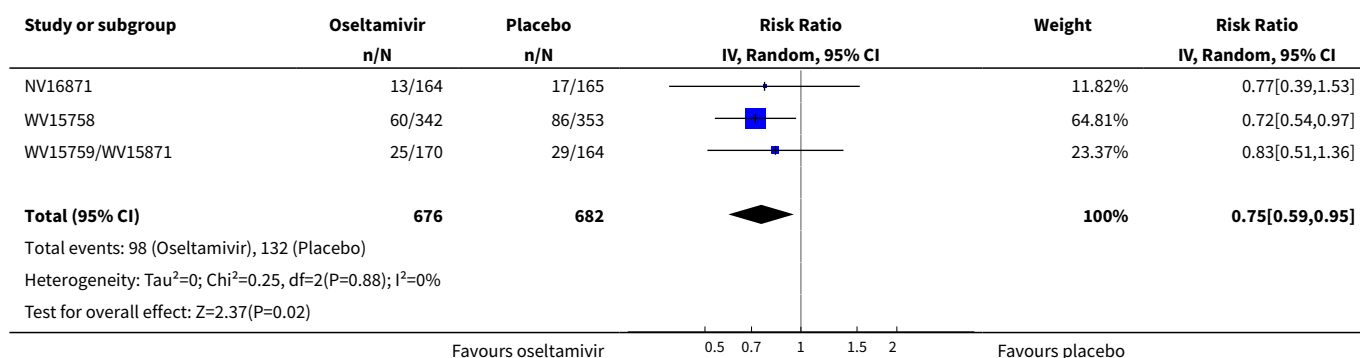


Analysis 1.71. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 71 Adverse events: general body system in child treatment (on-treatment).

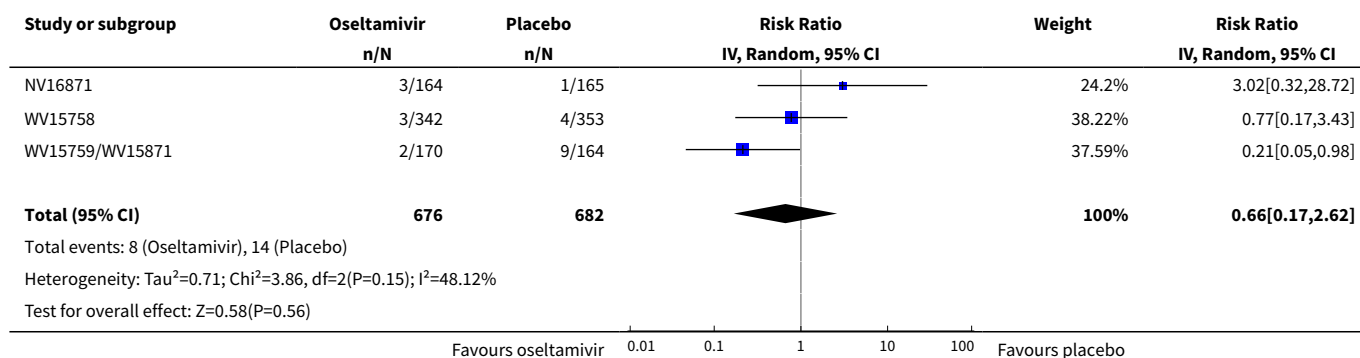




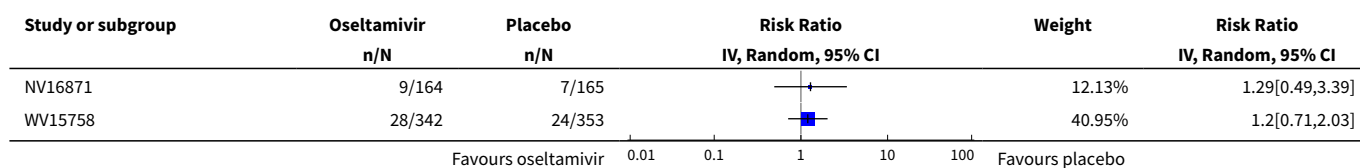
Analysis 1.72. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 72 Adverse events: infection body system in child treatment (on-treatment).

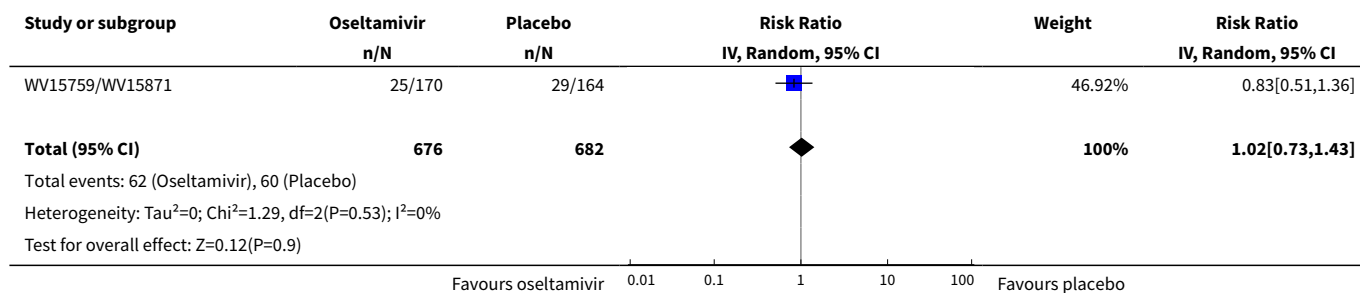


Analysis 1.73. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 73 Adverse events: neurological body system in child treatment (on-treatment).

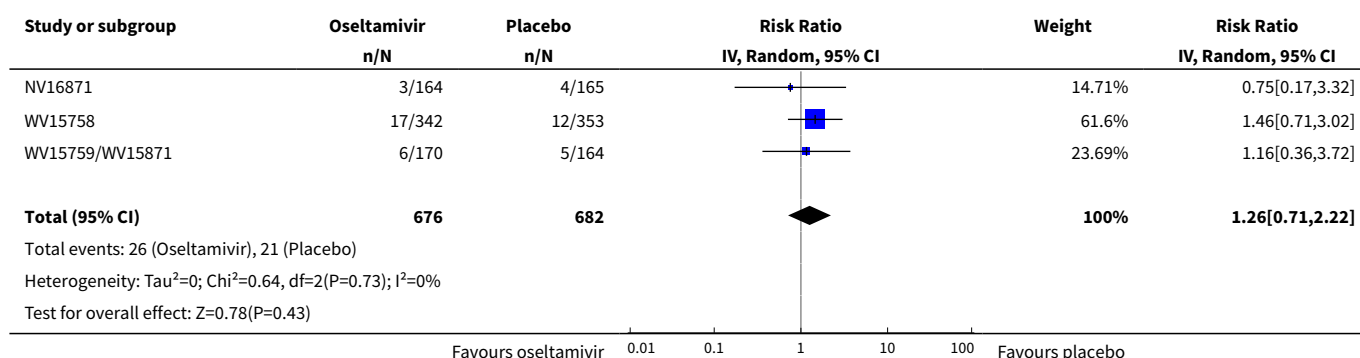


Analysis 1.74. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 74 Adverse events: respiratory body system in child treatment (on-treatment).

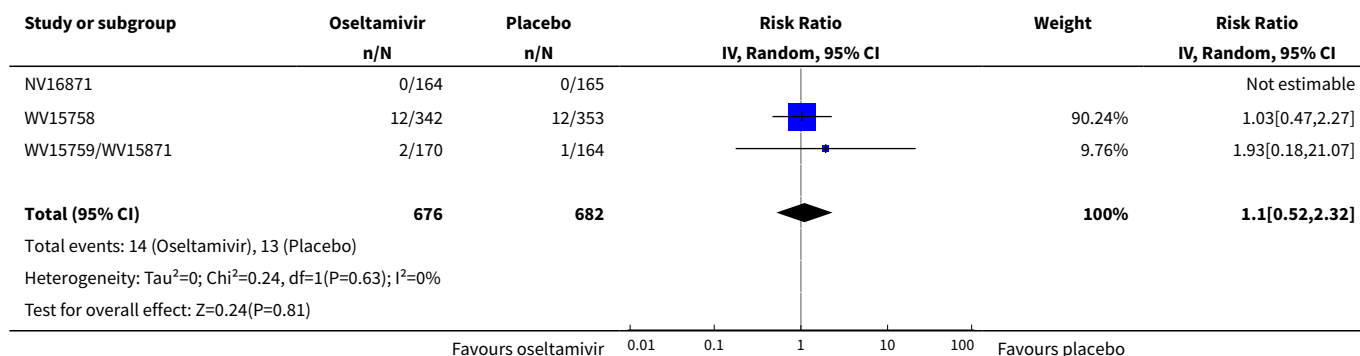




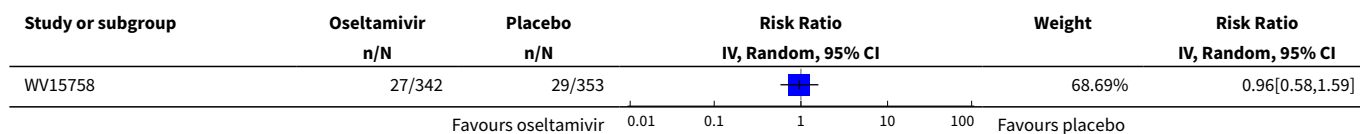
Analysis 1.75. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 75 Adverse events: skin body system in child treatment (on-treatment).

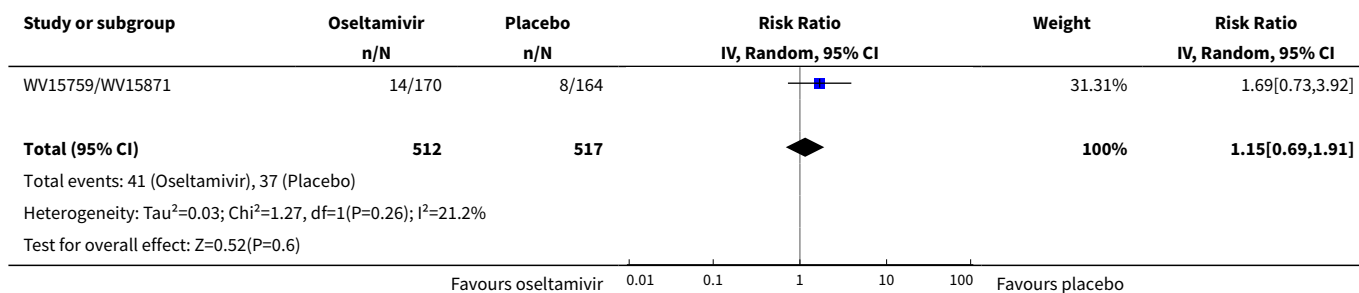


Analysis 1.76. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 76 Adverse events: ear body system in child treatment (off-treatment).

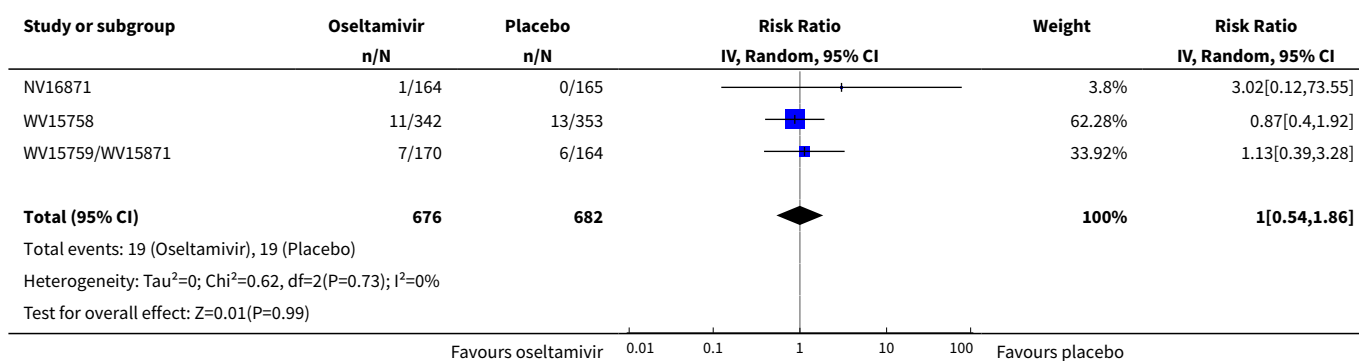


Analysis 1.77. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 77 Adverse events: gastrointestinal body system in child treatment (off-treatment).

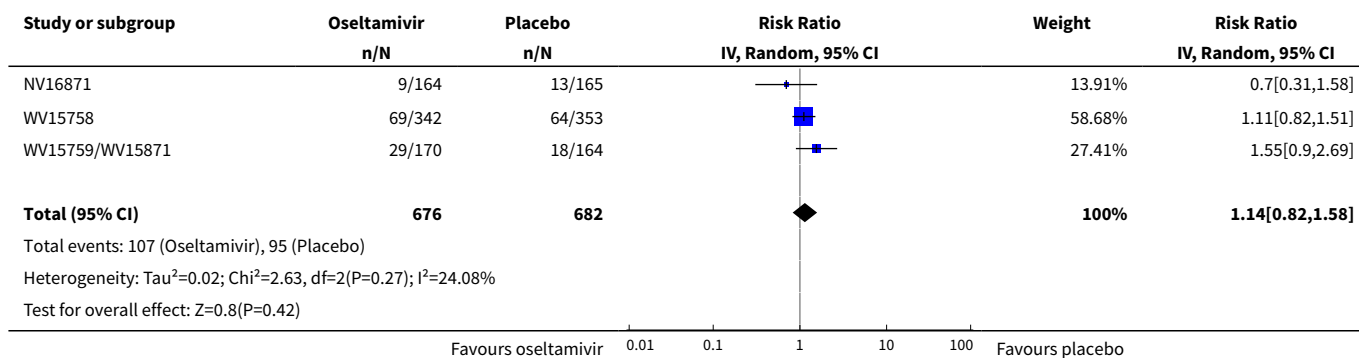




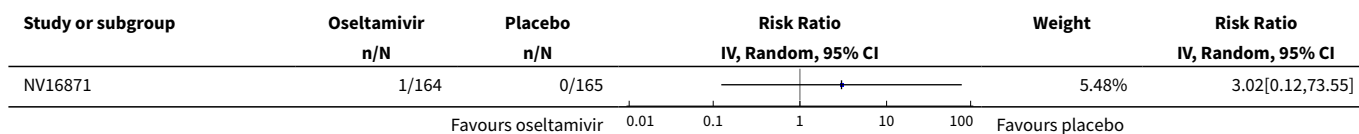
Analysis 1.78. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 78 Adverse events: general body system in child treatment (off-treatment).

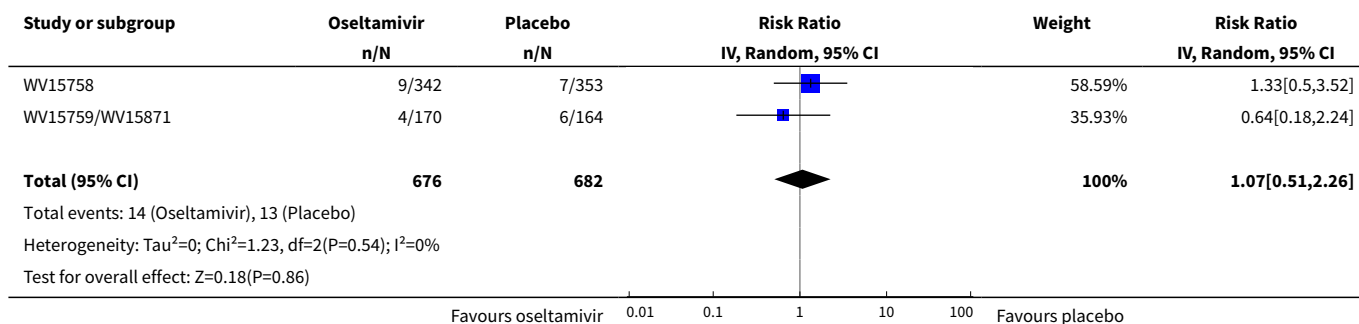


Analysis 1.79. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 79 Adverse events: infection body system in child treatment (off-treatment).

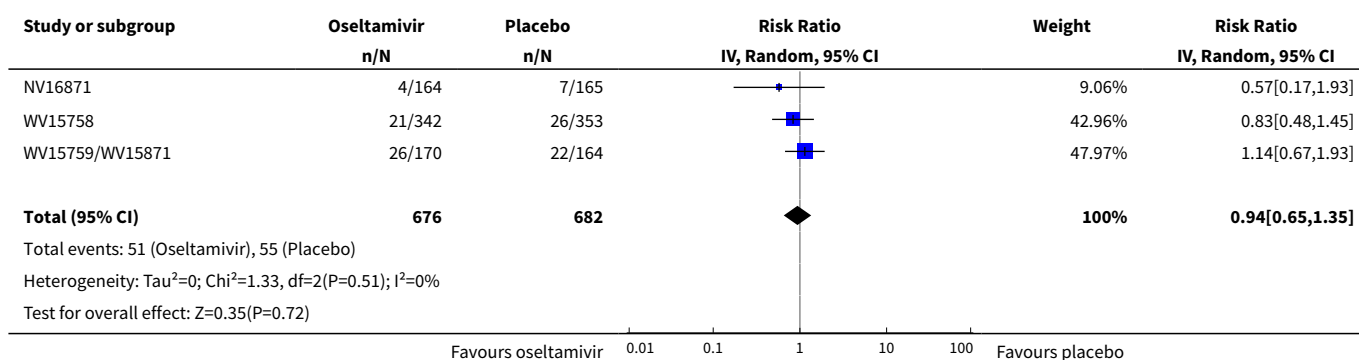


Analysis 1.80. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 80 Adverse events: neurological body system in child treatment (off-treatment).

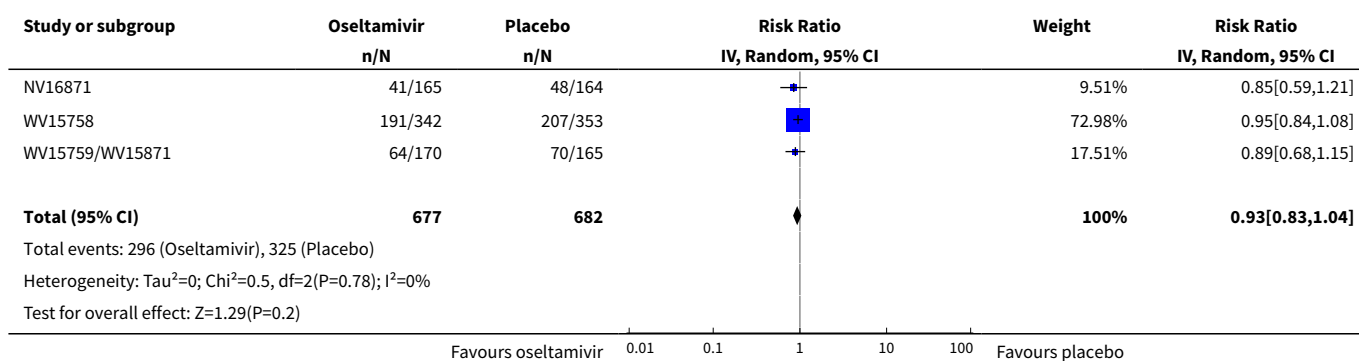




Analysis 1.81. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 81 Adverse events: respiratory body system in child treatment (off-treatment).



Analysis 1.82. Comparison 1 Oseltamivir versus placebo for treatment, Outcome 82 Culture-positive at baseline in child treatment.



Comparison 2. Oseltamivir versus placebo for prophylaxis

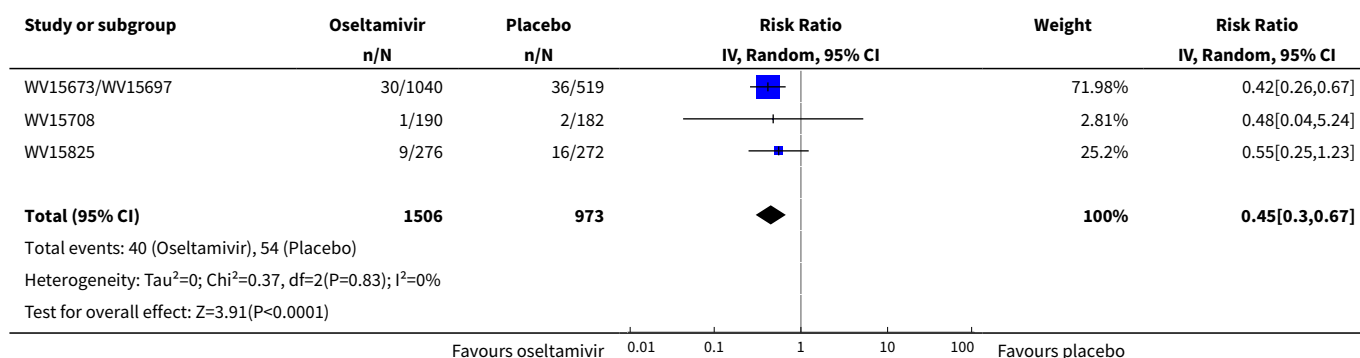
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic influenza in adult prophylaxis of individuals	3	2479	Risk Ratio (IV, Random, 95% CI)	0.45 [0.30, 0.67]
2 Asymptomatic influenza in adult prophylaxis of individuals	3	2479	Risk Ratio (IV, Random, 95% CI)	0.78 [0.49, 1.24]
3 Symptomatic influenza in household prophylaxis	1	405	Risk Ratio (IV, Random, 95% CI)	0.20 [0.09, 0.44]
4 Asymptomatic influenza in household prophylaxis	1	405	Risk Ratio (IV, Random, 95% CI)	1.14 [0.39, 3.33]
5 Influenza-like illness reported as adverse event (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.99 [0.73, 1.35]
6 Influenza-like illness reported as adverse event (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.62 [0.34, 1.16]
7 Hospitalisation in adult prophylaxis (safety population)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.14 [0.66, 1.94]
8 Complications: bronchitis in adult prophylaxis	4	3434	Risk Ratio (IV, Random, 95% CI)	0.74 [0.41, 1.35]
9 Complications: sinusitis in adult prophylaxis	4	3434	Risk Ratio (IV, Random, 95% CI)	1.41 [0.75, 2.62]
10 Adverse events leading to study withdrawal in adult prophylaxis	4	3434	Risk Ratio (IV, Random, 95% CI)	1.11 [0.57, 2.18]
11 All withdrawals in adult prophylaxis	4	3434	Risk Ratio (IV, Random, 95% CI)	1.15 [0.82, 1.61]
12 Serious adverse events in adult prophylaxis (on-treatment)	3	2479	Risk Ratio (IV, Random, 95% CI)	0.94 [0.53, 1.66]
13 Serious adverse events in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.57, 2.60]
14 Adverse events: abdominal pain in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.77, 1.82]
15 Adverse events: cough in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.96 [0.68, 1.36]
16 Adverse events: diarrhoea in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.09 [0.64, 1.86]
17 Adverse events: dizziness in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.15 [0.66, 2.01]
18 Adverse events: fatigue in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.12 [0.89, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Adverse events: headache in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.18 [1.05, 1.33]
20 Adverse events: nausea in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.96 [1.20, 3.20]
21 Adverse events: vomiting in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.91 [0.70, 5.22]
22 Adverse events: cough in adult prophylaxis (off-treatment)	3	2479	Risk Ratio (IV, Random, 95% CI)	0.72 [0.36, 1.45]
23 Adverse events: fatigue in adult prophylaxis (off-treatment)	3	2479	Risk Ratio (IV, Random, 95% CI)	1.33 [0.57, 3.13]
24 Adverse events: headache in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.88 [0.63, 1.24]
25 Adverse events: blood body system in adult prophylaxis (on-treatment)	3	2479	Risk Ratio (IV, Random, 95% CI)	0.99 [0.30, 3.25]
26 Adverse events: cardiac body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.75 [0.36, 1.58]
27 Adverse events: ear body system in adult prophylaxis (on treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.44 [0.61, 3.40]
28 Adverse events: eye body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.01 [0.56, 1.81]
29 Adverse events: gastrointestinal body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.38 [1.17, 1.63]
30 Adverse events: general body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.03 [0.88, 1.20]
31 Adverse events: infection body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.97 [0.84, 1.11]
32 Adverse events: immune body system in adult prophylaxis (on-treatment)	1	1559	Risk Ratio (IV, Random, 95% CI)	0.86 [0.45, 1.64]
33 Adverse events: injury body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.97 [0.60, 1.56]
34 Adverse events: metabolism body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.36 [0.73, 2.54]
35 Adverse events: musculoskeletal body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.98 [0.79, 1.22]
36 Adverse events: neurological body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.21 [1.03, 1.42]

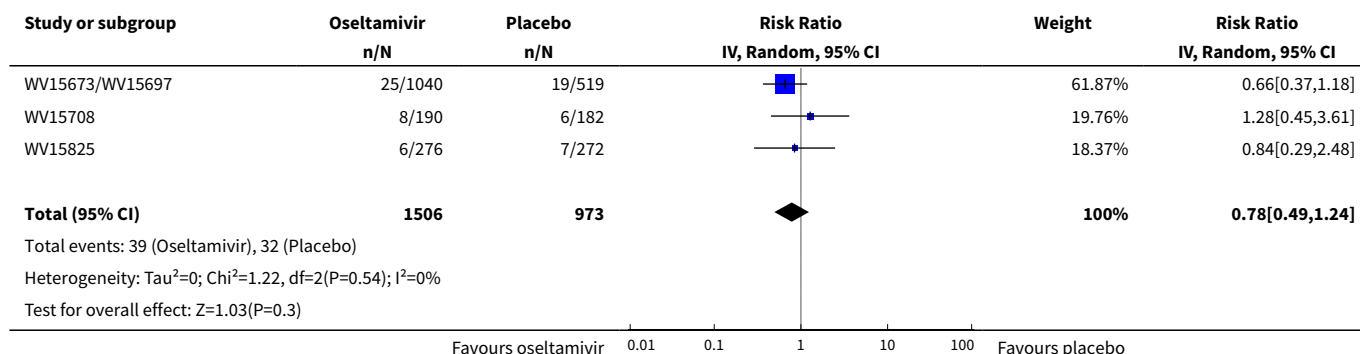
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
37 Adverse events: psychiatric body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.81 [0.97, 3.37]
38 Adverse events: renal body system in adult prophylaxis (on-treatment)	3	2479	Risk Ratio (IV, Random, 95% CI)	3.17 [0.96, 10.49]
39 Adverse events: reproductive body system in adult prophylaxis (on treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.05 [0.77, 1.42]
40 Adverse events: respiratory body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.04 [0.90, 1.20]
41 Adverse events: skin body system in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.92 [0.63, 1.34]
42 Adverse events: surgical events in adult prophylaxis (on-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.98 [0.42, 2.29]
43 Adverse events: vascular body system in adult prophylaxis (on-treatment)	3	2479	Risk Ratio (IV, Random, 95% CI)	0.90 [0.45, 1.80]
44 Adverse events: cardiac body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.50 [0.67, 3.35]
45 Adverse events: gastrointestinal body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.98 [0.62, 1.53]
46 Adverse events: general body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.02 [0.69, 1.49]
47 Adverse events: infection body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.89 [0.68, 1.17]
48 Adverse events: injury body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.01 [0.49, 2.09]
49 Adverse events: musculoskeletal body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.04 [0.63, 1.72]
50 Adverse events: neurological body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.93 [0.68, 1.28]
51 Adverse events: reproductive body system in adult prophylaxis (off-treatment)	2	2514	Risk Ratio (IV, Random, 95% CI)	0.49 [0.24, 1.00]
52 Adverse events: respiratory body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.95 [0.69, 1.32]
53 Adverse events: skin body system in adult prophylaxis (off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	0.73 [0.32, 1.69]
54 Adverse events: psychiatric body system in adult prophylaxis (on and off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	1.80 [1.05, 3.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
55 Adverse events: renal body system in adult prophylaxis (on and off-treatment)	4	3434	Risk Ratio (IV, Random, 95% CI)	2.01 [0.74, 5.47]

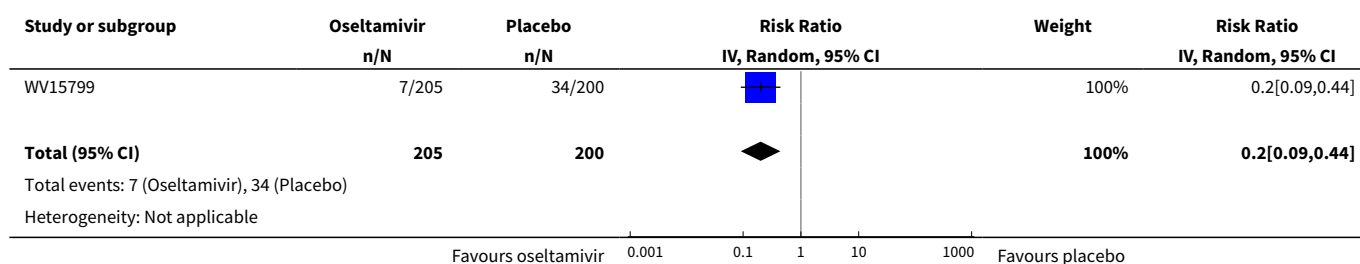
Analysis 2.1. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 1 Symptomatic influenza in adult prophylaxis of individuals.

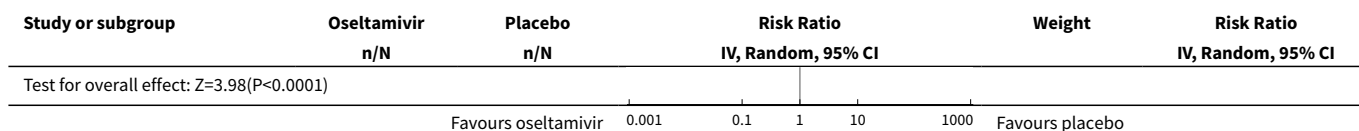


Analysis 2.2. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 2 Asymptomatic influenza in adult prophylaxis of individuals.

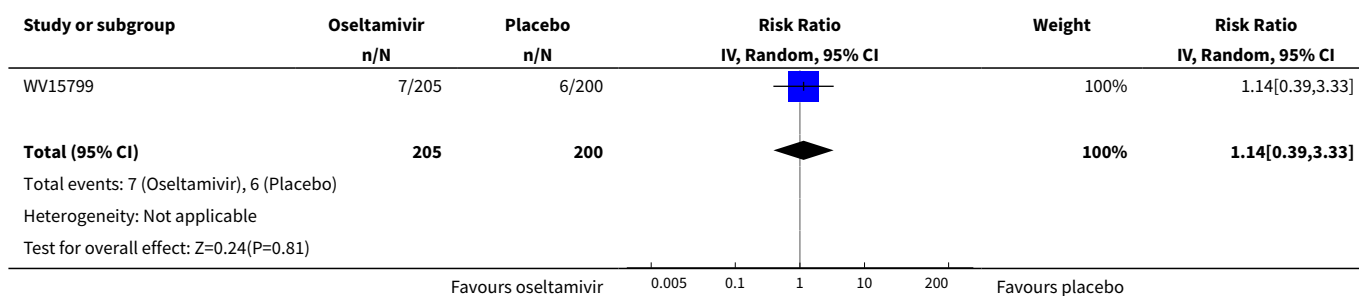


Analysis 2.3. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 3 Symptomatic influenza in household prophylaxis.

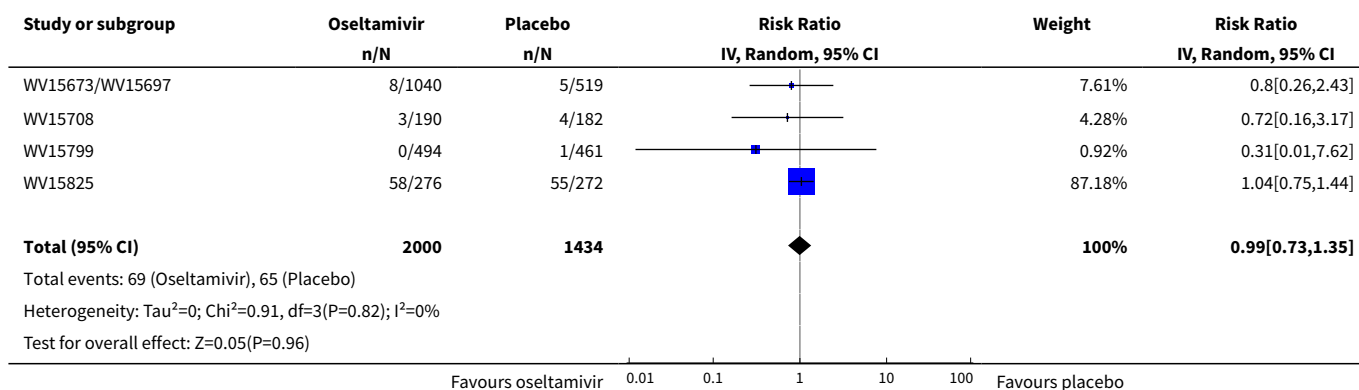




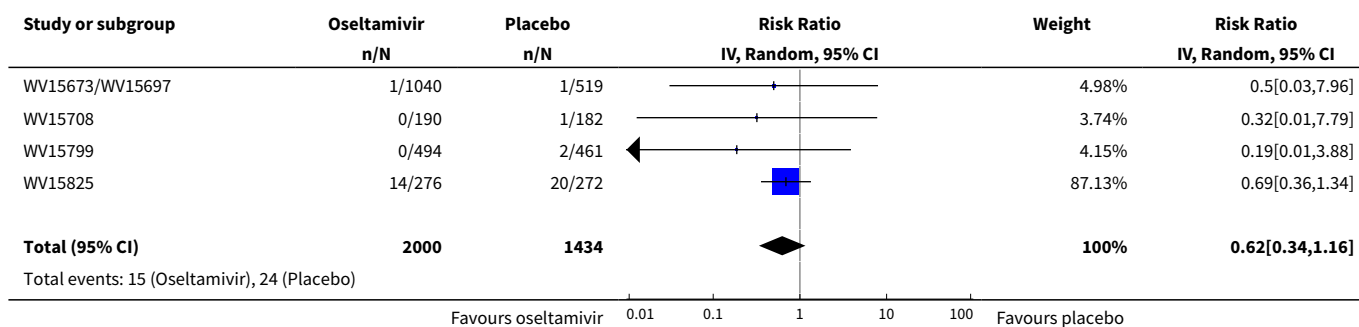
Analysis 2.4. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 4 Asymptomatic influenza in household prophylaxis.

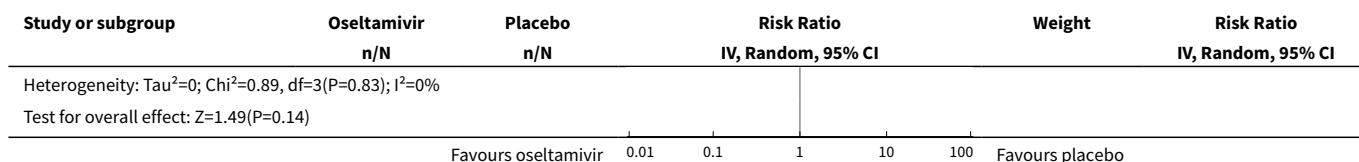


Analysis 2.5. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 5 Influenza-like illness reported as adverse event (on-treatment).

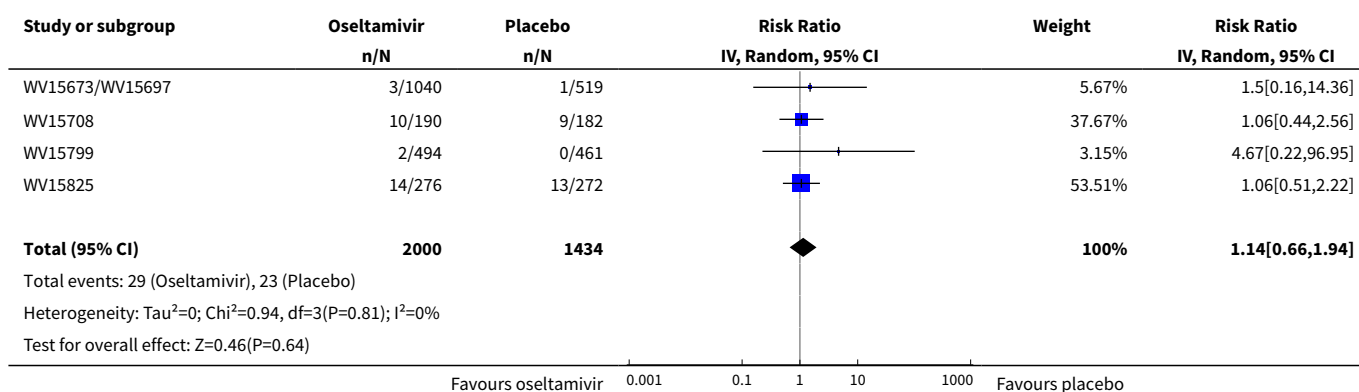


Analysis 2.6. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 6 Influenza-like illness reported as adverse event (off-treatment).

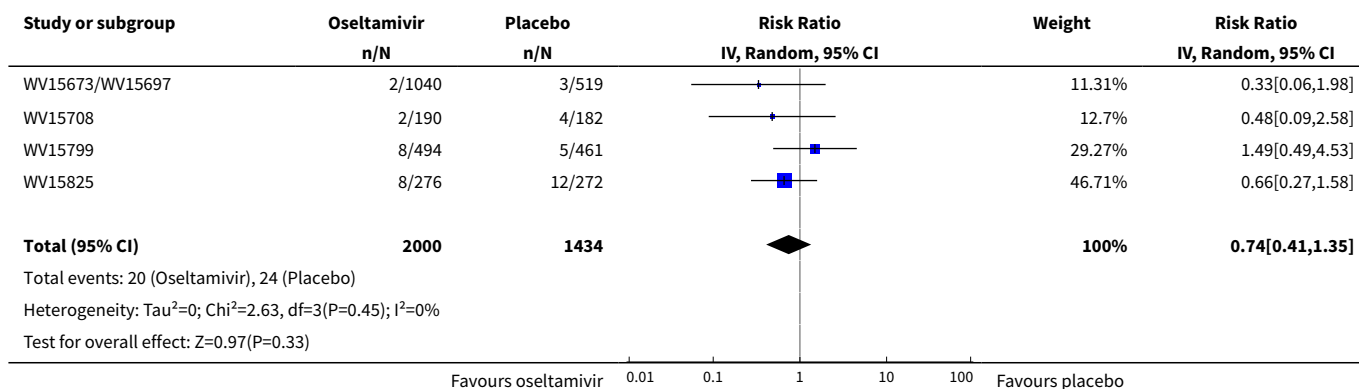




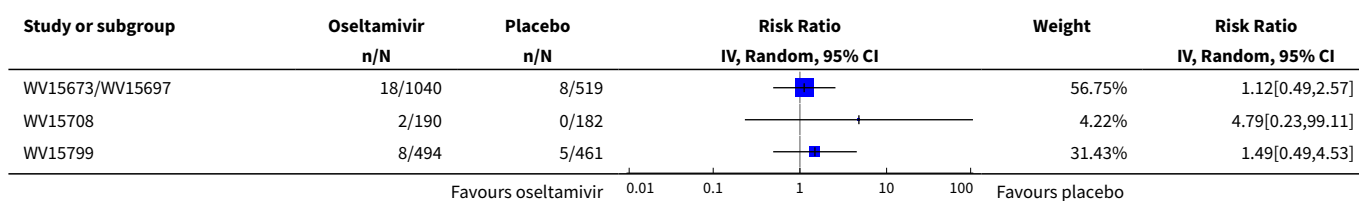
Analysis 2.7. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 7 Hospitalisation in adult prophylaxis (safety population).

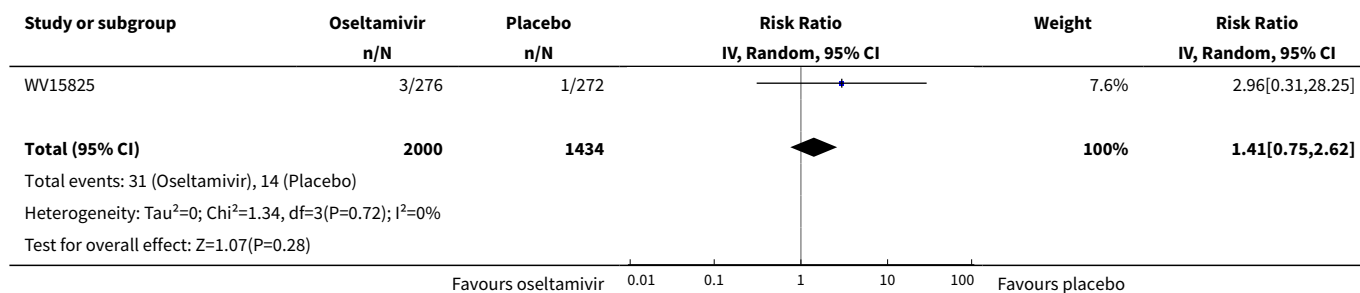


Analysis 2.8. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 8 Complications: bronchitis in adult prophylaxis.

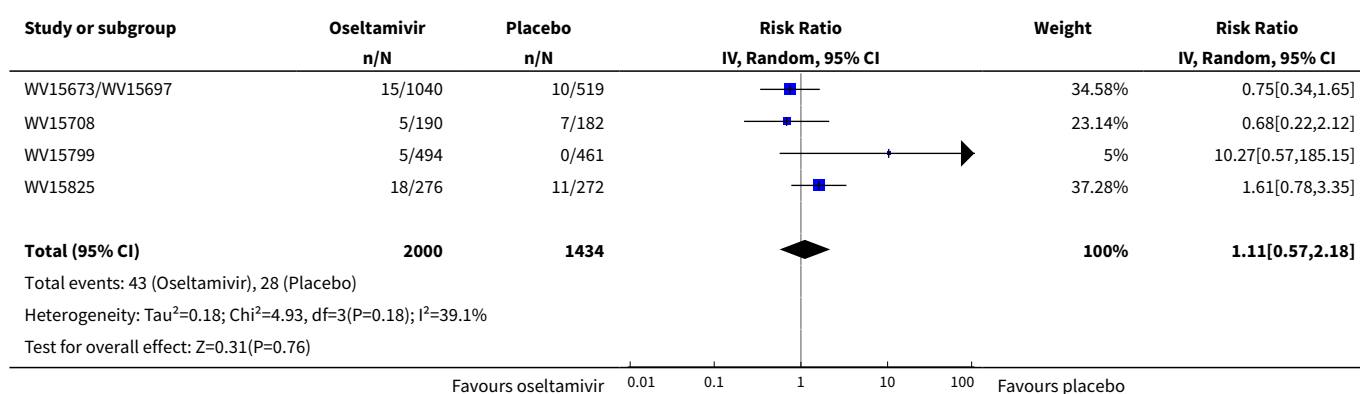


Analysis 2.9. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 9 Complications: sinusitis in adult prophylaxis.

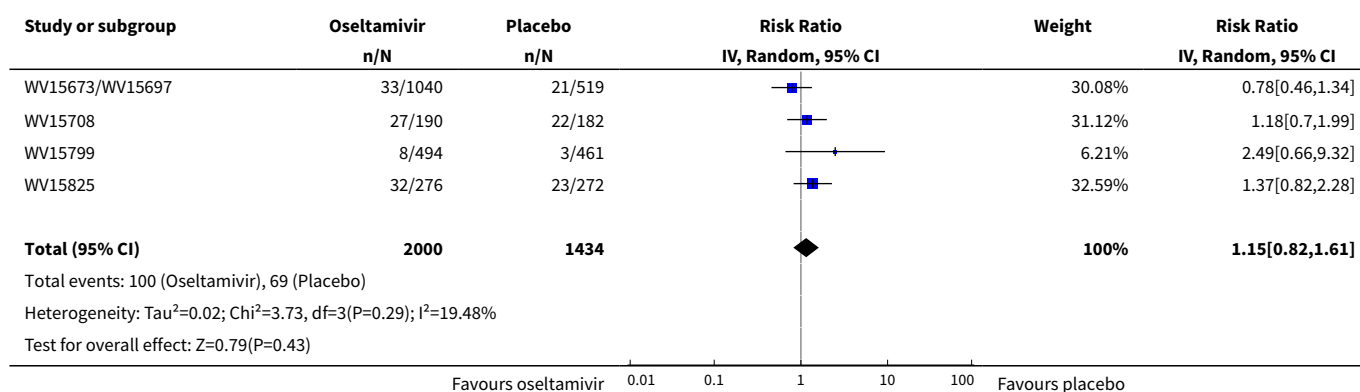




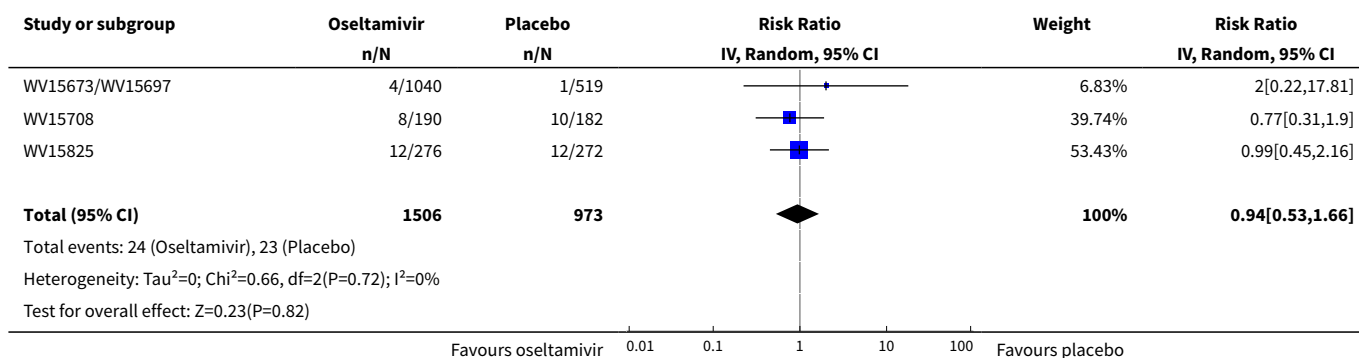
Analysis 2.10. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 10 Adverse events leading to study withdrawal in adult prophylaxis.



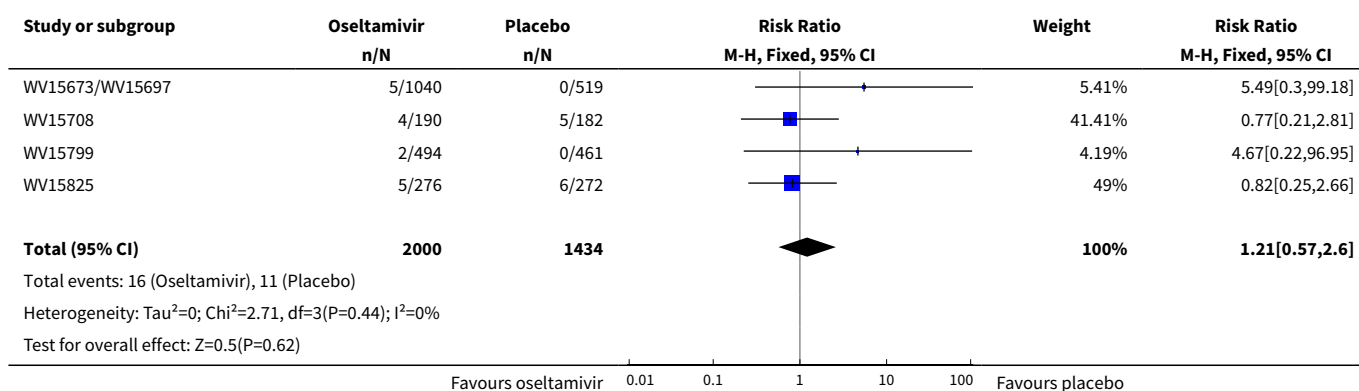
Analysis 2.11. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 11 All withdrawals in adult prophylaxis.



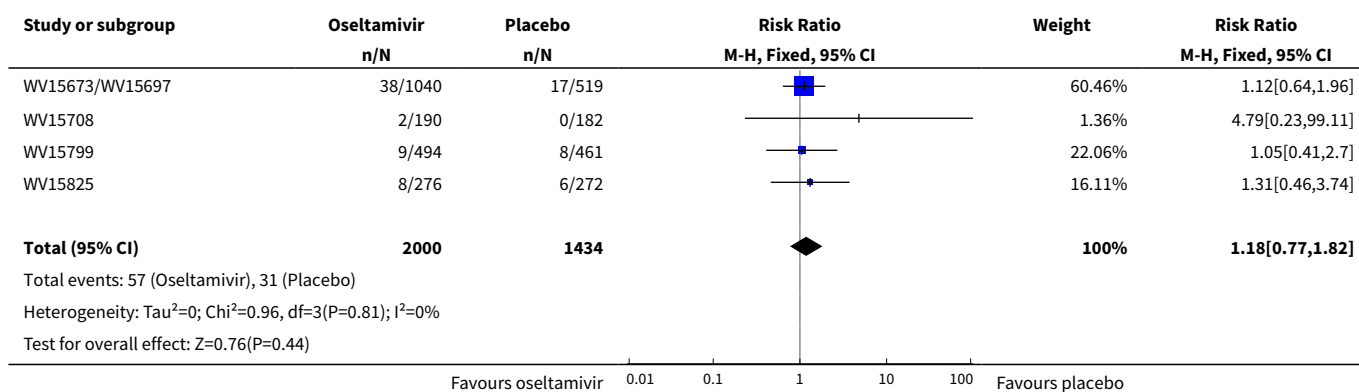
Analysis 2.12. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 12 Serious adverse events in adult prophylaxis (on-treatment).



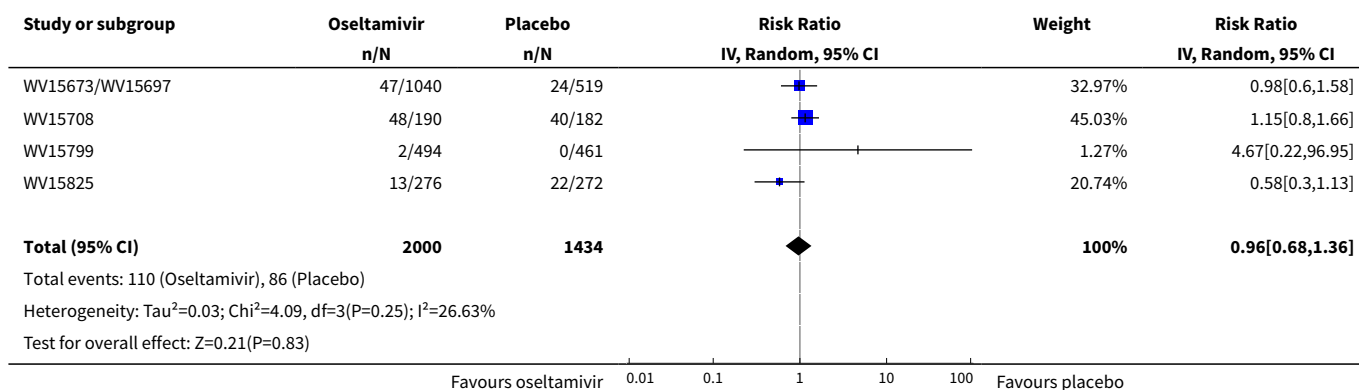
Analysis 2.13. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 13 Serious adverse events in adult prophylaxis (off-treatment).



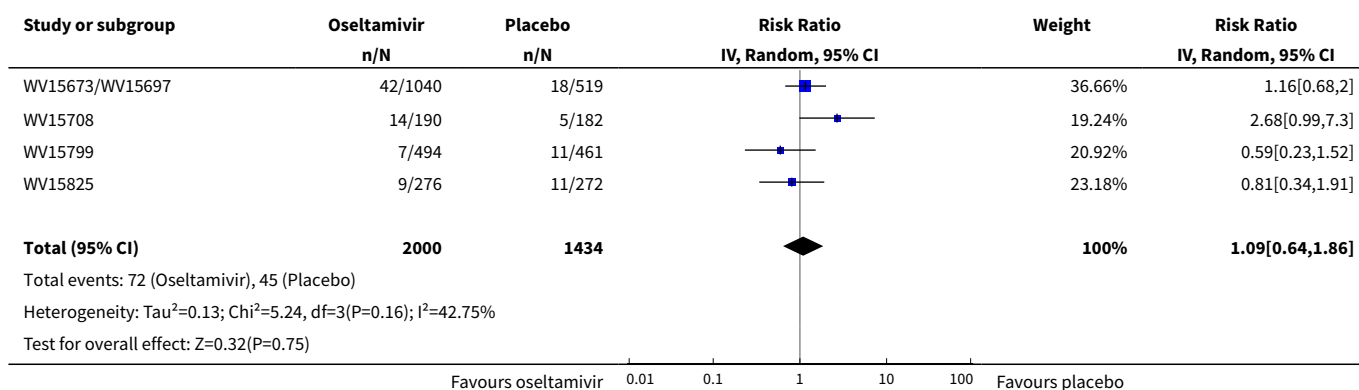
Analysis 2.14. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 14 Adverse events: abdominal pain in adult prophylaxis (on-treatment).



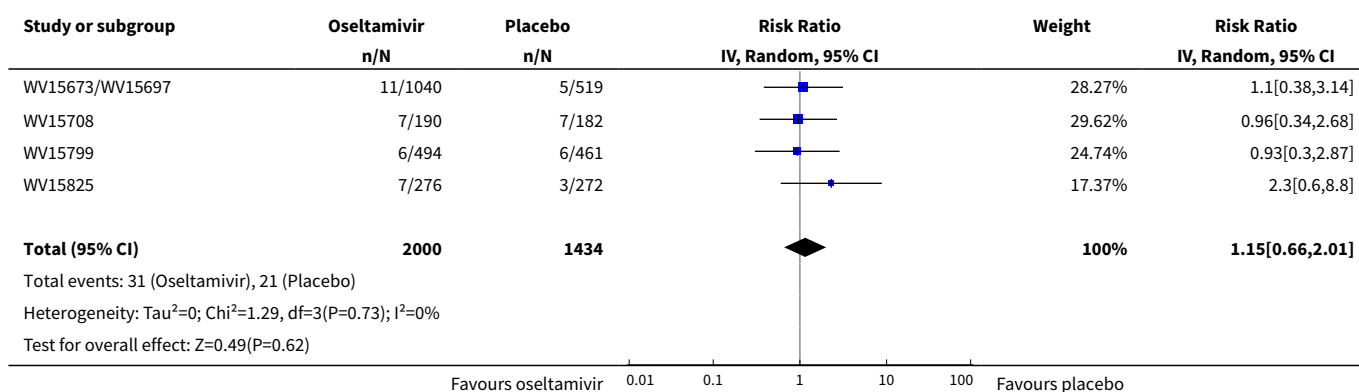
Analysis 2.15. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 15 Adverse events: cough in adult prophylaxis (on-treatment).



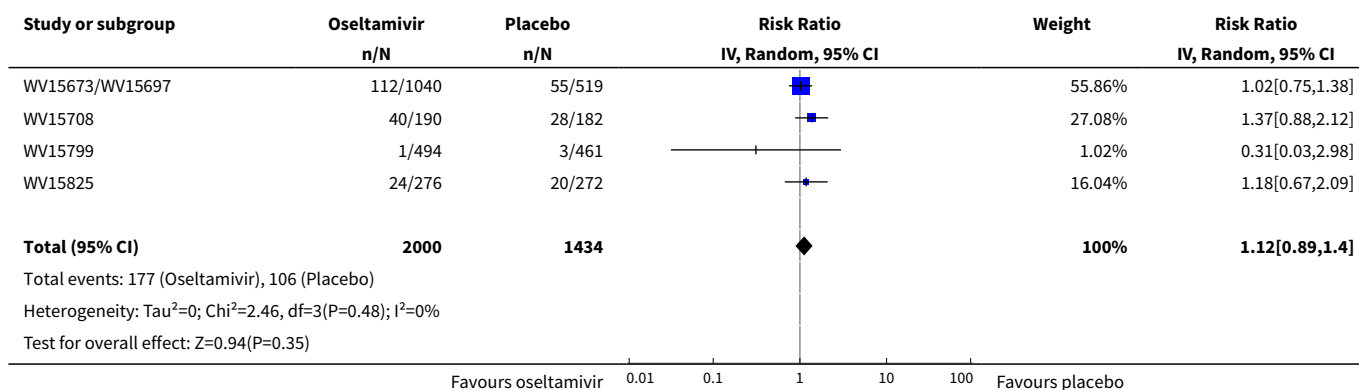
Analysis 2.16. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 16 Adverse events: diarrhoea in adult prophylaxis (on-treatment).



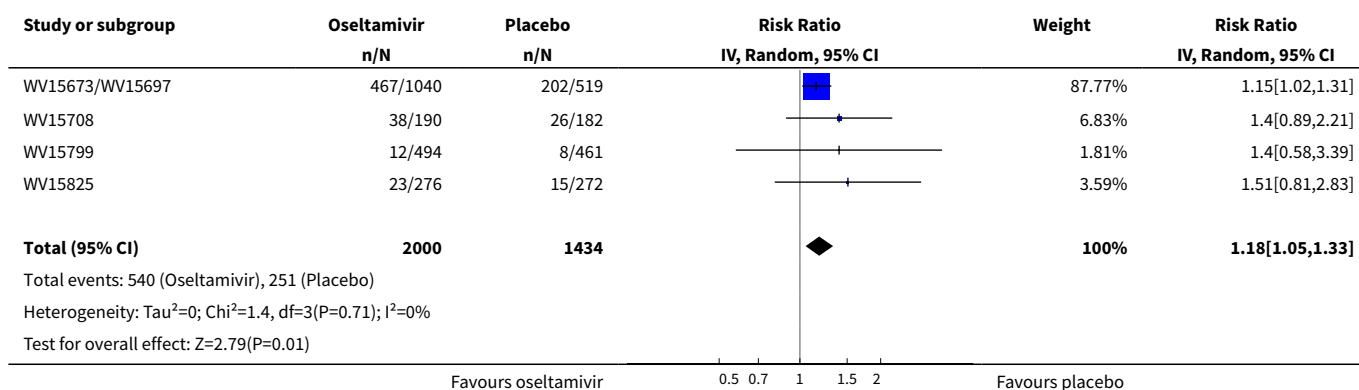
Analysis 2.17. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 17 Adverse events: dizziness in adult prophylaxis (on-treatment).



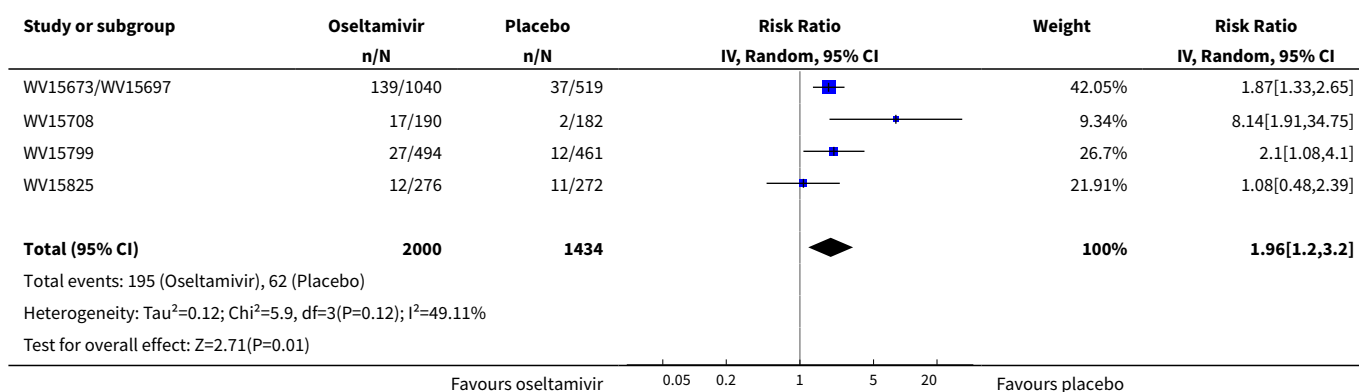
Analysis 2.18. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 18 Adverse events: fatigue in adult prophylaxis (on-treatment).



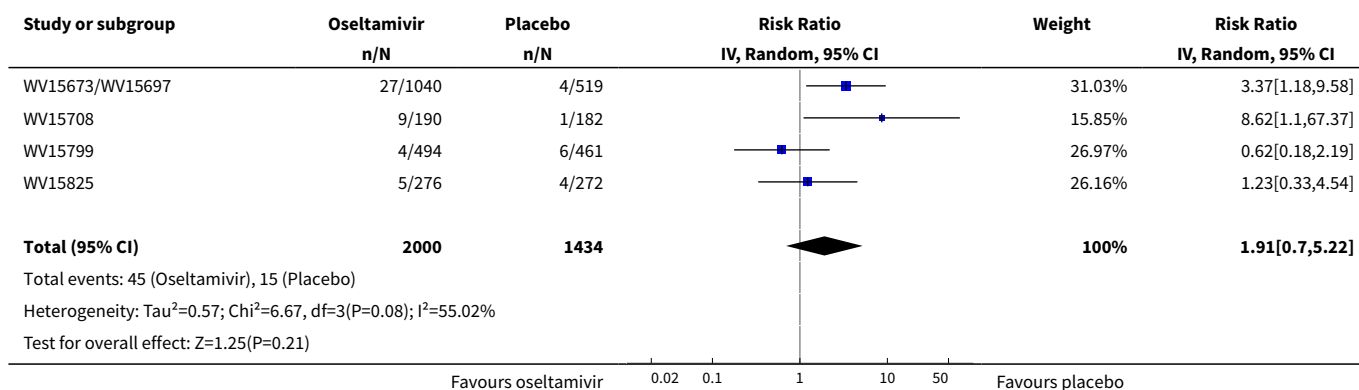
Analysis 2.19. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 19 Adverse events: headache in adult prophylaxis (on-treatment).



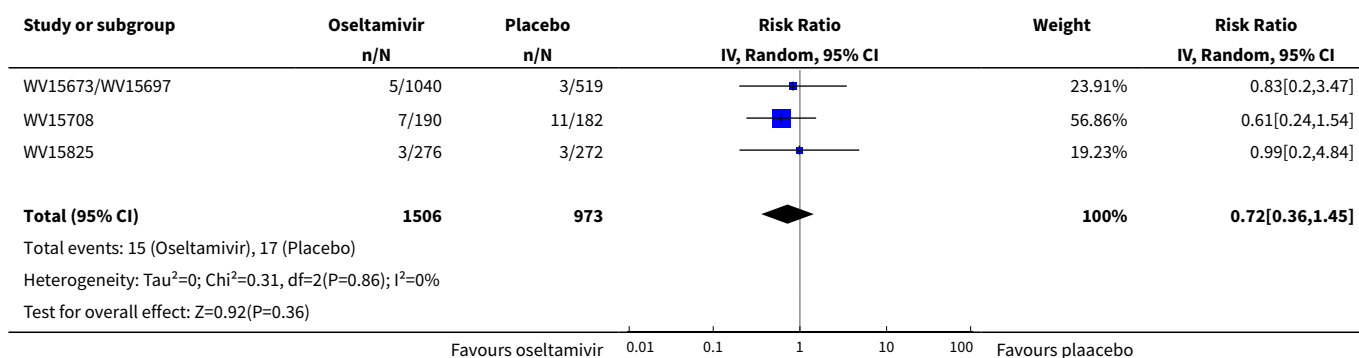
Analysis 2.20. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 20 Adverse events: nausea in adult prophylaxis (on-treatment).



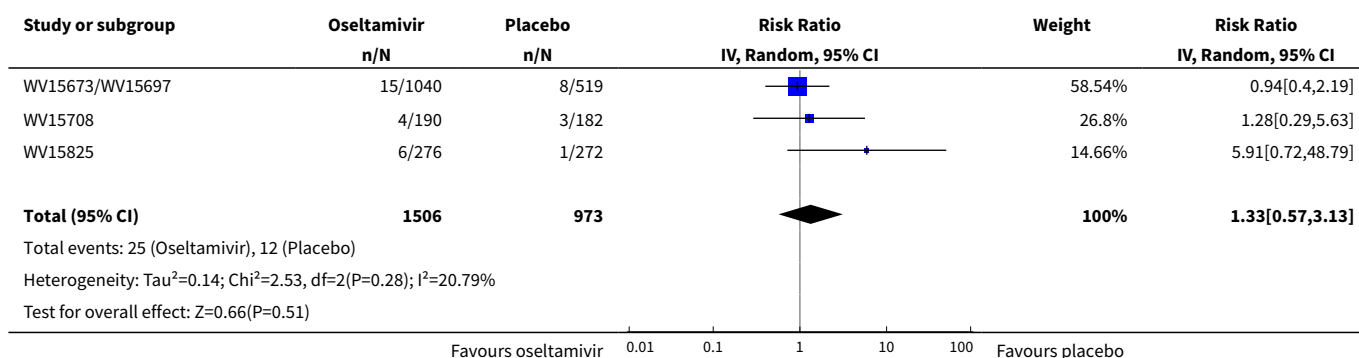
Analysis 2.21. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 21 Adverse events: vomiting in adult prophylaxis (on-treatment).



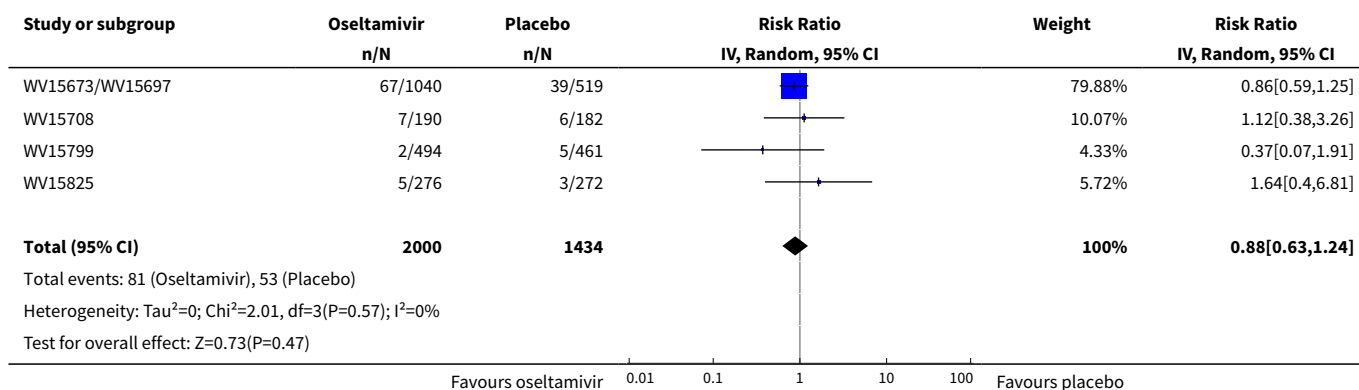
Analysis 2.22. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 22 Adverse events: cough in adult prophylaxis (off-treatment).



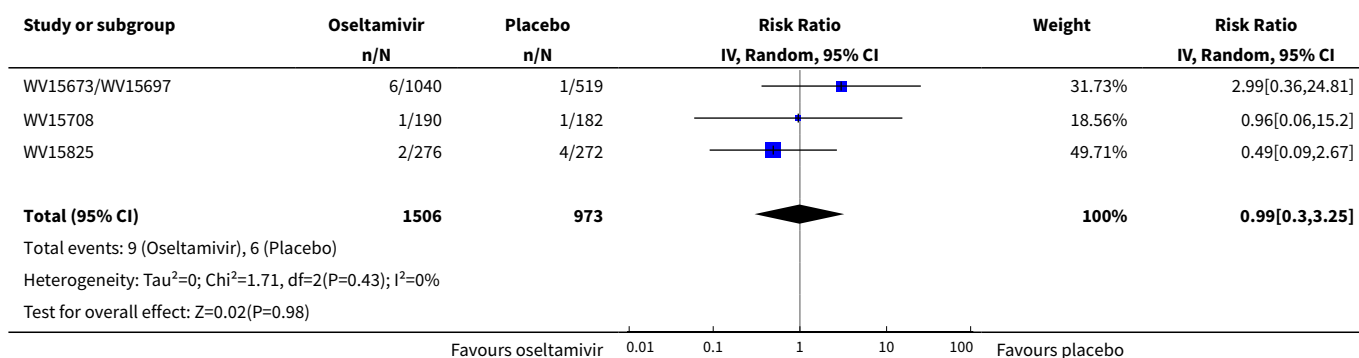
Analysis 2.23. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 23 Adverse events: fatigue in adult prophylaxis (off-treatment).



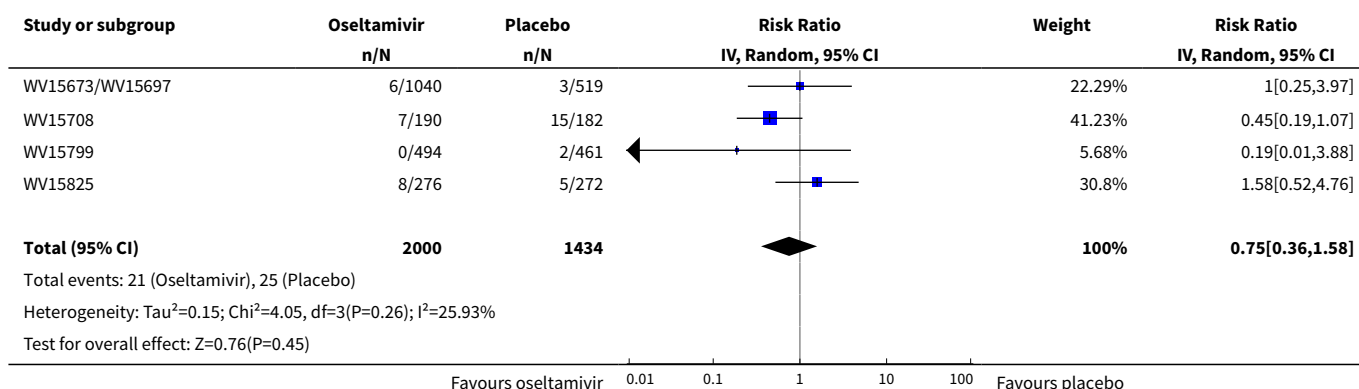
Analysis 2.24. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 24 Adverse events: headache in adult prophylaxis (off-treatment).



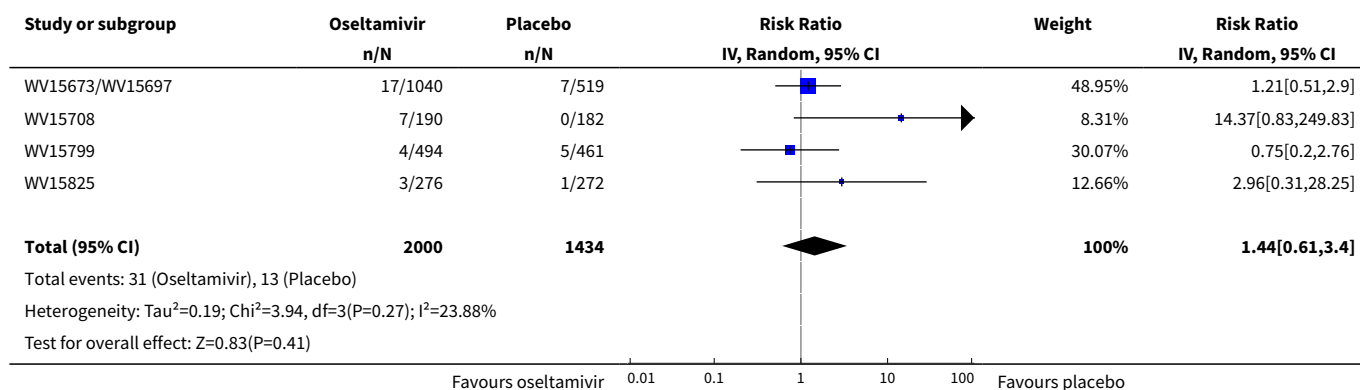
Analysis 2.25. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 25 Adverse events: blood body system in adult prophylaxis (on-treatment).



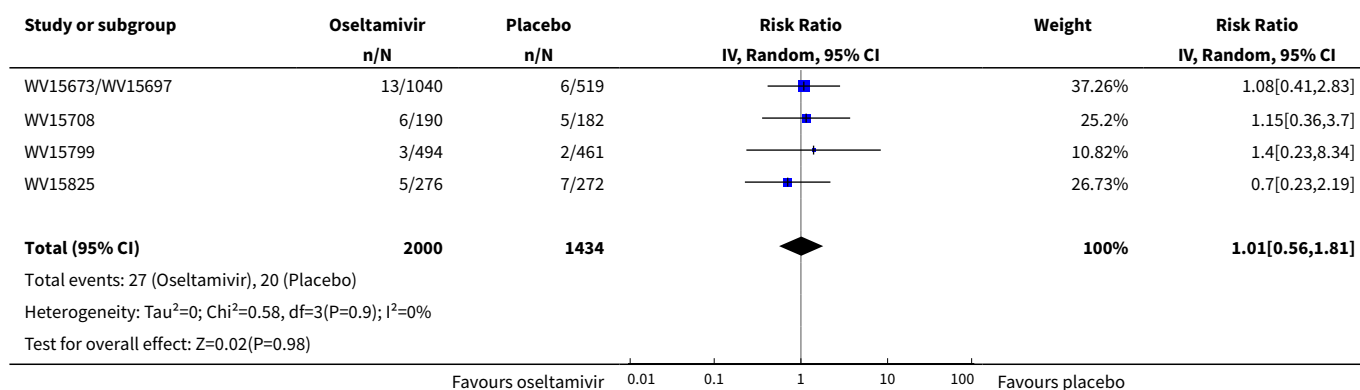
Analysis 2.26. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 26 Adverse events: cardiac body system in adult prophylaxis (on-treatment).



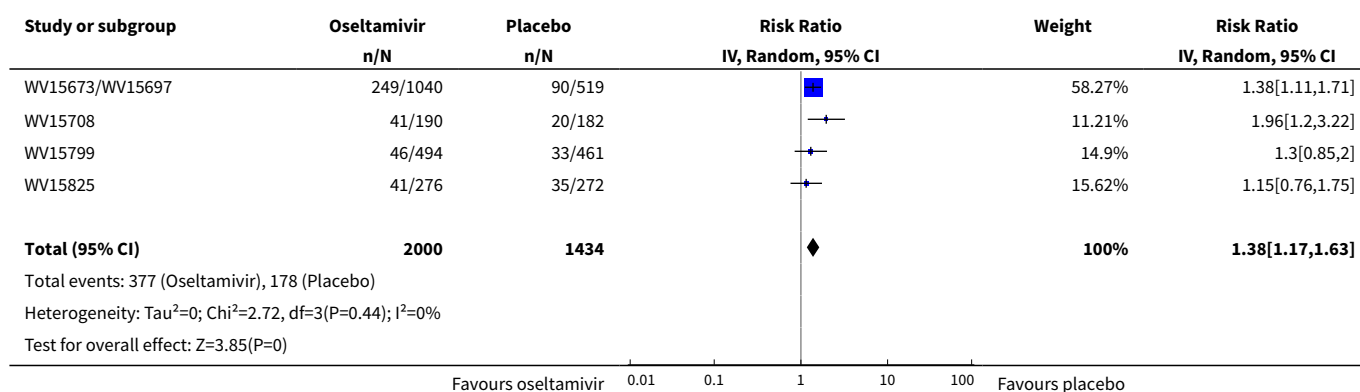
Analysis 2.27. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 27 Adverse events: ear body system in adult prophylaxis (on treatment).



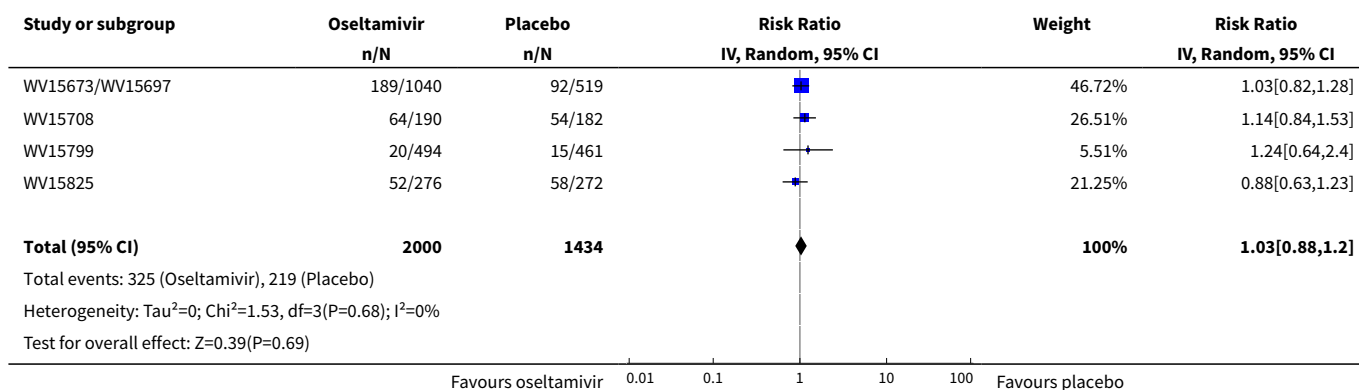
Analysis 2.28. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 28 Adverse events: eye body system in adult prophylaxis (on-treatment).



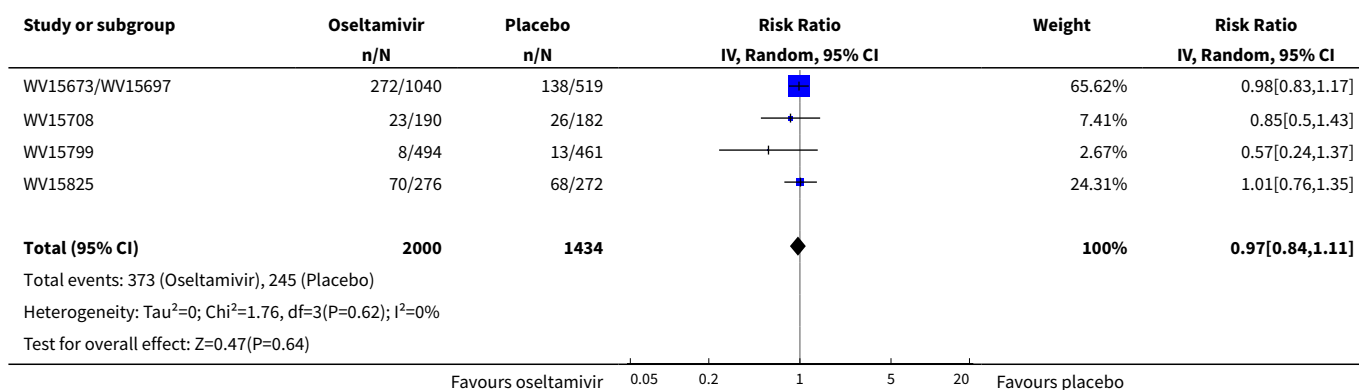
Analysis 2.29. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 29 Adverse events: gastrointestinal body system in adult prophylaxis (on-treatment).



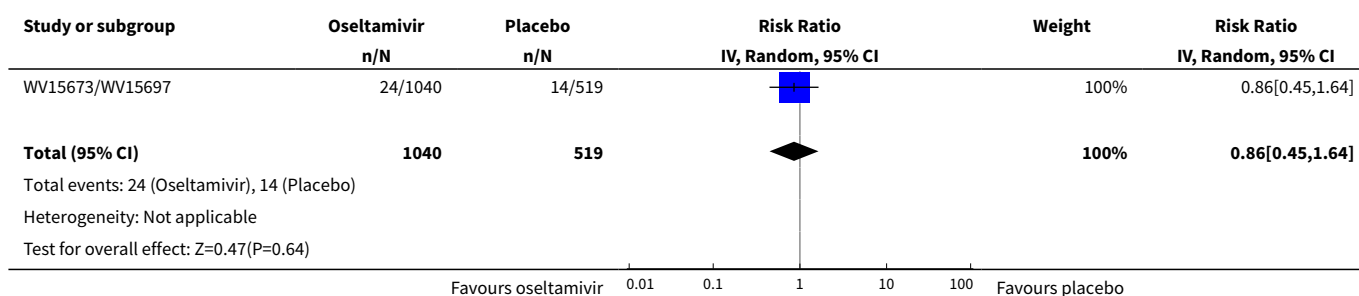
Analysis 2.30. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 30 Adverse events: general body system in adult prophylaxis (on-treatment).



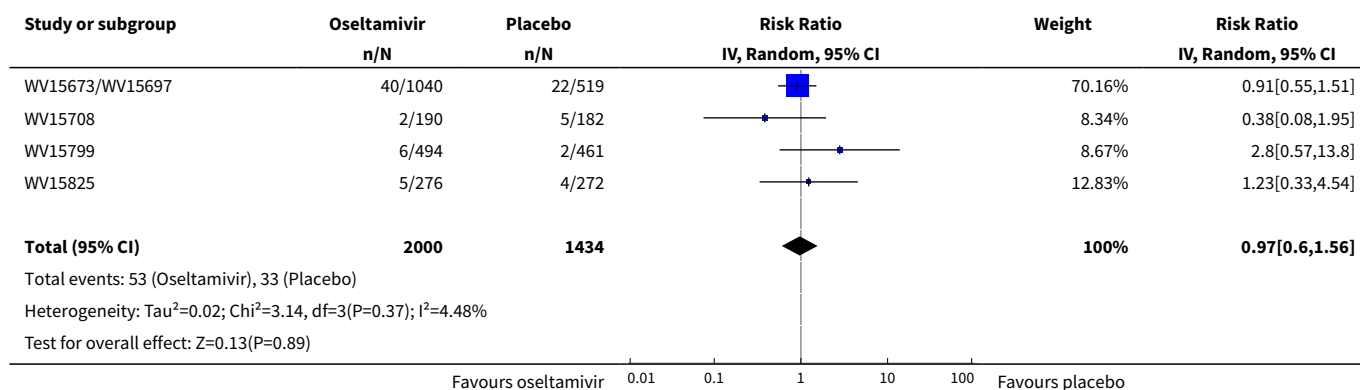
Analysis 2.31. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 31 Adverse events: infection body system in adult prophylaxis (on-treatment).



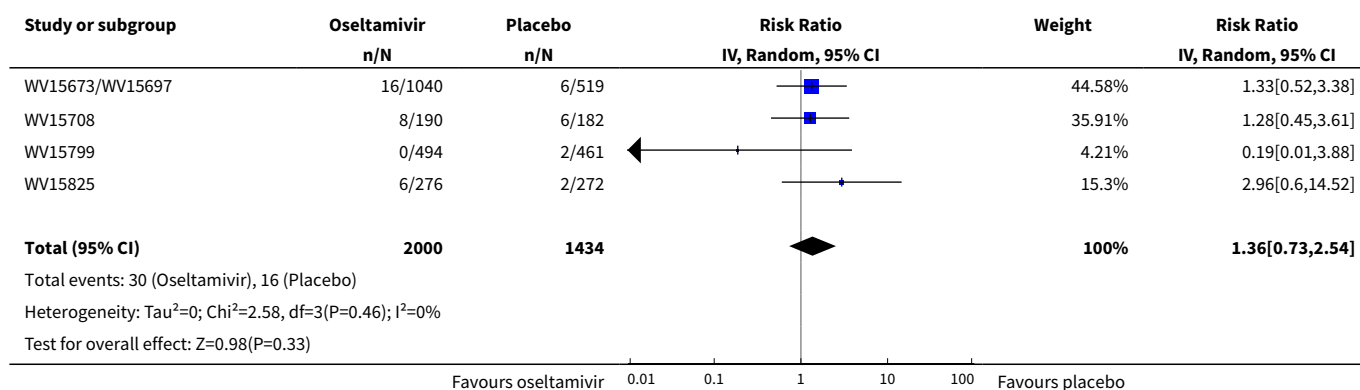
Analysis 2.32. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 32 Adverse events: immune body system in adult prophylaxis (on-treatment).



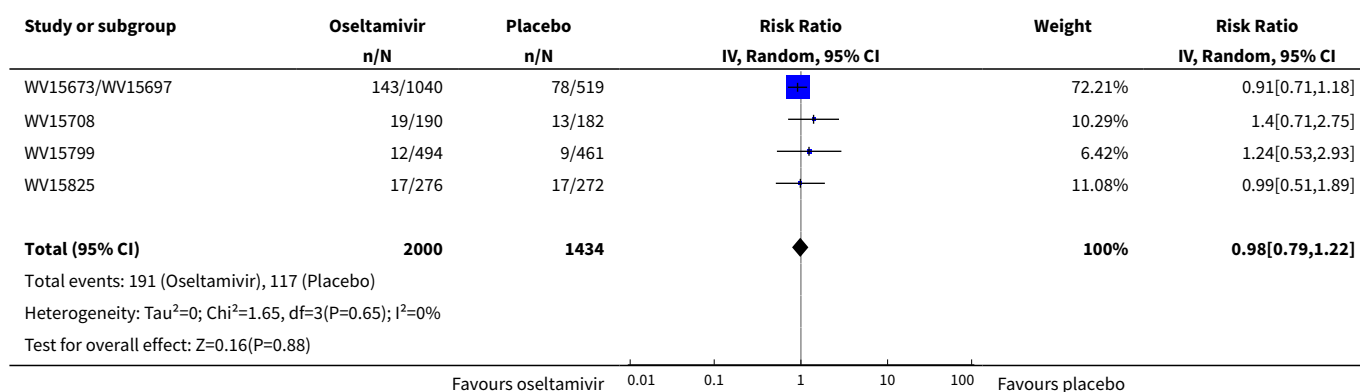
Analysis 2.33. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 33 Adverse events: injury body system in adult prophylaxis (on-treatment).



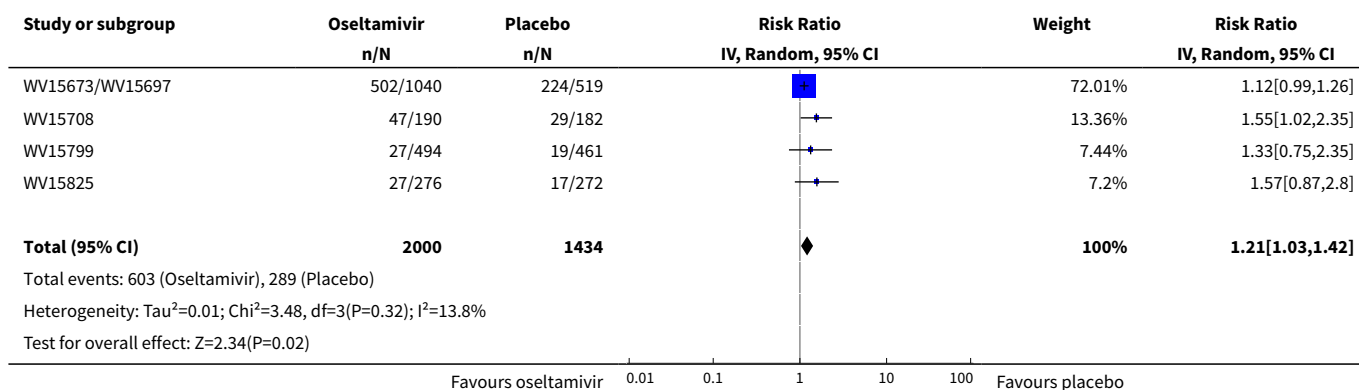
Analysis 2.34. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 34 Adverse events: metabolism body system in adult prophylaxis (on-treatment).



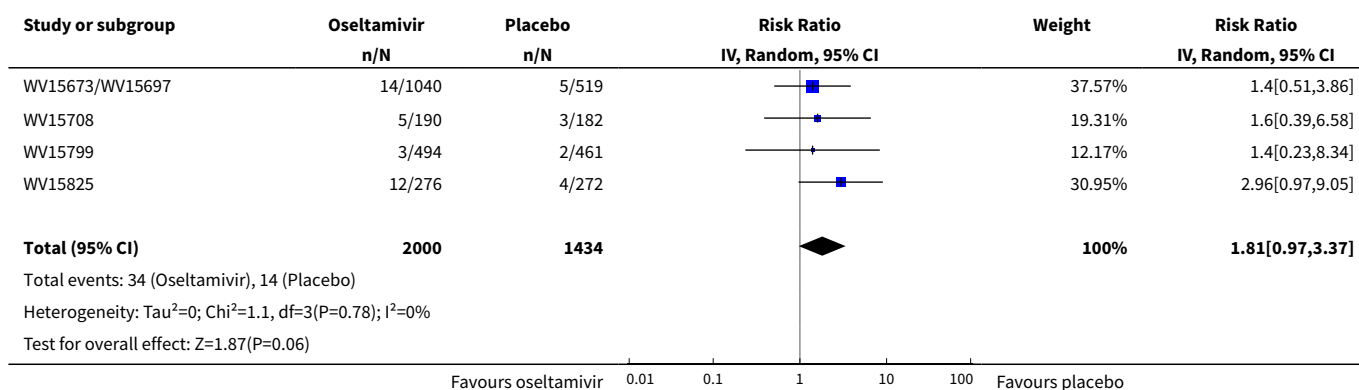
Analysis 2.35. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 35 Adverse events: musculoskeletal body system in adult prophylaxis (on-treatment).



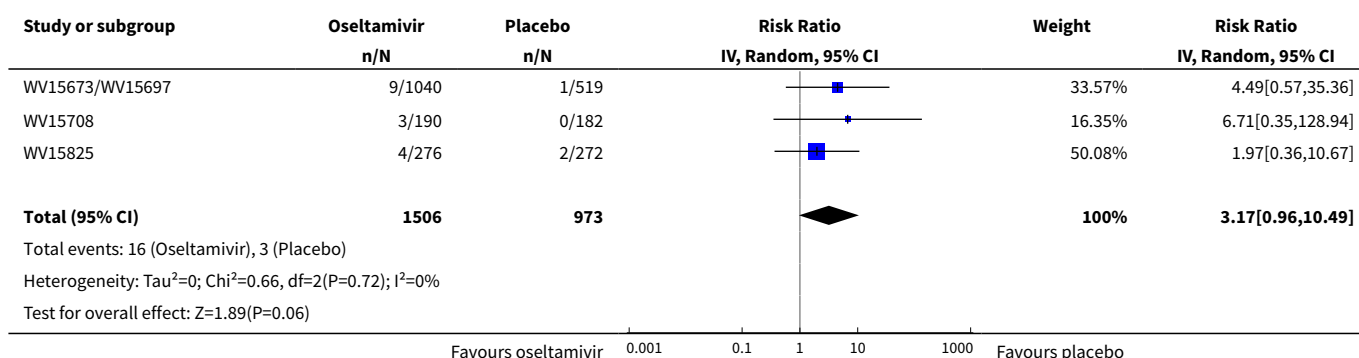
Analysis 2.36. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 36 Adverse events: neurological body system in adult prophylaxis (on-treatment).



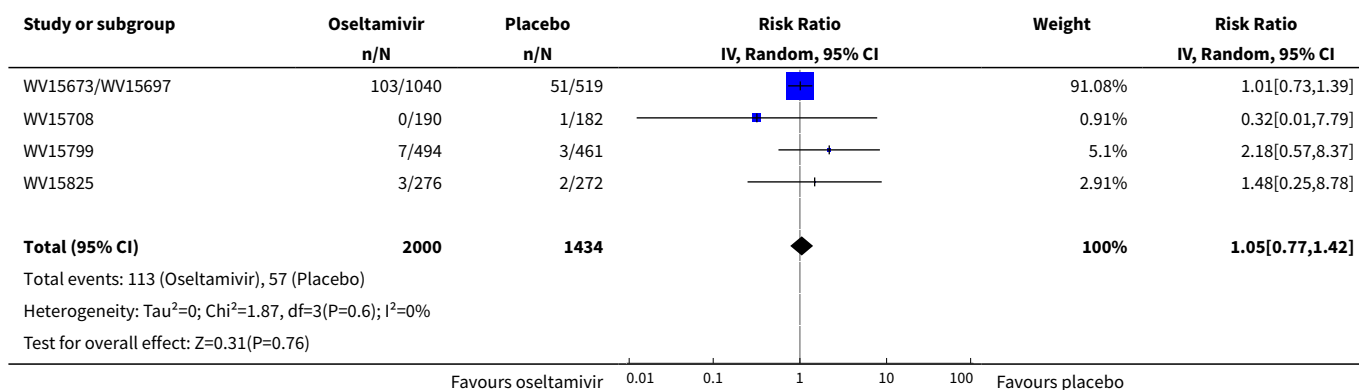
Analysis 2.37. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 37 Adverse events: psychiatric body system in adult prophylaxis (on-treatment).



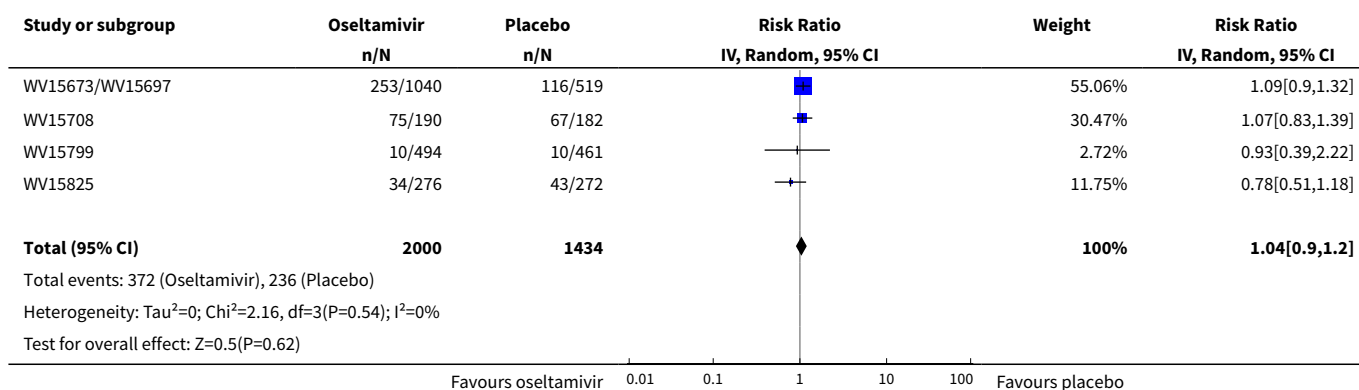
Analysis 2.38. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 38 Adverse events: renal body system in adult prophylaxis (on-treatment).



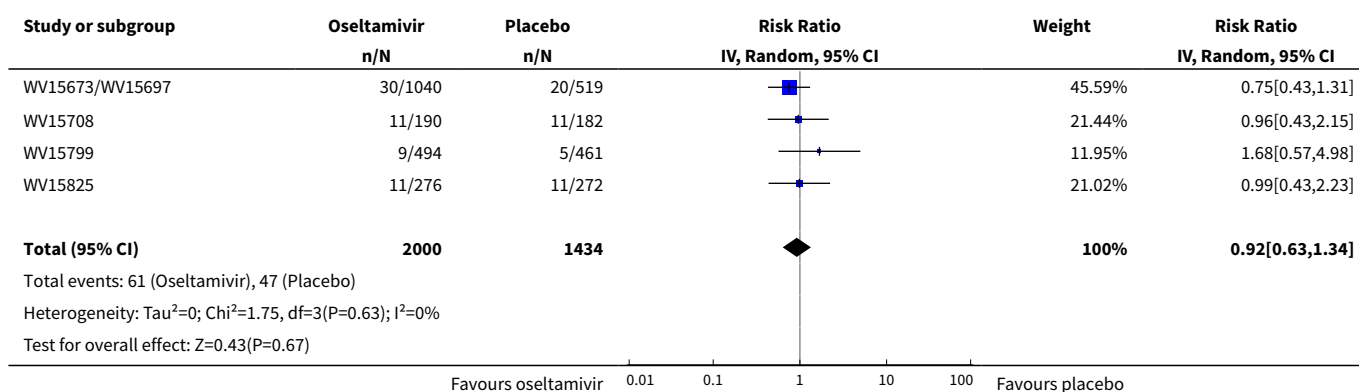
Analysis 2.39. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 39 Adverse events: reproductive body system in adult prophylaxis (on treatment).



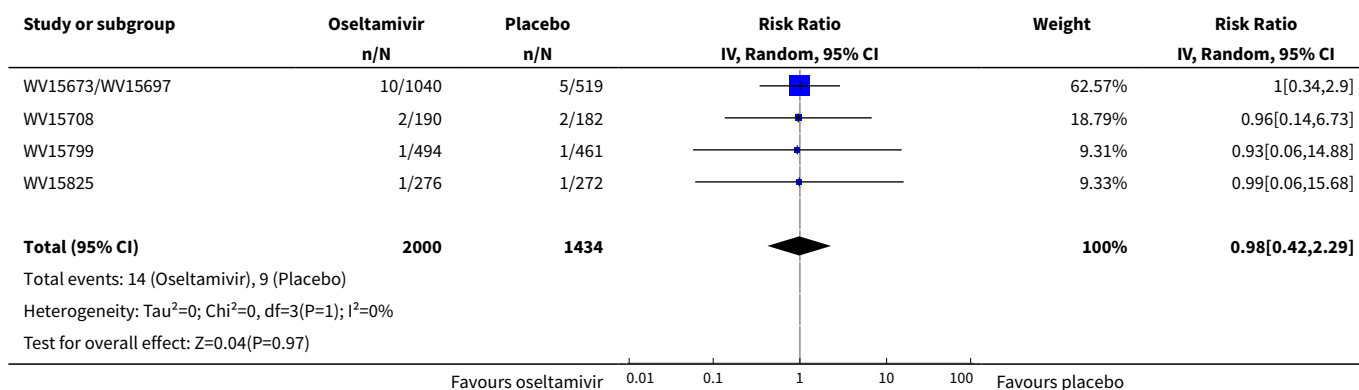
Analysis 2.40. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 40 Adverse events: respiratory body system in adult prophylaxis (on-treatment).



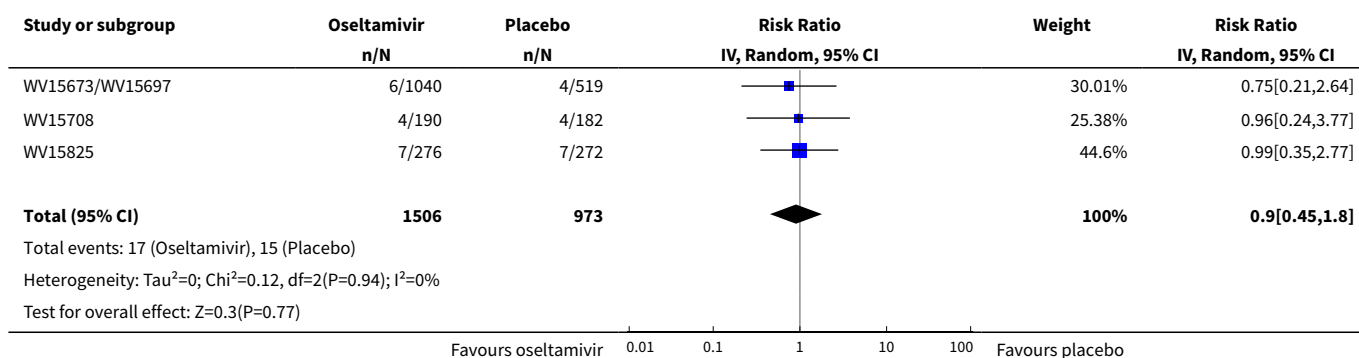
Analysis 2.41. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 41 Adverse events: skin body system in adult prophylaxis (on-treatment).



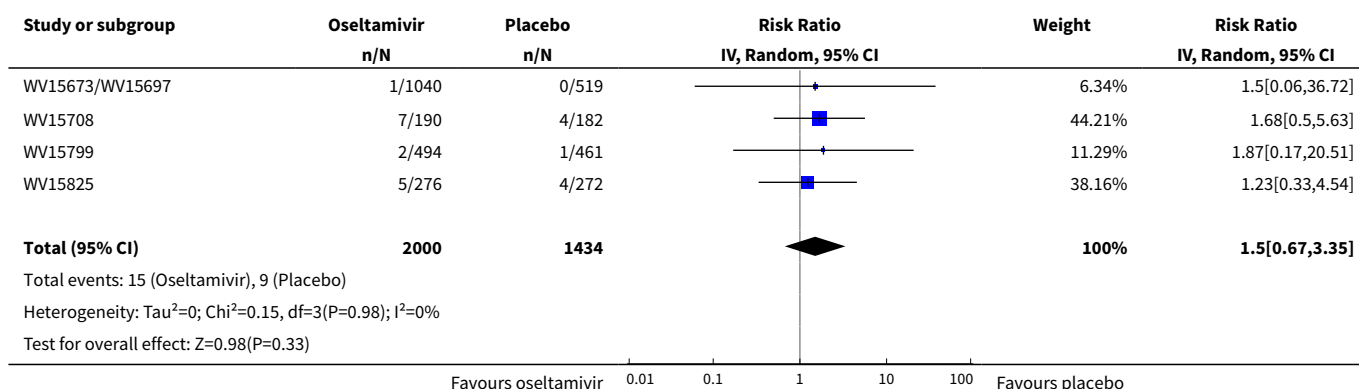
Analysis 2.42. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 42 Adverse events: surgical events in adult prophylaxis (on-treatment).



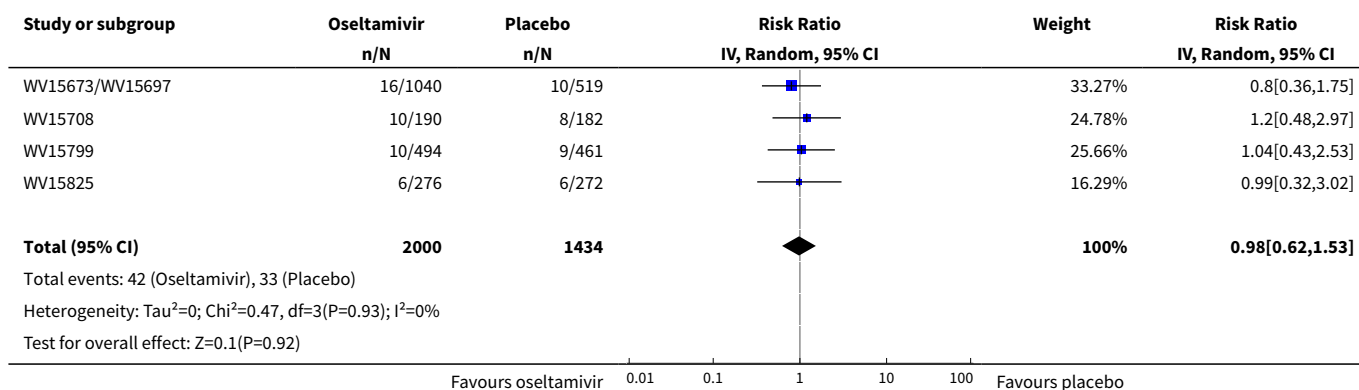
Analysis 2.43. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 43 Adverse events: vascular body system in adult prophylaxis (on-treatment).



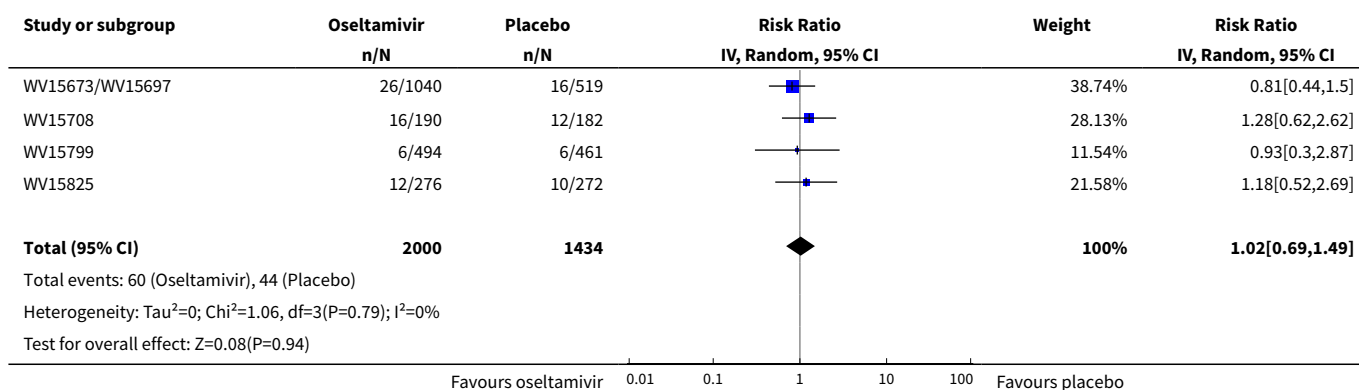
Analysis 2.44. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 44 Adverse events: cardiac body system in adult prophylaxis (off-treatment).



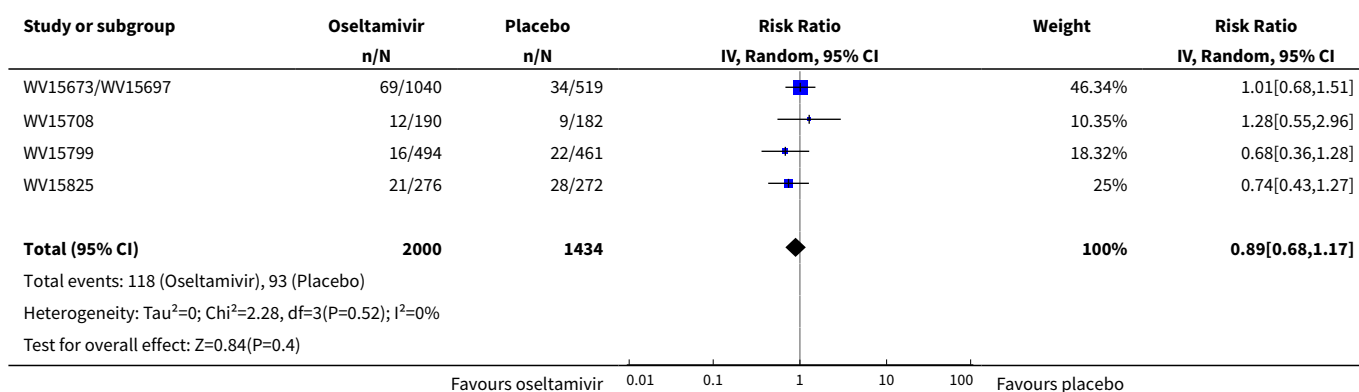
Analysis 2.45. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 45 Adverse events: gastrointestinal body system in adult prophylaxis (off-treatment).



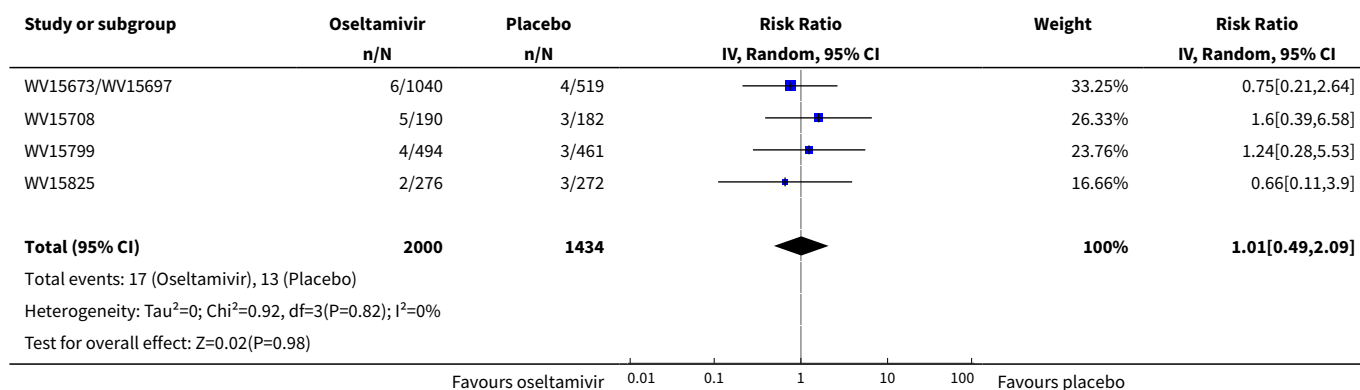
Analysis 2.46. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 46 Adverse events: general body system in adult prophylaxis (off-treatment).



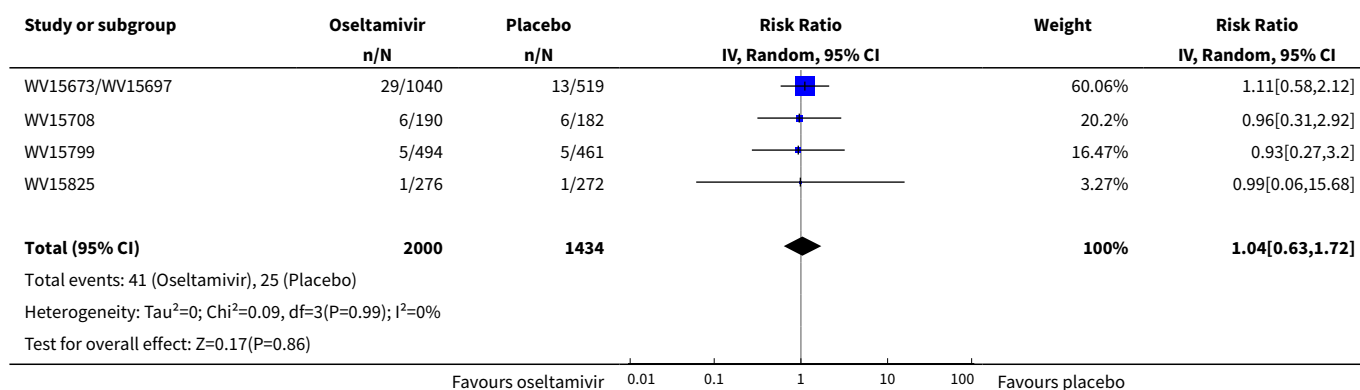
Analysis 2.47. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 47 Adverse events: infection body system in adult prophylaxis (off-treatment).



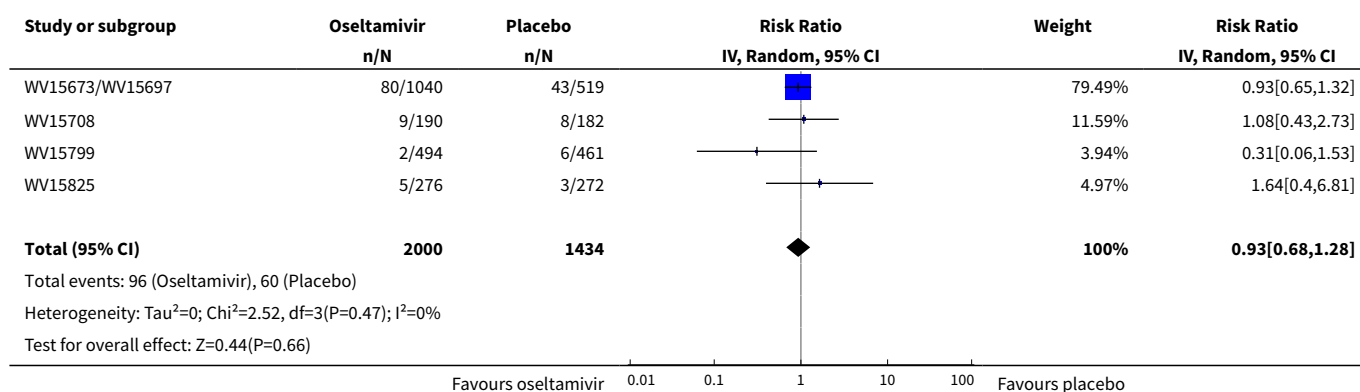
Analysis 2.48. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 48 Adverse events: injury body system in adult prophylaxis (off-treatment).



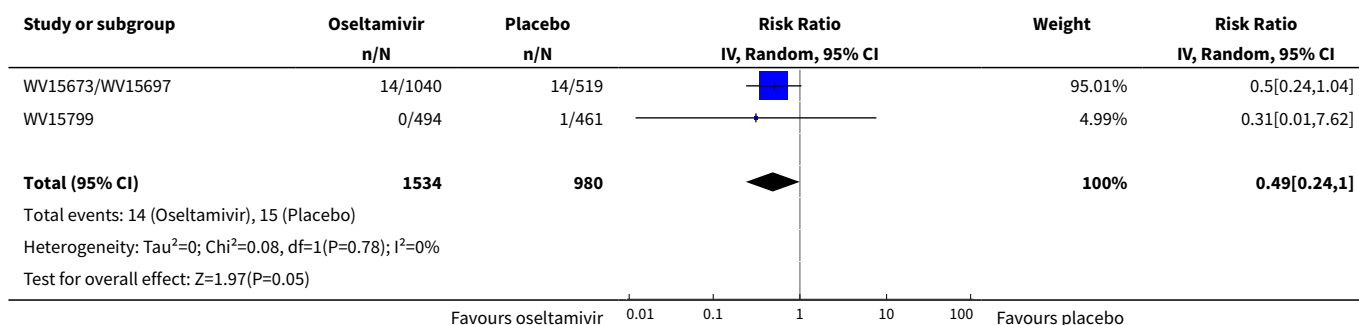
Analysis 2.49. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 49 Adverse events: musculoskeletal body system in adult prophylaxis (off-treatment).



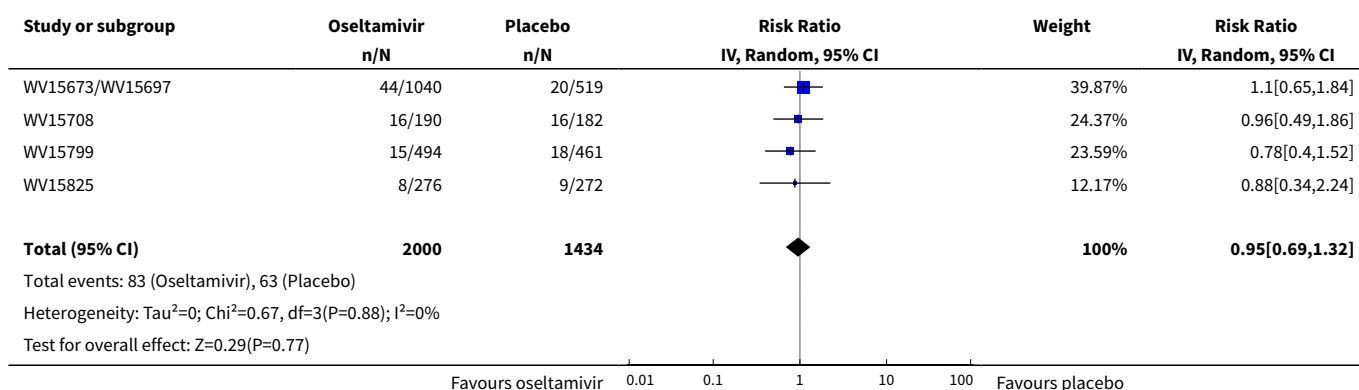
Analysis 2.50. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 50 Adverse events: neurological body system in adult prophylaxis (off-treatment).



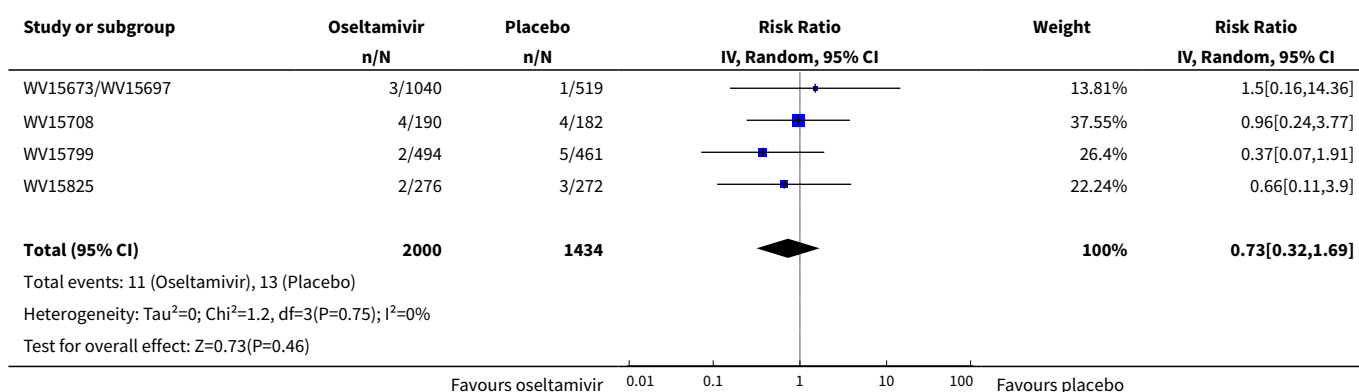
Analysis 2.51. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 51 Adverse events: reproductive body system in adult prophylaxis (off-treatment).



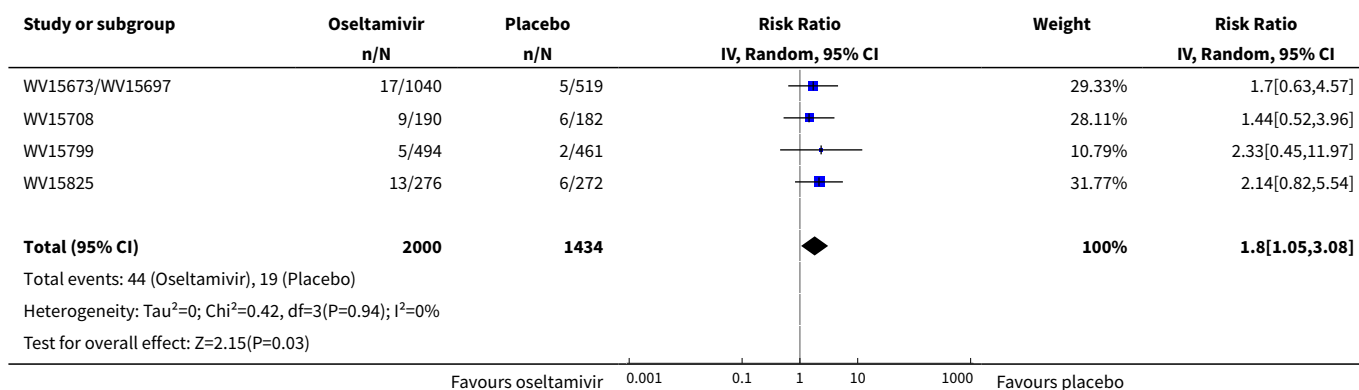
Analysis 2.52. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 52 Adverse events: respiratory body system in adult prophylaxis (off-treatment).



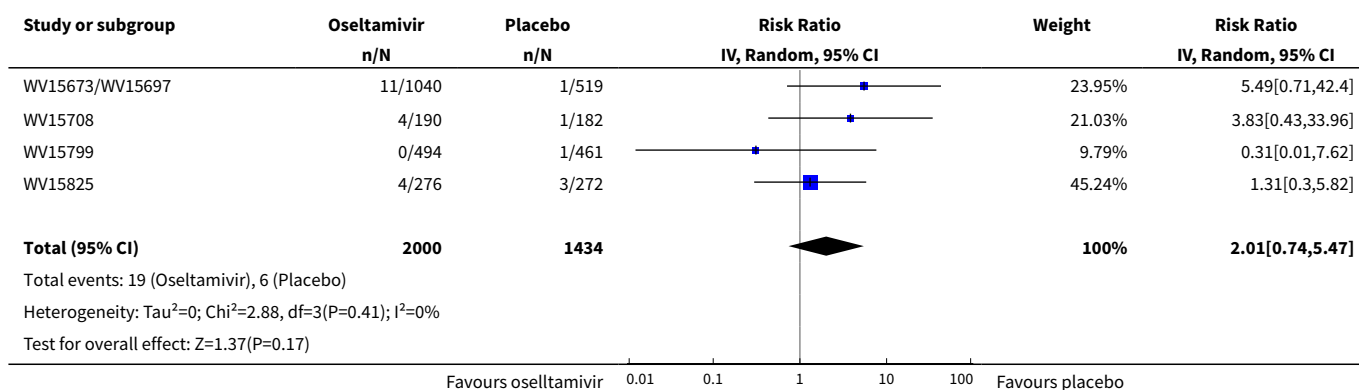
Analysis 2.53. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 53 Adverse events: skin body system in adult prophylaxis (off-treatment).



Analysis 2.54. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 54 Adverse events: psychiatric body system in adult prophylaxis (on and off-treatment).



Analysis 2.55. Comparison 2 Oseltamivir versus placebo for prophylaxis, Outcome 55 Adverse events: renal body system in adult prophylaxis (on and off-treatment).



Comparison 3. Zanamivir versus placebo for treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to first alleviation of symptoms in adult treatment (days)	13	5411	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.81, -0.39]
2 Complications: pneumonia in adult treatment	11	5876	Risk Ratio (IV, Random, 95% CI)	0.90 [0.58, 1.40]
3 Complications: pneumonia confirmed with X-ray in adult treatment	2	946	Risk Ratio (IV, Random, 95% CI)	1.02 [0.35, 3.02]
4 Complications: bronchitis in adult treatment	12	6072	Risk Ratio (IV, Random, 95% CI)	0.75 [0.61, 0.91]
5 Complications: sinusitis in adult treatment	12	6072	Risk Ratio (IV, Random, 95% CI)	1.12 [0.84, 1.48]

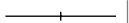
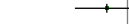
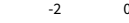
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Complications: otitis media in adult treatment	10	5494	Risk Ratio (IV, Random, 95% CI)	0.81 [0.54, 1.20]
7 Complications in adult trials classified as serious or leading to study withdrawal	8	4514	Risk Ratio (IV, Random, 95% CI)	1.10 [0.46, 2.63]
8 Proportion diagnosed as influenza-infected in adult treatment	15	6569	Risk Ratio (IV, Random, 95% CI)	1.02 [0.98, 1.06]
9 Proportion with four-fold rise in antibody titre in adult treatment	13	5113	Risk Ratio (IV, Random, 95% CI)	1.01 [0.96, 1.06]
10 Proportion with positive culture at baseline in adult treatment	12	5995	Risk Ratio (IV, Random, 95% CI)	1.01 [0.96, 1.05]
11 Serious adverse events in adult treatment	10	4388	Risk Ratio (IV, Random, 95% CI)	0.86 [0.49, 1.50]
12 Adverse events leading to study withdrawal in adult treatment	13	6116	Risk Ratio (IV, Random, 95% CI)	0.96 [0.66, 1.39]
13 All withdrawals in adult treatment	12	6065	Risk Difference (IV, Random, 95% CI)	-0.00 [-0.01, 0.01]
14 Time to first alleviation of symptoms in children (days)	2	723	Mean Difference (IV, Random, 95% CI)	-1.08 [-2.32, 0.15]
15 Complications: pneumonia in child treatment	2	737	Risk Ratio (IV, Random, 95% CI)	0.53 [0.12, 2.38]
16 Complications: bronchitis in child treatment	2	737	Risk Ratio (IV, Random, 95% CI)	0.86 [0.26, 2.80]
17 Complications: sinusitis in child treatment	2	737	Risk Ratio (IV, Random, 95% CI)	0.87 [0.12, 6.45]
18 Complications: otitis media in child treatment	2	737	Risk Ratio (IV, Random, 95% CI)	1.00 [0.59, 1.72]
19 Proportion diagnosed as influenza-infected in child treatment	1	471	Risk Ratio (IV, Random, 95% CI)	0.99 [0.89, 1.11]
20 Proportion with four-fold increase in antibodies in child treatment	1	431	Risk Ratio (IV, Random, 95% CI)	1.02 [0.86, 1.20]
21 Proportion with positive culture at baseline in child treatment	1	469	Risk Ratio (IV, Random, 95% CI)	1.06 [0.87, 1.27]
22 All withdrawals in child treatment	2	737	Risk Ratio (IV, Random, 95% CI)	1.18 [0.16, 8.88]
23 Adverse events: nausea and vomiting in child treatment (on-treatment)	2	737	Odds Ratio (IV, Random, 95% CI)	0.54 [0.24, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24 Adverse events: diarrhoea in child treatment (on-treatment)	2	737	Risk Ratio (IV, Random, 95% CI)	0.52 [0.15, 1.75]
25 Adverse events: gastrointestinal body system in child treatment (on-treatment)	2	737	Risk Ratio (IV, Random, 95% CI)	0.95 [0.52, 1.73]
26 Adverse events: respiratory body system in child treatment (on-treatment)	2	737	Risk Ratio (IV, Random, 95% CI)	0.56 [0.29, 1.10]
27 Adverse events: neurological body system in child treatment (on-treatment)	2	737	Risk Ratio (IV, Random, 95% CI)	0.61 [0.20, 1.85]
28 Adverse events: ear, nose and throat body system in child treatment (on-treatment)	2	737	Risk Ratio (IV, Random, 95% CI)	1.02 [0.63, 1.67]
29 Adverse events: skin body system in child treatment (on-treatment)	2	737	Risk Ratio (IV, Random, 95% CI)	1.01 [0.34, 2.98]
30 Adverse events: gastrointestinal body system in child treatment (off-treatment)	2	737	Risk Ratio (IV, Random, 95% CI)	1.39 [0.50, 3.83]
31 Adverse events: ear nose and throat body system in child treatment (off-treatment)	2	737	Risk Ratio (IV, Random, 95% CI)	0.93 [0.54, 1.63]
32 Adverse events: nausea/vomiting in adult treatment (on-treatment)	15	6553	Risk Ratio (IV, Random, 95% CI)	0.60 [0.39, 0.94]
33 Adverse events: diarrhoea in adult treatment (on-treatment)	15	6553	Risk Ratio (IV, Random, 95% CI)	0.87 [0.66, 1.14]
34 Adverse events: dizziness in adult treatment (on-treatment)	13	5641	Risk Ratio (IV, Random, 95% CI)	1.20 [0.68, 2.15]
35 Adverse events: headache in adult treatment (on-treatment)	15	6553	Risk Ratio (IV, Random, 95% CI)	0.84 [0.60, 1.18]
36 Adverse events: cough in adult treatment (on-treatment)	15	6553	Risk Ratio (IV, Random, 95% CI)	0.69 [0.49, 0.96]
37 Adverse events: gastrointestinal body system in adult treatment (on-treatment)	15	6453	Risk Ratio (IV, Random, 95% CI)	0.89 [0.72, 1.09]
38 Adverse events: respiratory body system in adult treatment (on-treatment)	15	6553	Risk Ratio (IV, Random, 95% CI)	0.81 [0.67, 0.97]
39 Adverse events: neurological body system in adult treatment (on-treatment)	15	6553	Risk Ratio (IV, Random, 95% CI)	1.03 [0.82, 1.29]
40 Adverse events: ear, nose and throat body system in adult treatment (on-treatment)	14	6229	Risk Ratio (IV, Random, 95% CI)	0.89 [0.76, 1.05]
41 Adverse events: skin body system in adult treatment (on-treatment)	13	6181	Risk Ratio (IV, Random, 95% CI)	0.84 [0.60, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
42 Adverse events: musculoskeletal body system in adult treatment (on-treatment)	15	6553	Risk Ratio (IV, Random, 95% CI)	0.72 [0.49, 1.04]
43 Adverse events: eye body system in adult treatment (on-treatment)	13	6181	Risk Ratio (IV, Random, 95% CI)	0.98 [0.55, 1.74]
44 Adverse events: hepato body system in adult treatment (on-treatment)	9	4788	Risk Ratio (IV, Random, 95% CI)	0.83 [0.39, 1.76]
45 Adverse events: renal body system in adult treatment (on-treatment)	11	5205	Risk Ratio (IV, Random, 95% CI)	0.84 [0.41, 1.72]
46 Adverse events: cardiovascular body system in adult treatment (on-treatment)	11	5204	Risk Ratio (IV, Random, 95% CI)	0.98 [0.50, 1.91]
47 Adverse events: blood body system in adult treatment (on-treatment)	11	5272	Risk Ratio (IV, Random, 95% CI)	0.80 [0.43, 1.49]
48 Adverse events: psychiatric body system in adult treatment (on-treatment)	10	4732	Risk Ratio (IV, Random, 95% CI)	1.16 [0.57, 2.38]
49 Adverse events: reproduction body system in adult treatment (on-treatment)	9	4924	Risk Ratio (IV, Random, 95% CI)	0.68 [0.33, 1.43]
50 Adverse events: endocrine and metabolic body system in adult treatment (on-treatment)	11	5477	Risk Ratio (IV, Random, 95% CI)	0.94 [0.58, 1.53]
51 Adverse events: injury body system in adult treatment (on-treatment)	9	5293	Risk Ratio (IV, Random, 95% CI)	1.22 [0.57, 2.60]
52 Adverse events: non-site specific events in adult treatment (on-treatment)	12	6065	Risk Ratio (IV, Random, 95% CI)	1.04 [0.78, 1.39]
53 Adverse events: nausea/vomiting in adult treatment (off-treatment)	10	5403	Risk Ratio (IV, Random, 95% CI)	1.12 [0.67, 1.85]
54 Adverse events: cough in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	0.96 [0.71, 1.29]
55 Adverse events: respiratory body system in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	0.90 [0.71, 1.14]
56 Adverse events: headache in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	0.91 [0.69, 1.20]
57 Adverse events: diarrhoea in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	1.01 [0.59, 1.72]
58 Adverse events: fatigue in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	0.70 [0.37, 1.32]
59 Adverse events: gastrointestinal body system in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	0.97 [0.73, 1.29]

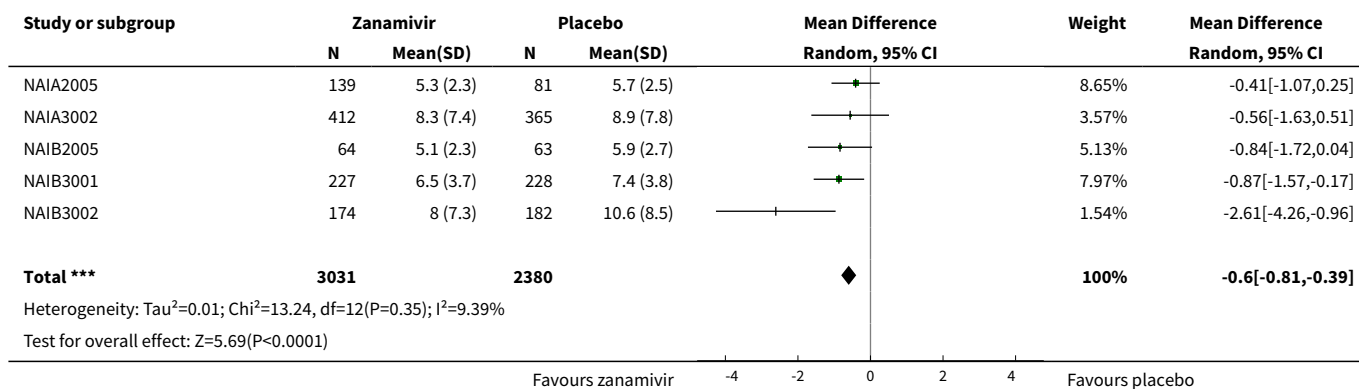
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
60 Adverse events: neurological body system in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	0.91 [0.72, 1.16]
61 Adverse events: ear, nose and throat in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	1.04 [0.91, 1.19]
62 Adverse events: skin body system in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	1.10 [0.68, 1.78]
63 Adverse events: musculoskeletal body system in adult treatment (off-treatment)	11	5369	Risk Ratio (IV, Random, 95% CI)	1.16 [0.87, 1.55]
64 Adverse events: non-site specific in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	0.76 [0.56, 1.03]
65 Adverse events: injury body system in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	1.14 [0.60, 2.15]
66 Adverse events: endocrine and metabolic body system in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	0.90 [0.49, 1.68]
67 Adverse events: eye body system in adult treatment (off-treatment)	11	5599	Risk Ratio (IV, Random, 95% CI)	1.11 [0.55, 2.24]
68 Time to first alleviation of symptoms in adults with/without relief medication [days]	7	3396	Mean Difference (IV, Random, 95% CI)	0.41 [-0.47, 1.29]
69 Time to first alleviation of symptoms in adults by infection status [days]	12	4873	Mean Difference (IV, Random, 95% CI)	-0.57 [-0.78, -0.37]
69.1 Influenza-infected	12	3233	Mean Difference (IV, Random, 95% CI)	-0.67 [-0.99, -0.35]
69.2 Not influenza-infected	12	1640	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.86, -0.18]

Analysis 3.1. Comparison 3 Zanamivir versus placebo for treatment, Outcome 1 Time to first alleviation of symptoms in adult treatment (days).

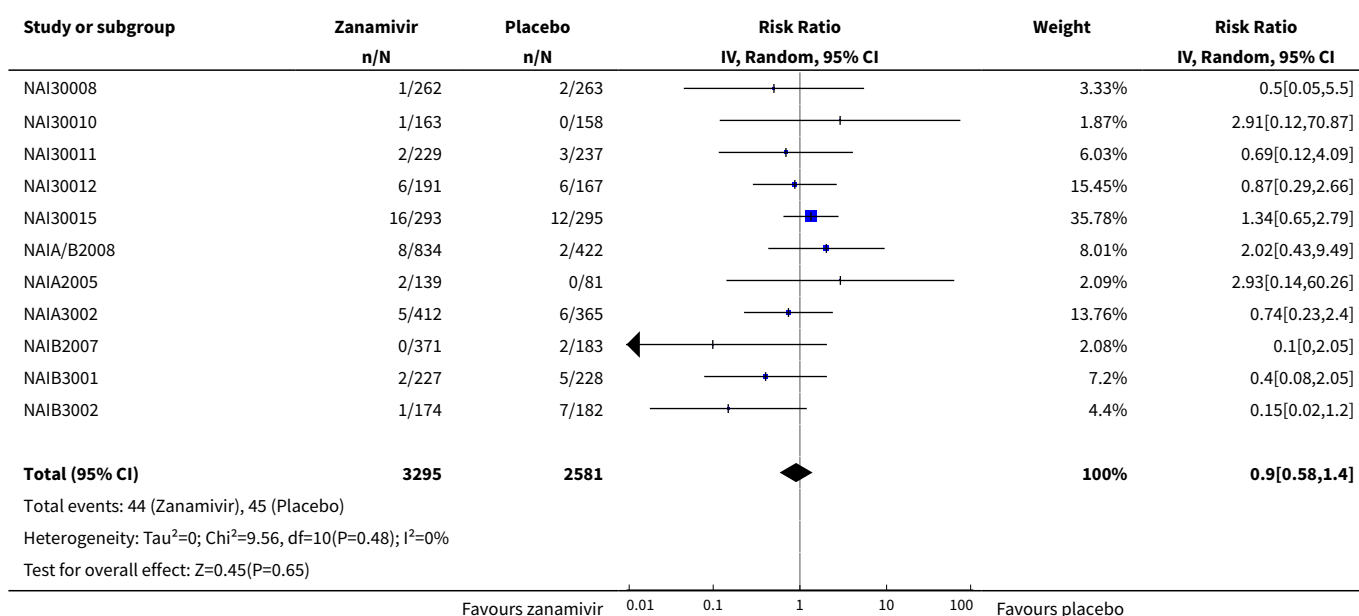
Study or subgroup	Zanamivir		Placebo		Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
JNAI-01	29	3.1 (1.3)	31	3.9 (1)		10.66%	-0.77[-1.36,-0.18]
JNAI-04	32	3.8 (2.1)	16	5.7 (2.8)		1.8%	-1.84[-3.36,-0.32]
JNAI-07	211	4.4 (2)	107	4.7 (2)		16.29%	-0.26[-0.72,0.2]
NAI30008	262	9.6 (8.1)	263	10.7 (8.5)		2.07%	-1.11[-2.53,0.31]
NAI30010	163	7.1 (6.5)	158	7.9 (6.6)		2.03%	-0.82[-2.25,0.61]
NAI30012	191	10.5 (8.9)	169	10.9 (8.5)		1.31%	-0.48[-2.27,1.31]
NAI30015	293	4.3 (5.2)	295	4.9 (5.6)		5.18%	-0.57[-1.45,0.31]
NAIA/B2008	834	5.9 (2.5)	422	6.3 (2.3)		33.8%	-0.47[-0.74,-0.2]
							

Favours zanamivir

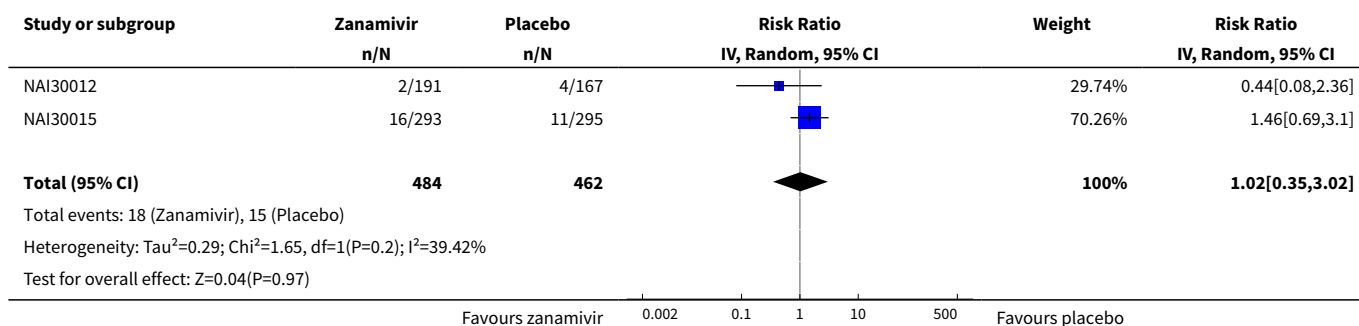
Favours placebo



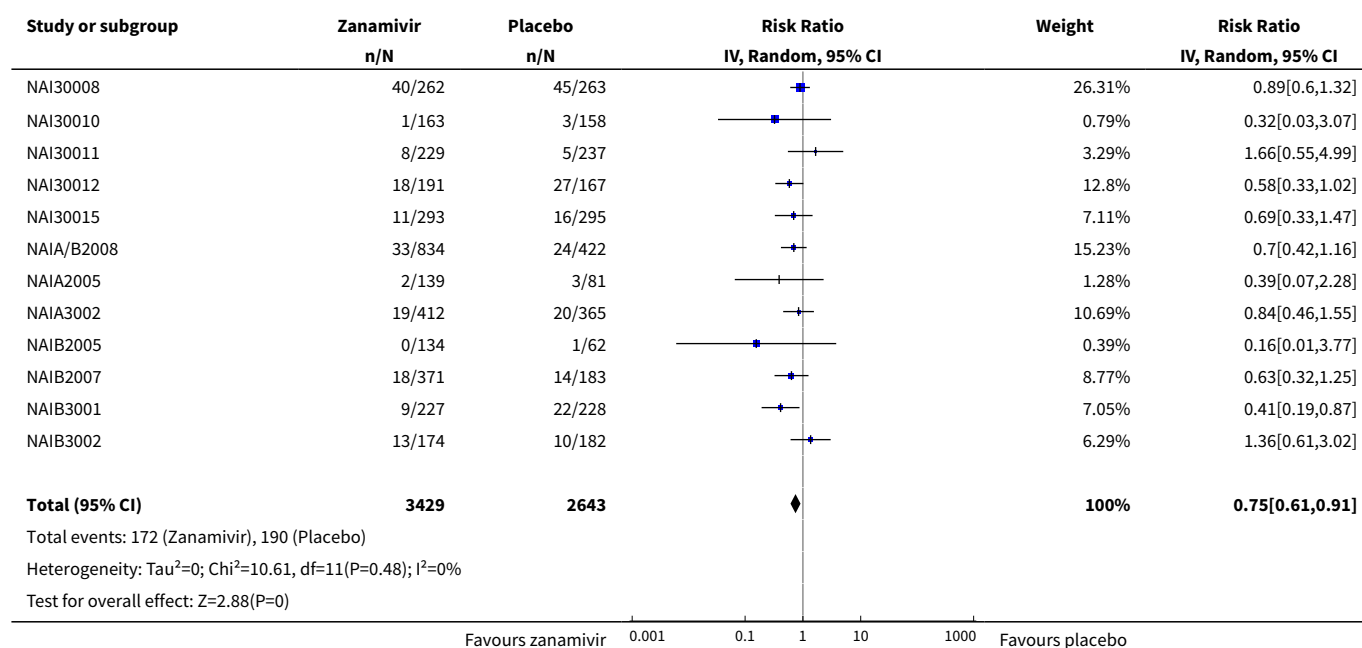
Analysis 3.2. Comparison 3 Zanamivir versus placebo for treatment, Outcome 2 Complications: pneumonia in adult treatment.



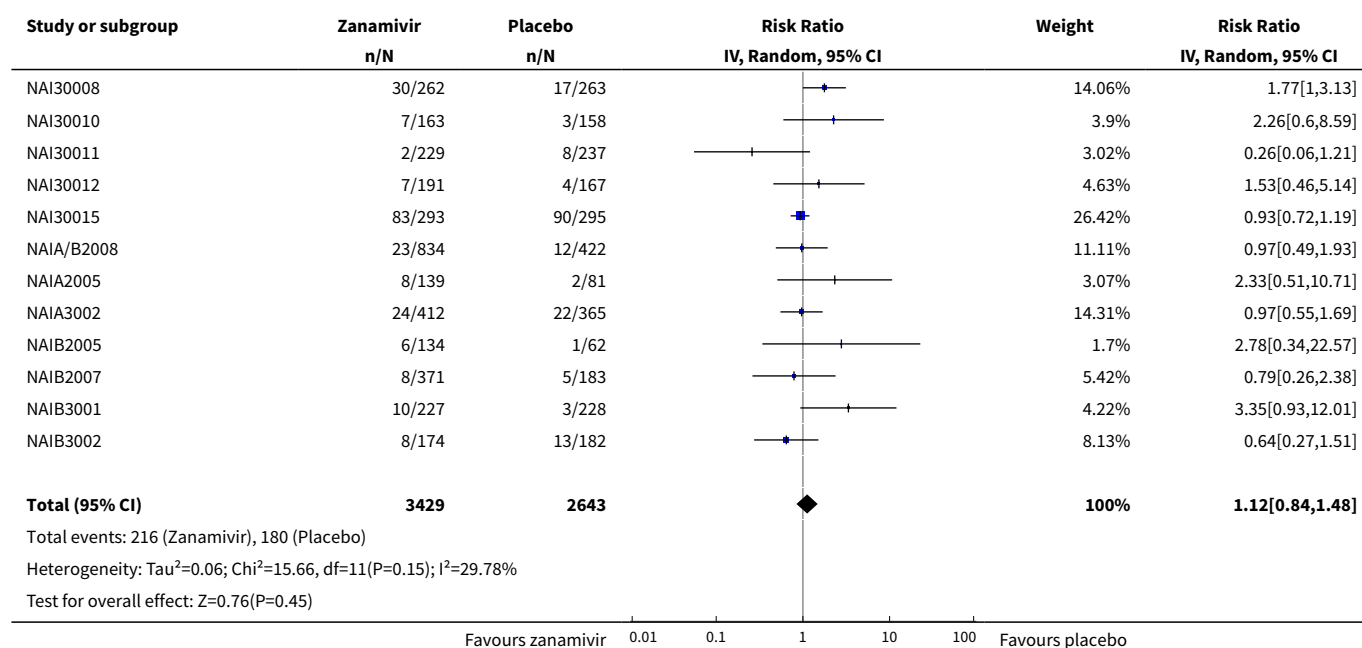
Analysis 3.3. Comparison 3 Zanamivir versus placebo for treatment, Outcome 3 Complications: pneumonia confirmed with X-ray in adult treatment.



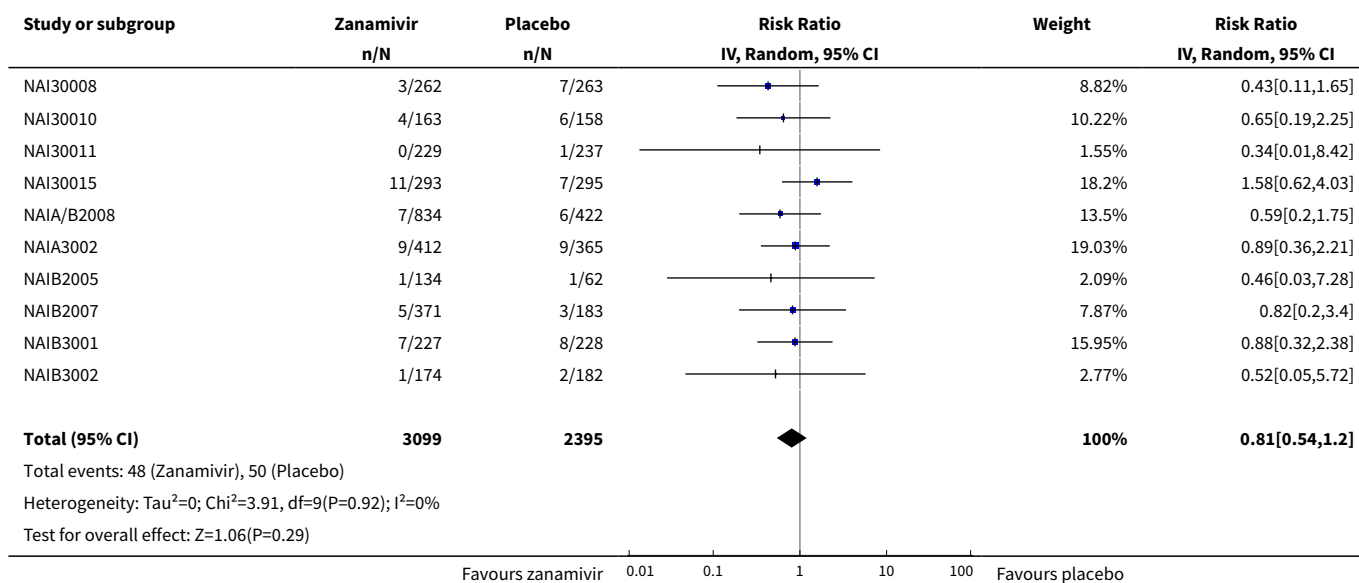
Analysis 3.4. Comparison 3 Zanamivir versus placebo for treatment, Outcome 4 Complications: bronchitis in adult treatment.



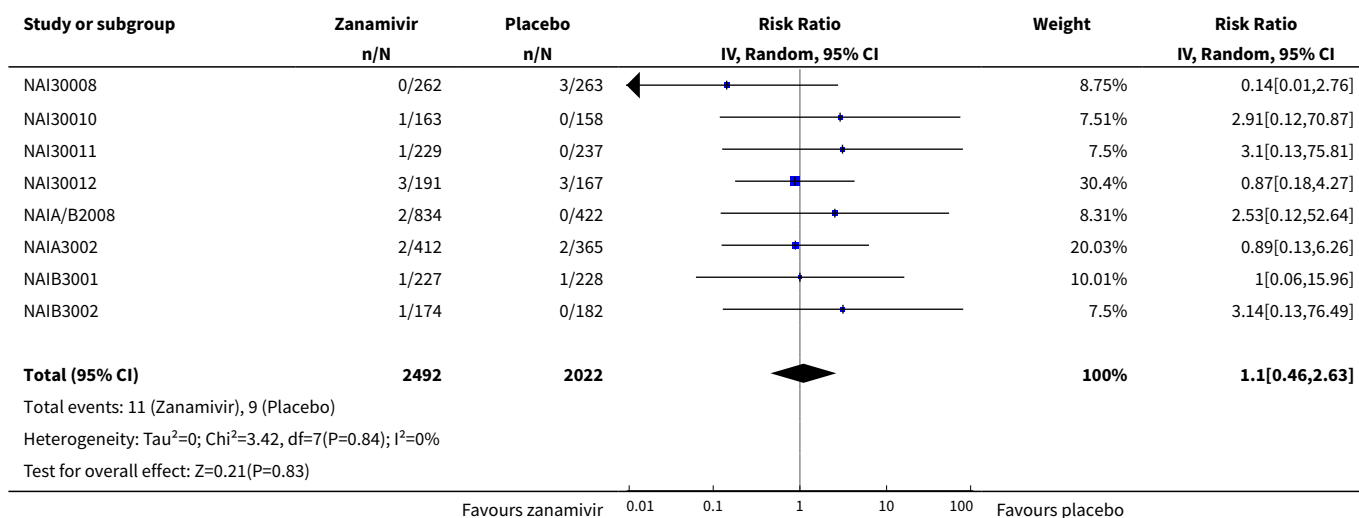
Analysis 3.5. Comparison 3 Zanamivir versus placebo for treatment, Outcome 5 Complications: sinusitis in adult treatment.



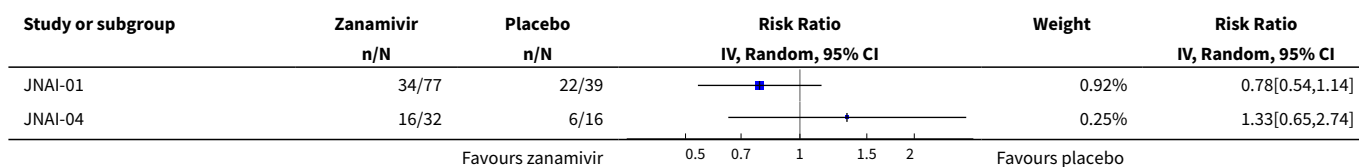
Analysis 3.6. Comparison 3 Zanamivir versus placebo for treatment, Outcome 6 Complications: otitis media in adult treatment.

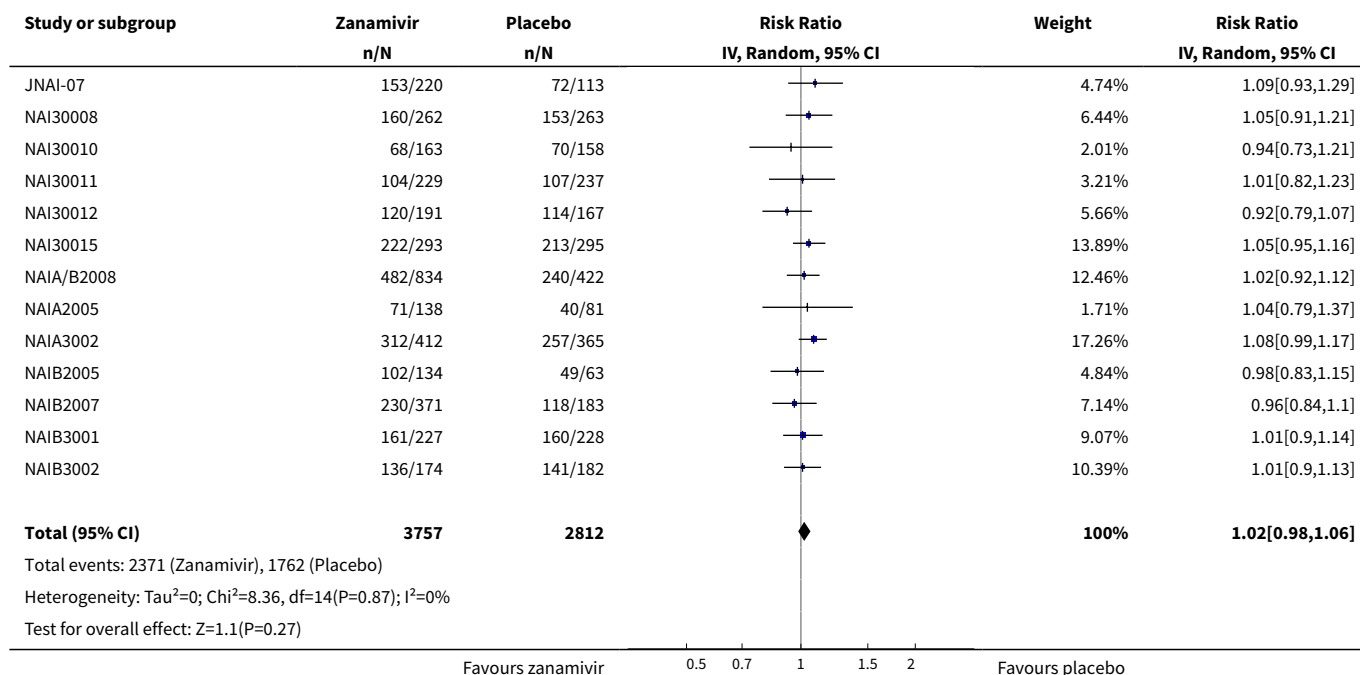


Analysis 3.7. Comparison 3 Zanamivir versus placebo for treatment, Outcome 7 Complications in adult trials classified as serious or leading to study withdrawal.

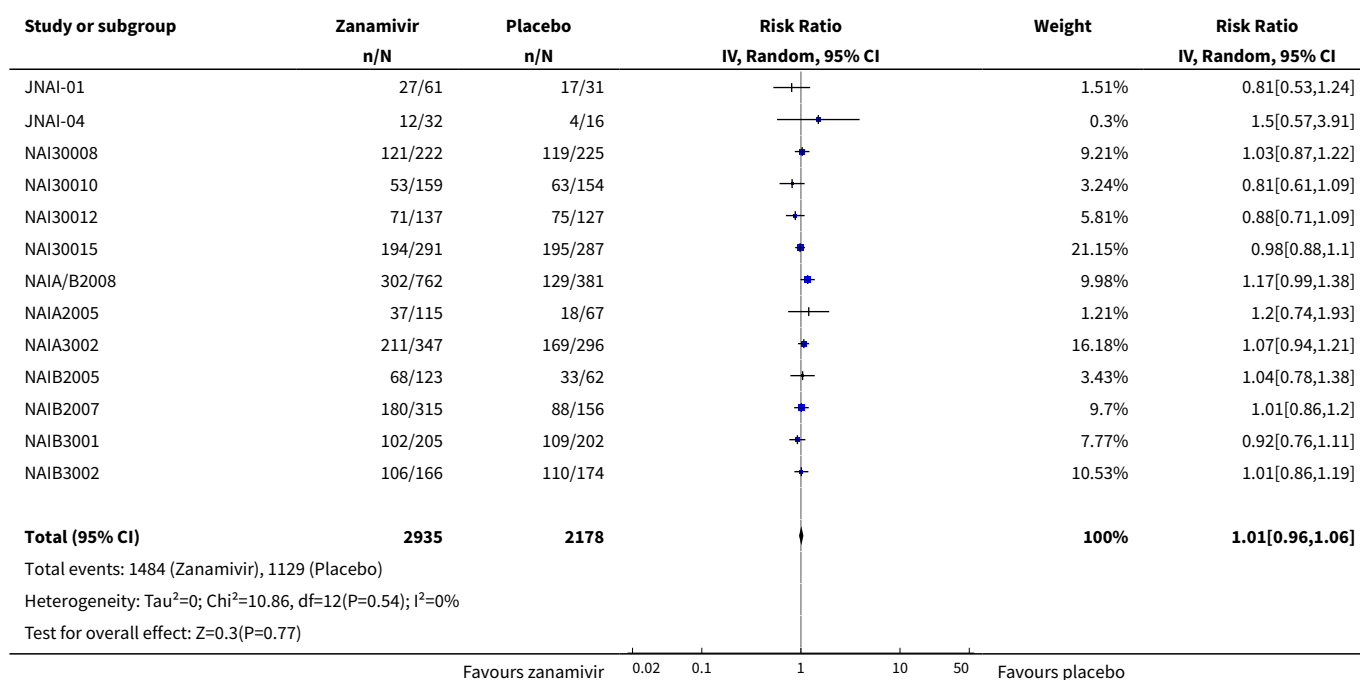


Analysis 3.8. Comparison 3 Zanamivir versus placebo for treatment, Outcome 8 Proportion diagnosed as influenza-infected in adult treatment.

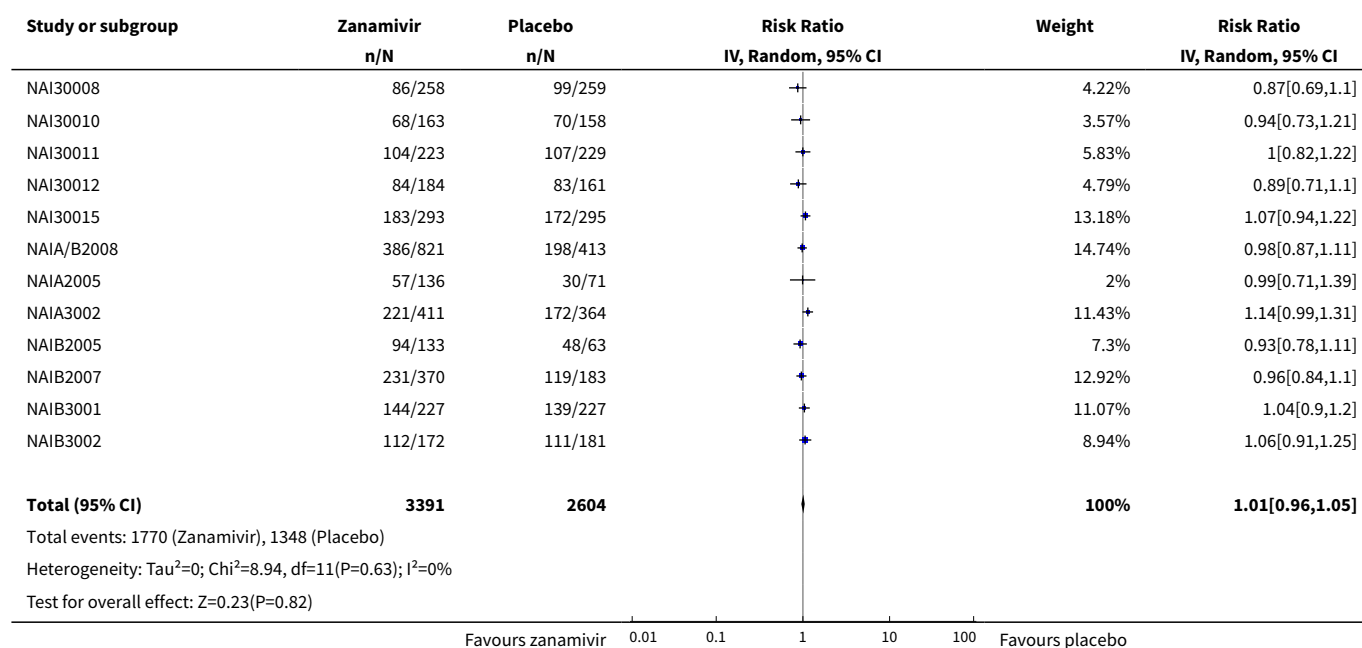




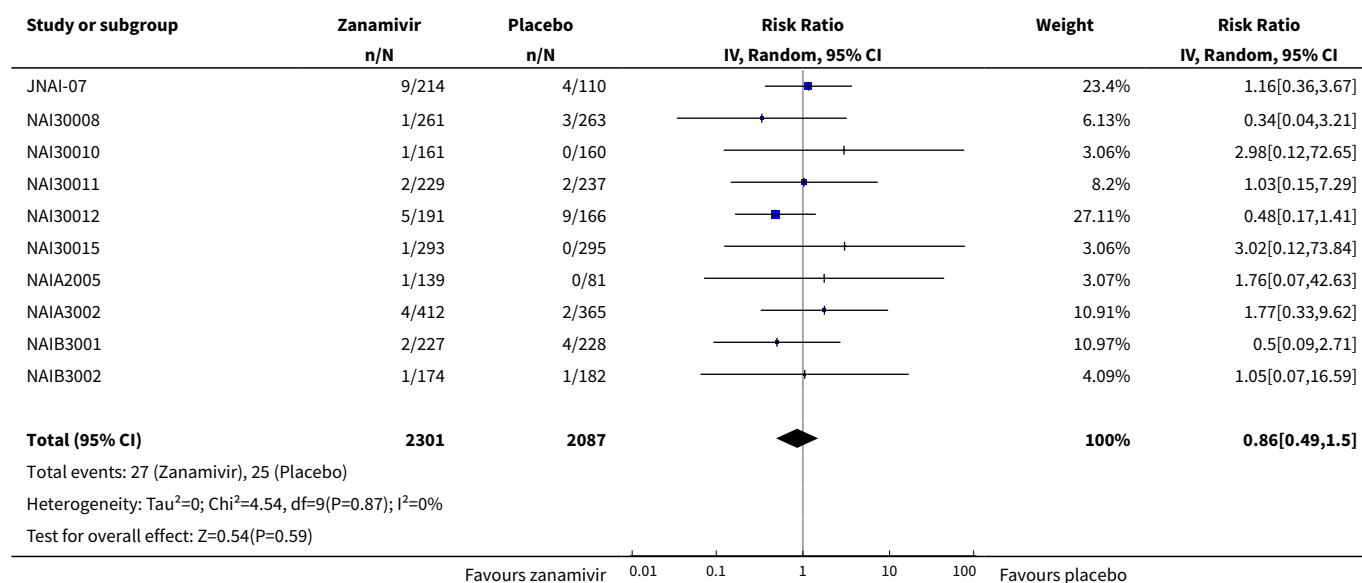
Analysis 3.9. Comparison 3 Zanamivir versus placebo for treatment, Outcome 9 Proportion with four-fold rise in antibody titre in adult treatment.



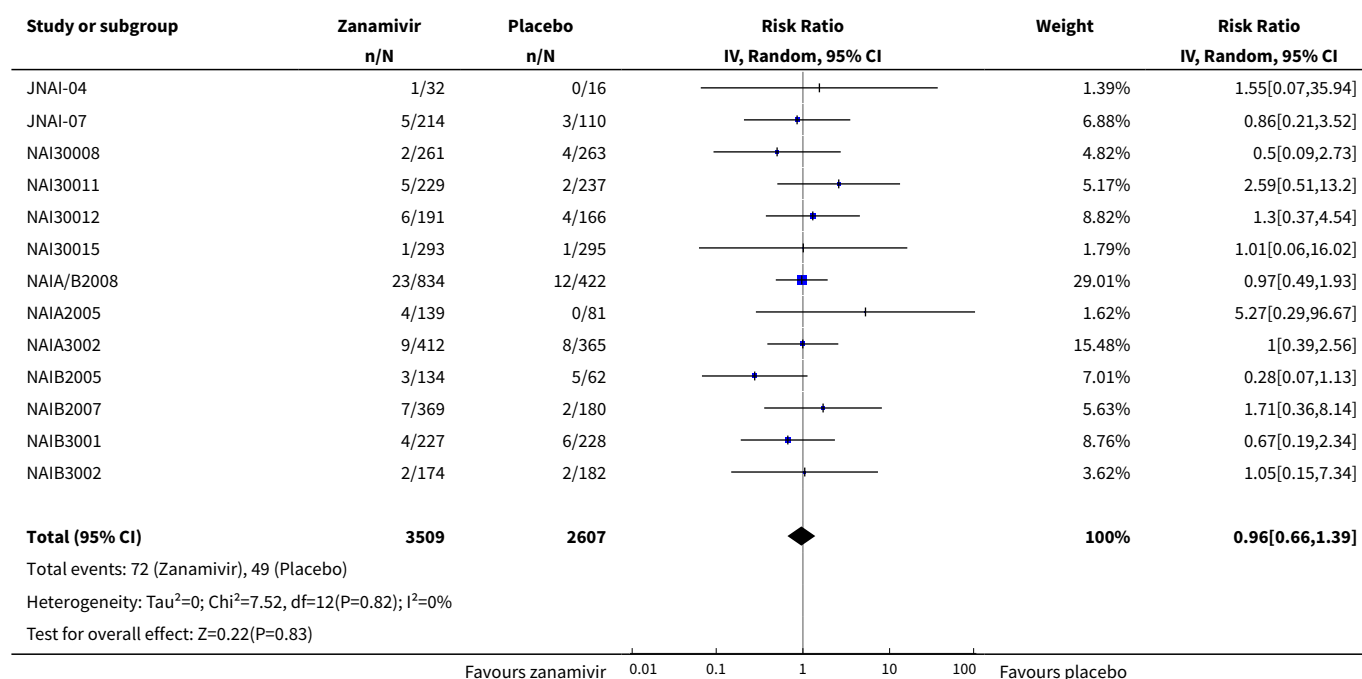
Analysis 3.10. Comparison 3 Zanamivir versus placebo for treatment, Outcome 10 Proportion with positive culture at baseline in adult treatment.



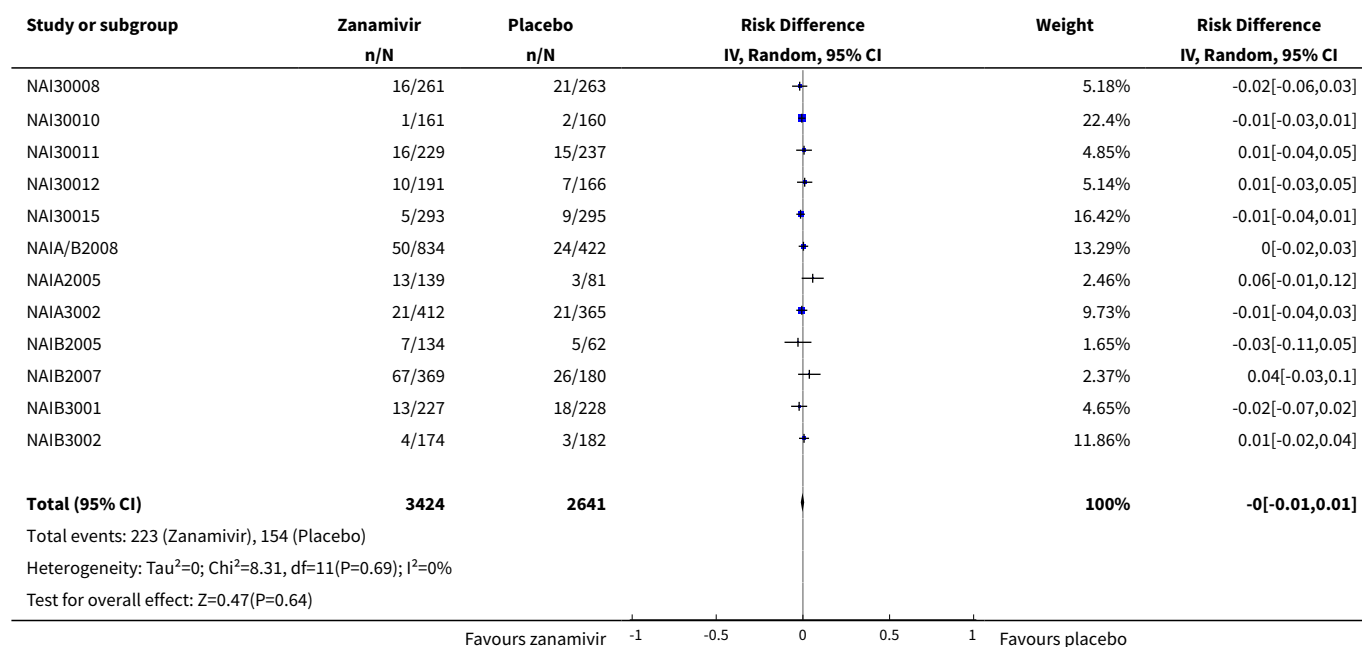
Analysis 3.11. Comparison 3 Zanamivir versus placebo for treatment, Outcome 11 Serious adverse events in adult treatment.



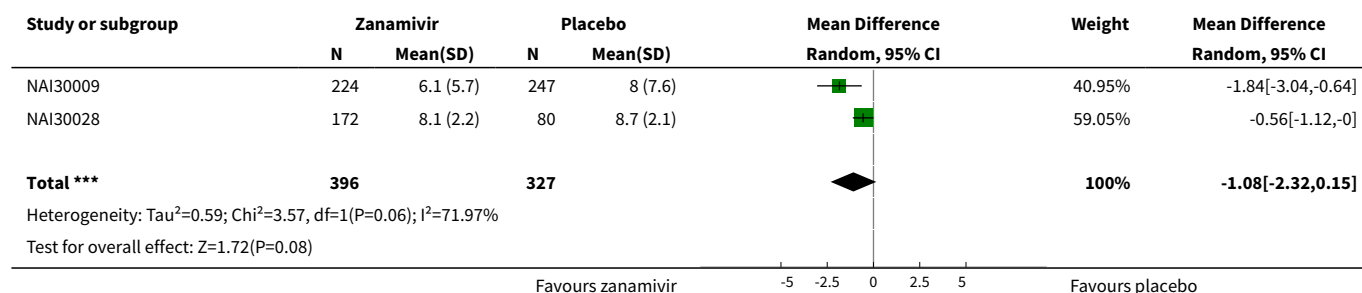
Analysis 3.12. Comparison 3 Zanamivir versus placebo for treatment, Outcome 12 Adverse events leading to study withdrawal in adult treatment.



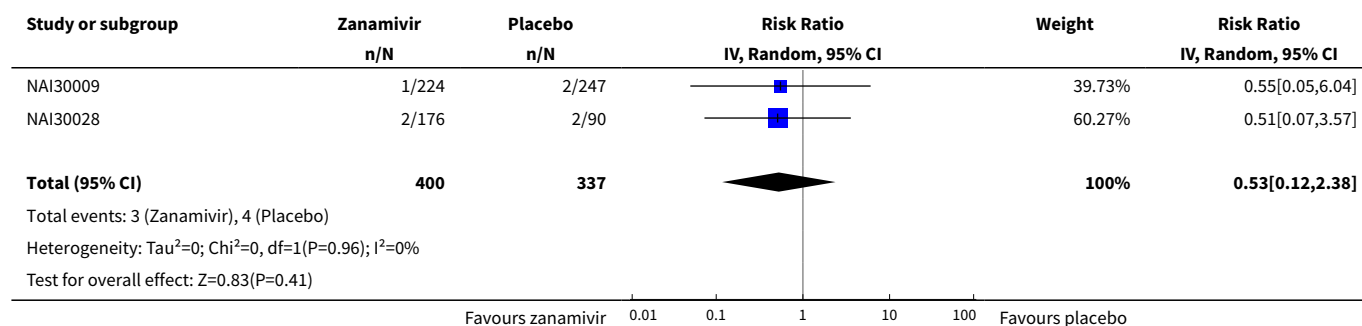
Analysis 3.13. Comparison 3 Zanamivir versus placebo for treatment, Outcome 13 All withdrawals in adult treatment.



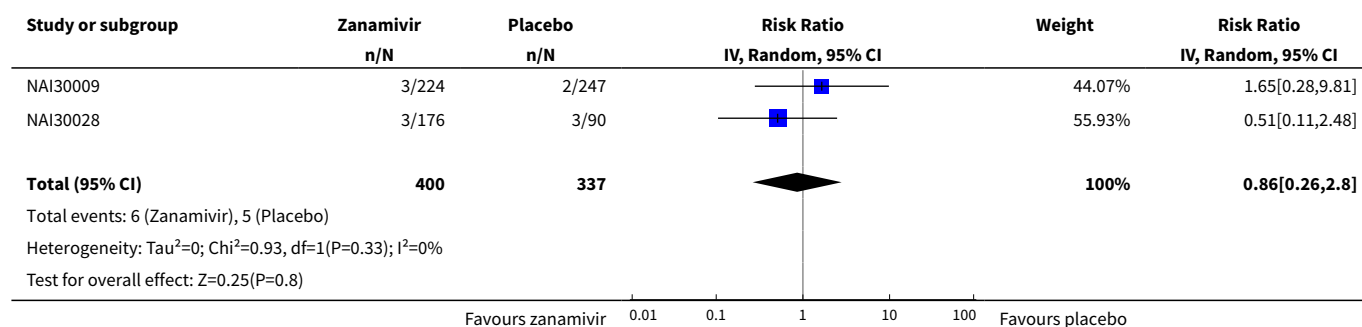
Analysis 3.14. Comparison 3 Zanamivir versus placebo for treatment, Outcome 14 Time to first alleviation of symptoms in children (days).



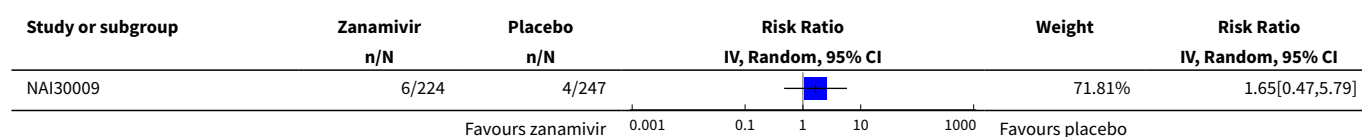
Analysis 3.15. Comparison 3 Zanamivir versus placebo for treatment, Outcome 15 Complications: pneumonia in child treatment.

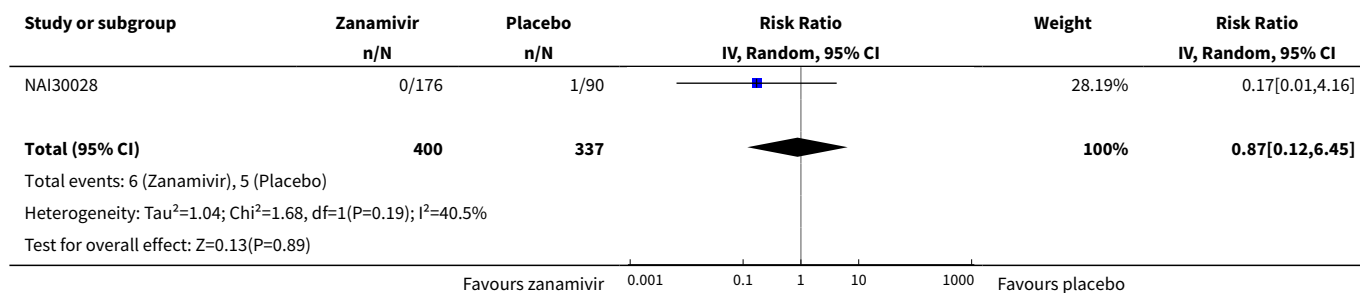


Analysis 3.16. Comparison 3 Zanamivir versus placebo for treatment, Outcome 16 Complications: bronchitis in child treatment.

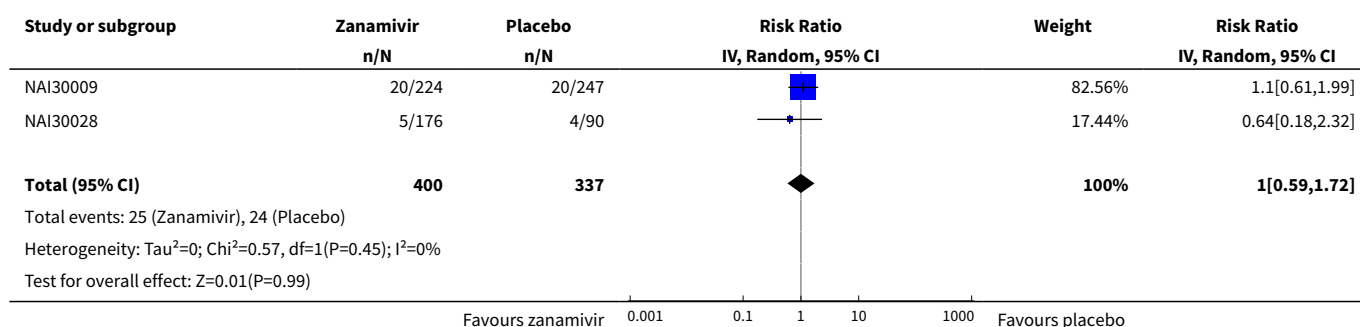


Analysis 3.17. Comparison 3 Zanamivir versus placebo for treatment, Outcome 17 Complications: sinusitis in child treatment.

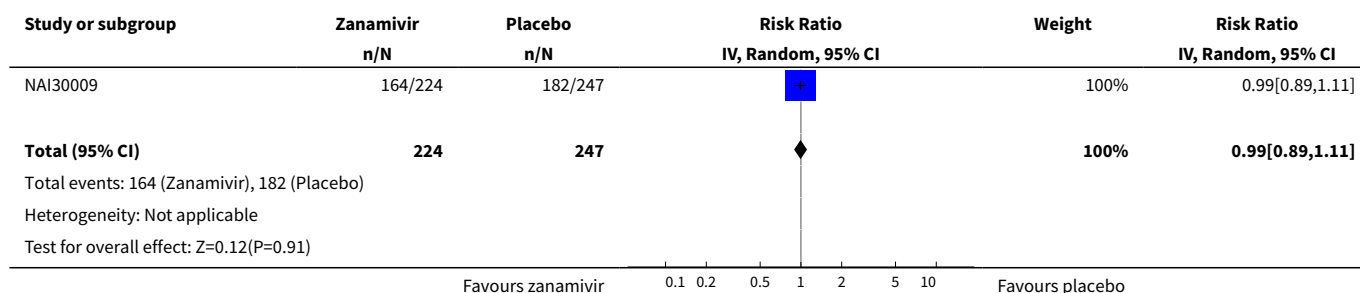




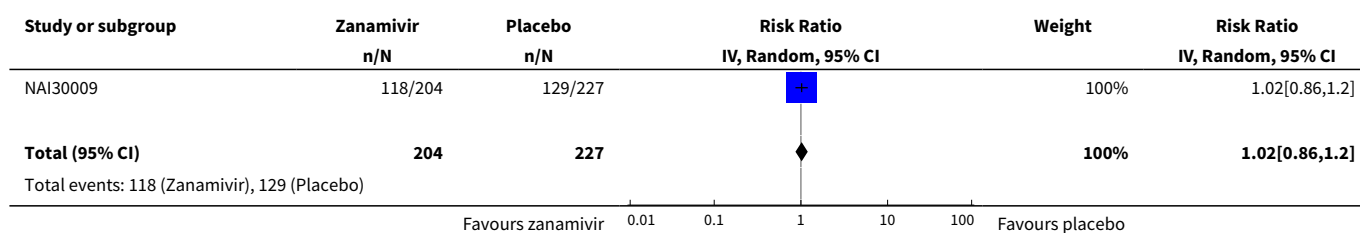
Analysis 3.18. Comparison 3 Zanamivir versus placebo for treatment, Outcome 18 Complications: otitis media in child treatment.

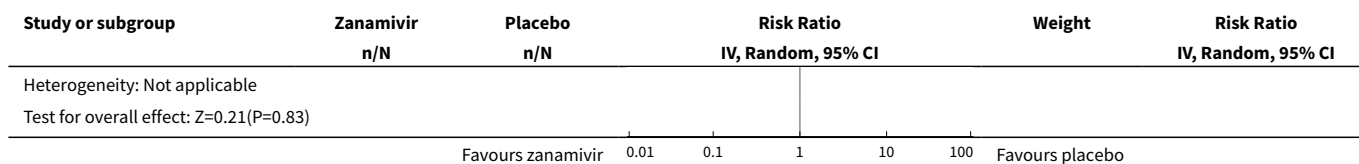


Analysis 3.19. Comparison 3 Zanamivir versus placebo for treatment, Outcome 19 Proportion diagnosed as influenza-infected in child treatment.

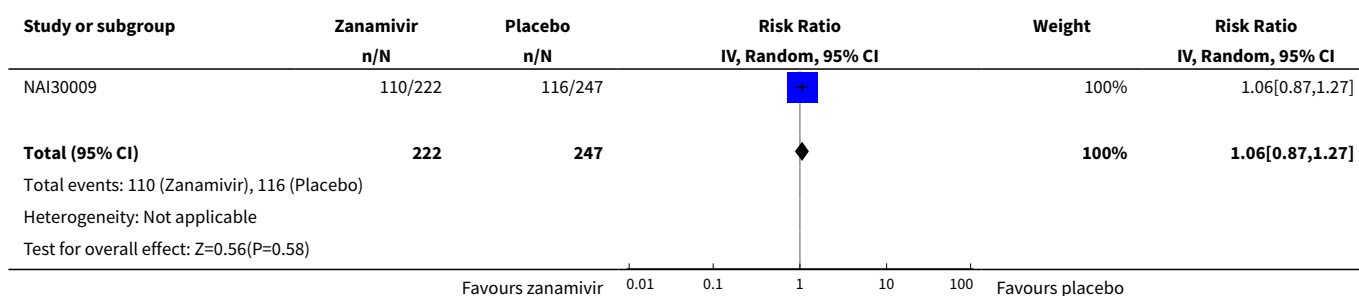


Analysis 3.20. Comparison 3 Zanamivir versus placebo for treatment, Outcome 20 Proportion with four-fold increase in antibodies in child treatment.

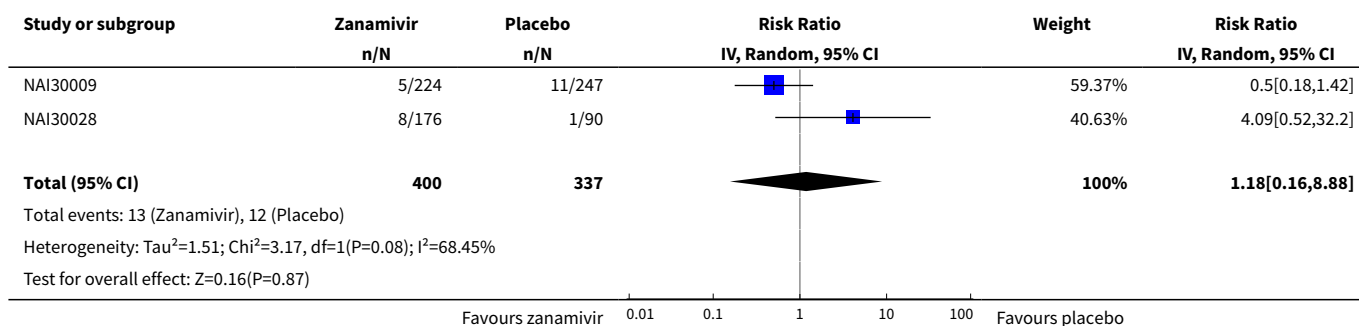




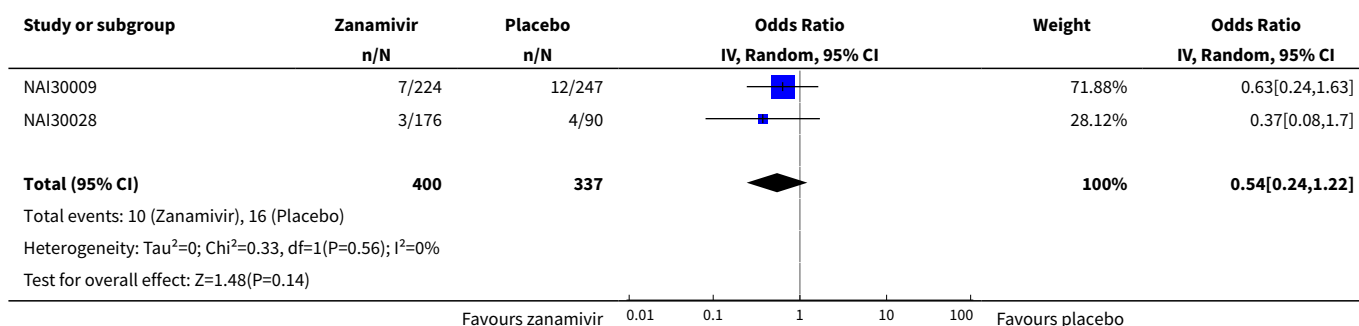
Analysis 3.21. Comparison 3 Zanamivir versus placebo for treatment, Outcome 21 Proportion with positive culture at baseline in child treatment.



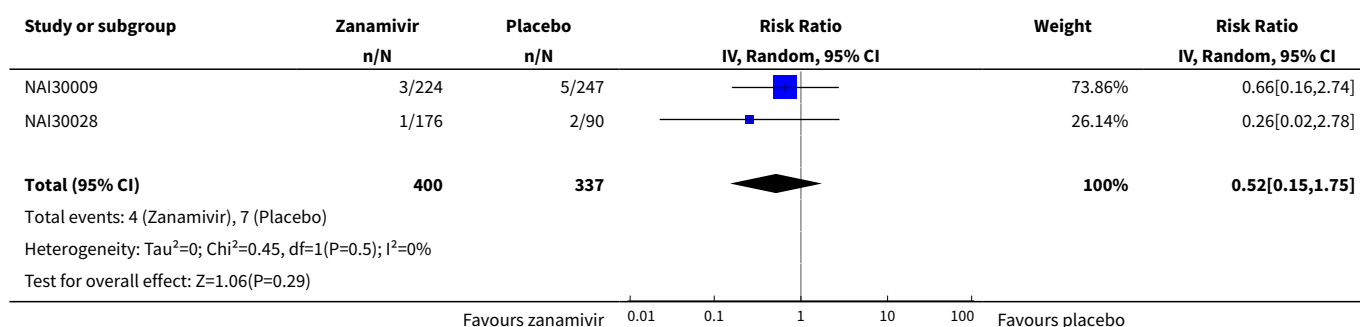
Analysis 3.22. Comparison 3 Zanamivir versus placebo for treatment, Outcome 22 All withdrawals in child treatment.



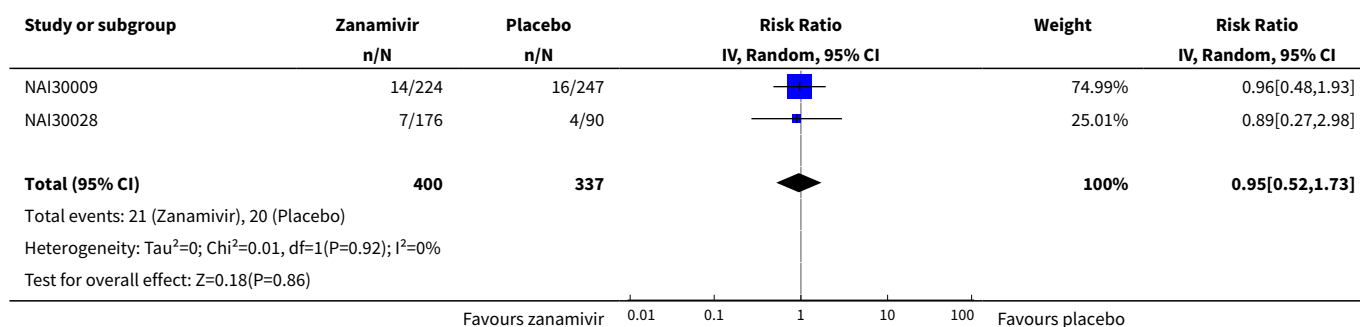
Analysis 3.23. Comparison 3 Zanamivir versus placebo for treatment, Outcome 23 Adverse events: nausea and vomiting in child treatment (on-treatment).



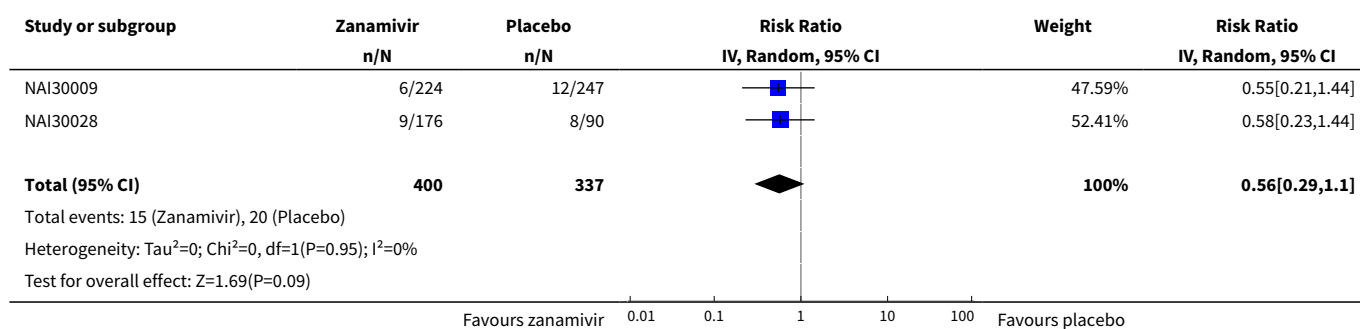
Analysis 3.24. Comparison 3 Zanamivir versus placebo for treatment, Outcome 24 Adverse events: diarrhoea in child treatment (on-treatment).



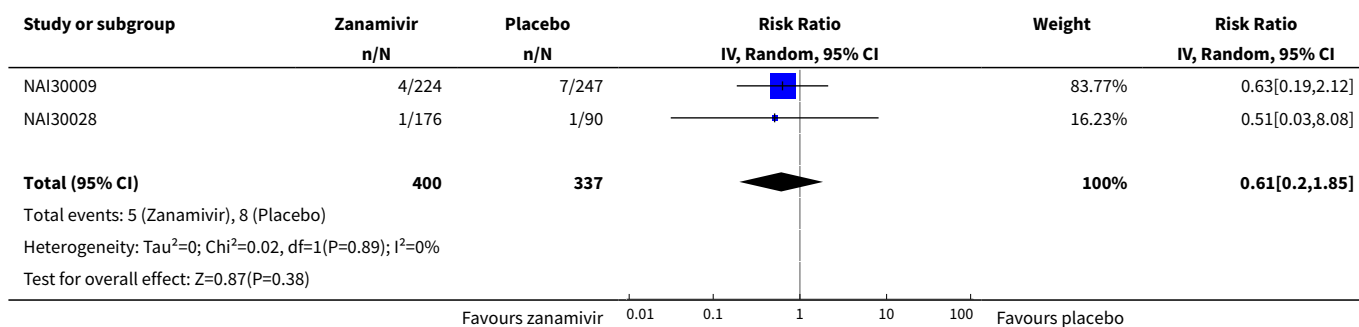
Analysis 3.25. Comparison 3 Zanamivir versus placebo for treatment, Outcome 25 Adverse events: gastrointestinal body system in child treatment (on-treatment).



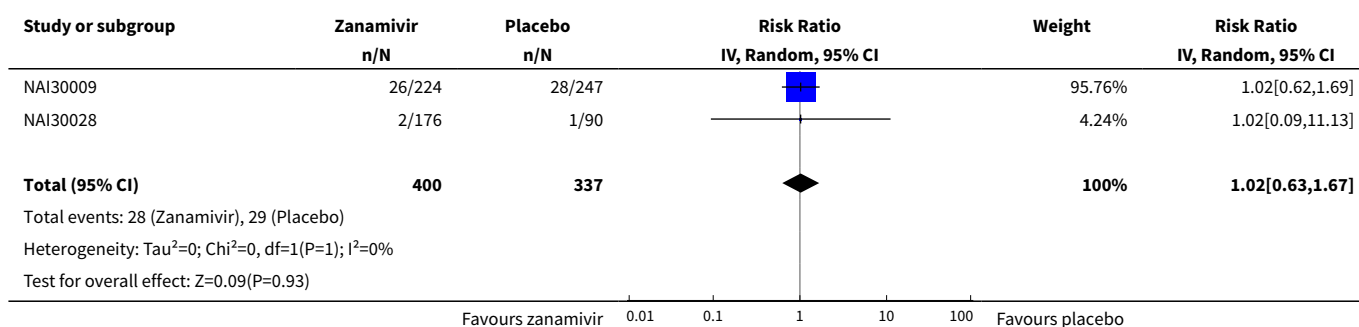
Analysis 3.26. Comparison 3 Zanamivir versus placebo for treatment, Outcome 26 Adverse events: respiratory body system in child treatment (on-treatment).



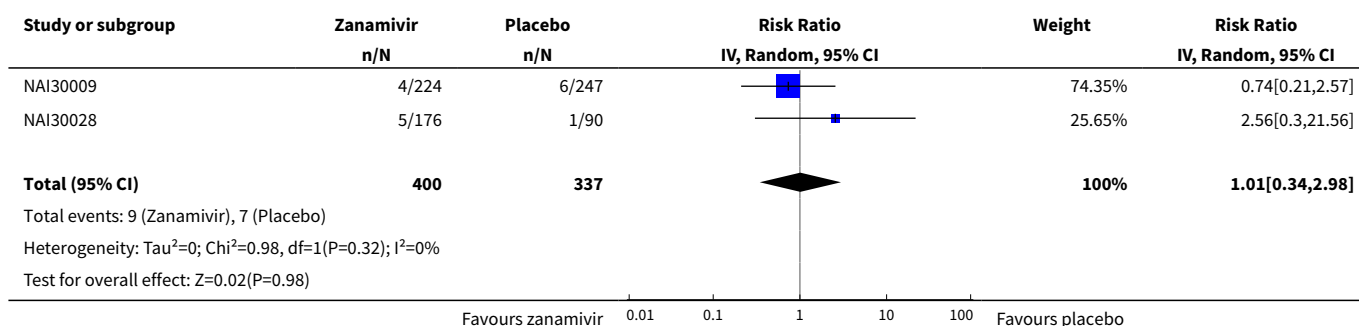
Analysis 3.27. Comparison 3 Zanamivir versus placebo for treatment, Outcome 27 Adverse events: neurological body system in child treatment (on-treatment).



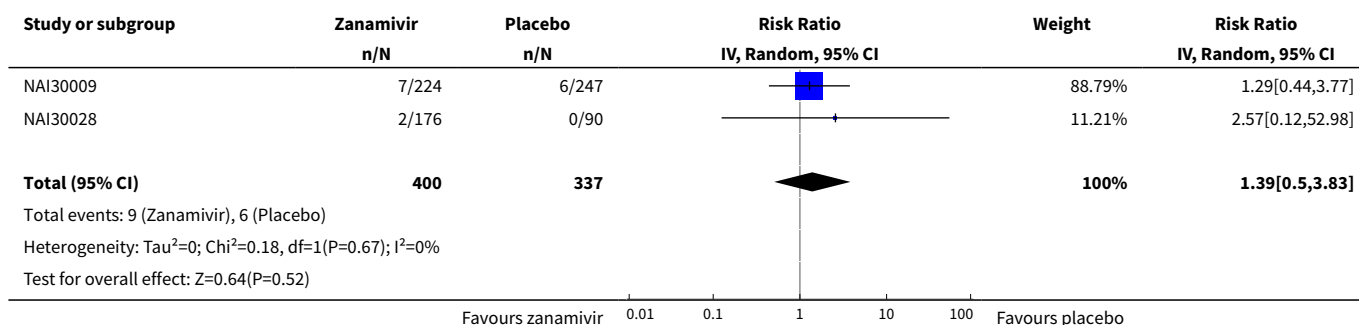
Analysis 3.28. Comparison 3 Zanamivir versus placebo for treatment, Outcome 28 Adverse events: ear, nose and throat body system in child treatment (on-treatment).



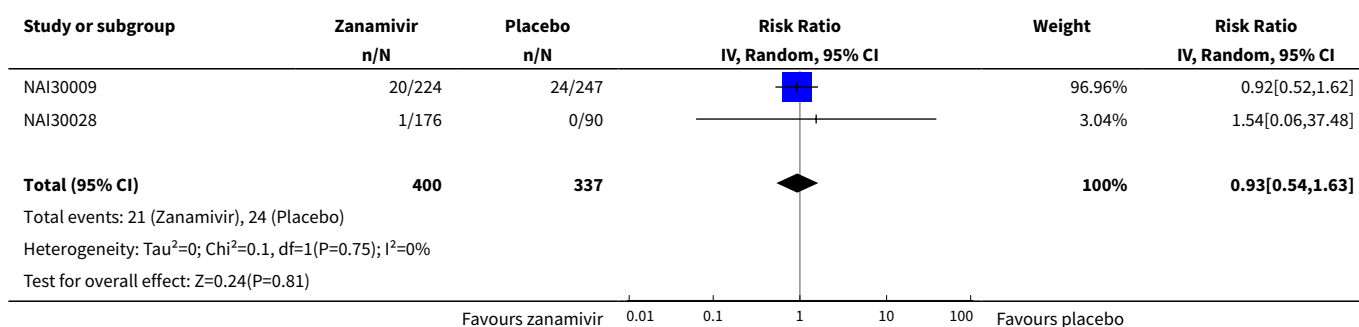
Analysis 3.29. Comparison 3 Zanamivir versus placebo for treatment, Outcome 29 Adverse events: skin body system in child treatment (on-treatment).



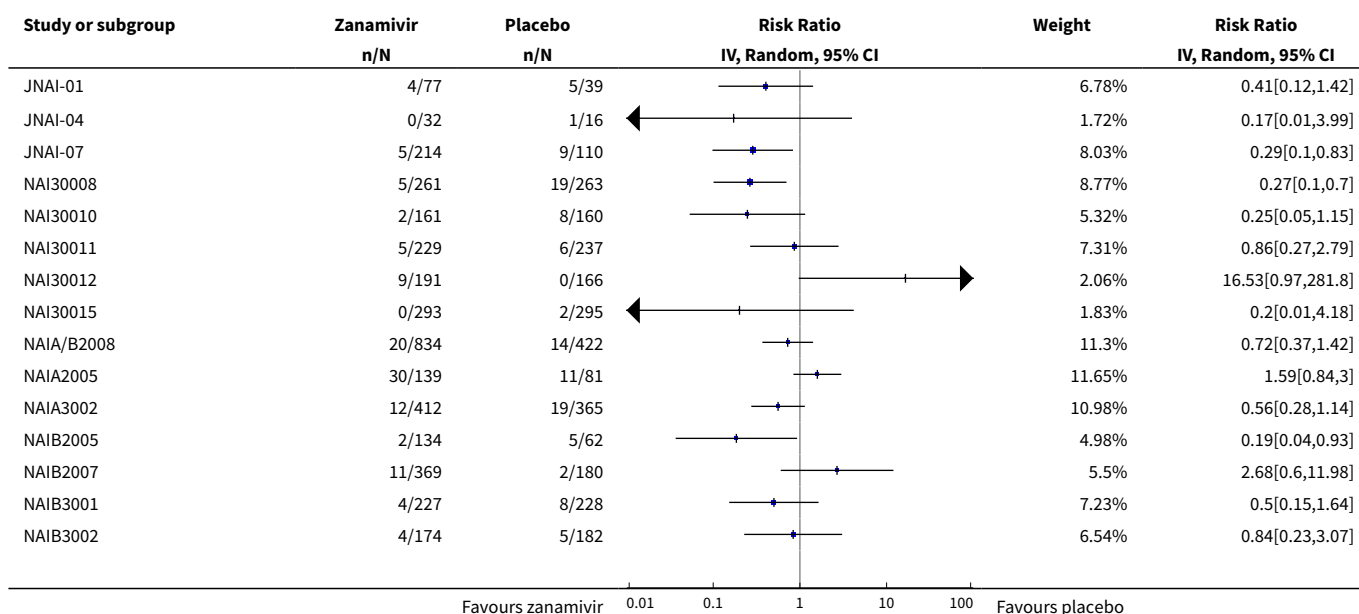
**Analysis 3.30. Comparison 3 Zanamivir versus placebo for treatment, Outcome 30
Adverse events: gastrointestinal body system in child treatment (off-treatment).**

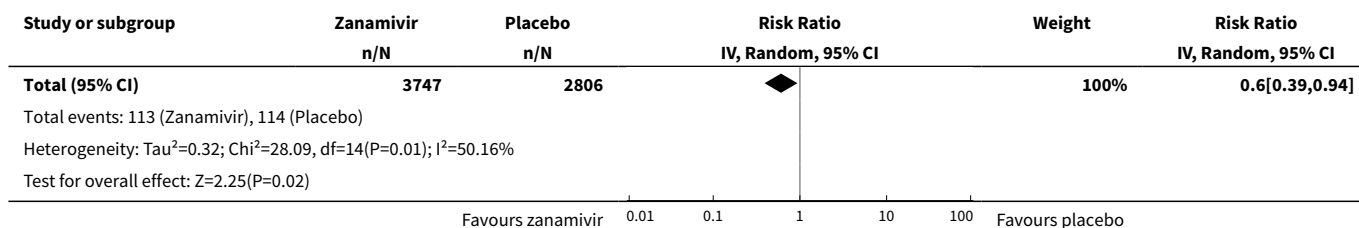


**Analysis 3.31. Comparison 3 Zanamivir versus placebo for treatment, Outcome 31
Adverse events: ear nose and throat body system in child treatment (off-treatment).**

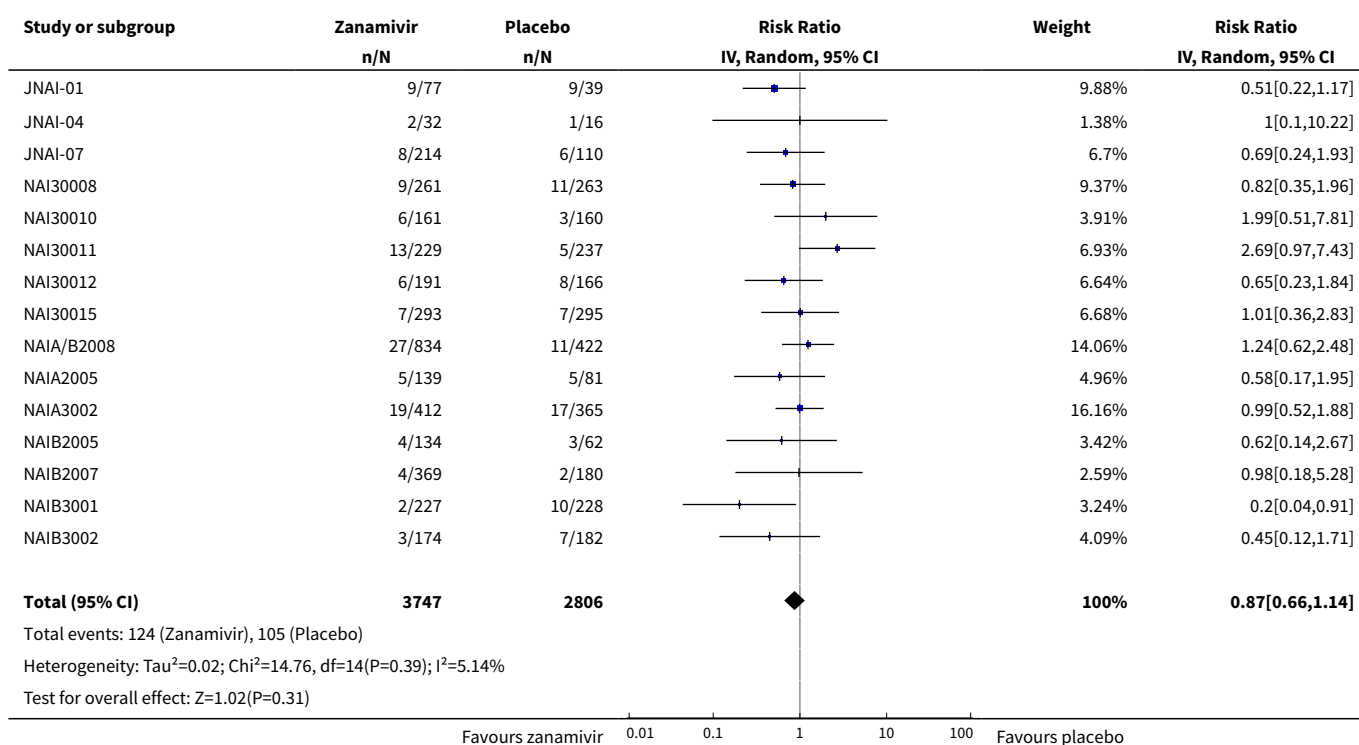


**Analysis 3.32. Comparison 3 Zanamivir versus placebo for treatment, Outcome 32
Adverse events: nausea/vomiting in adult treatment (on-treatment).**

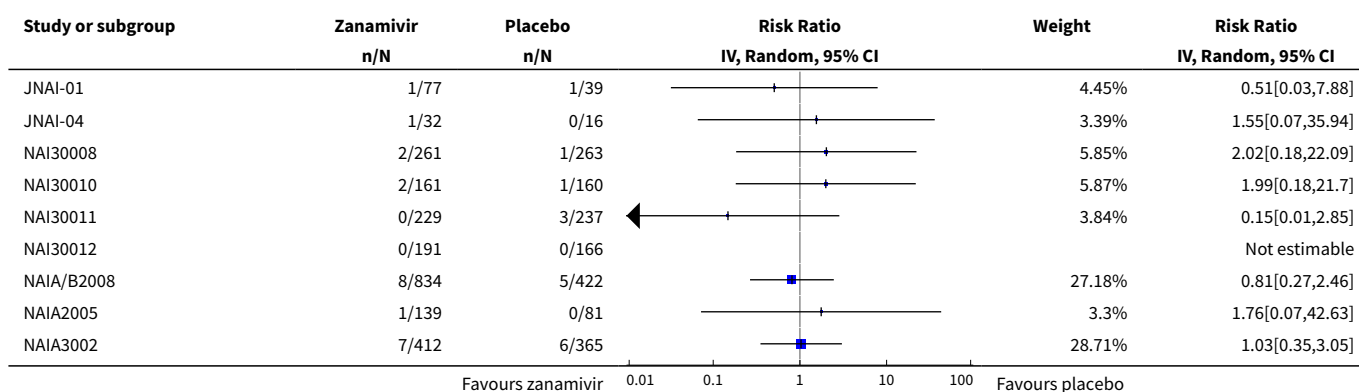


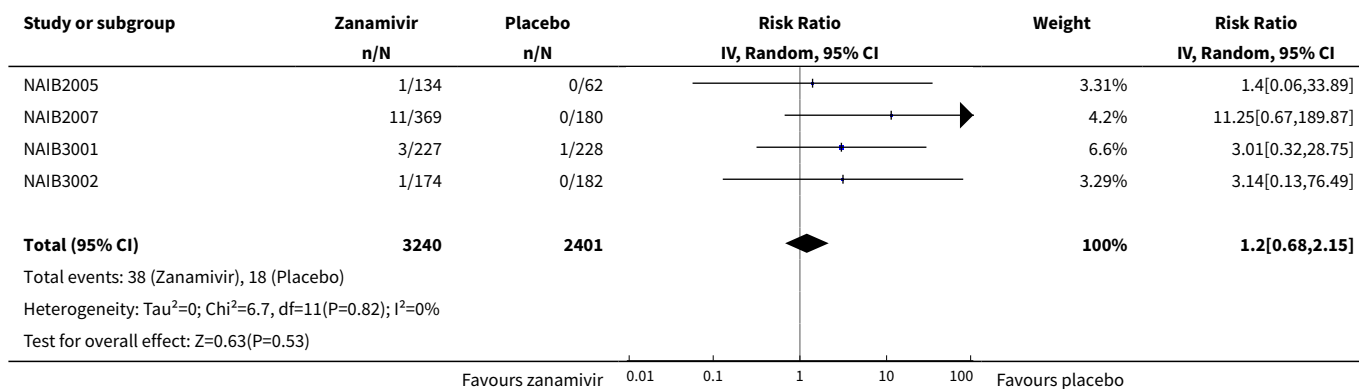


Analysis 3.33. Comparison 3 Zanamivir versus placebo for treatment, Outcome 33 Adverse events: diarrhoea in adult treatment (on-treatment).

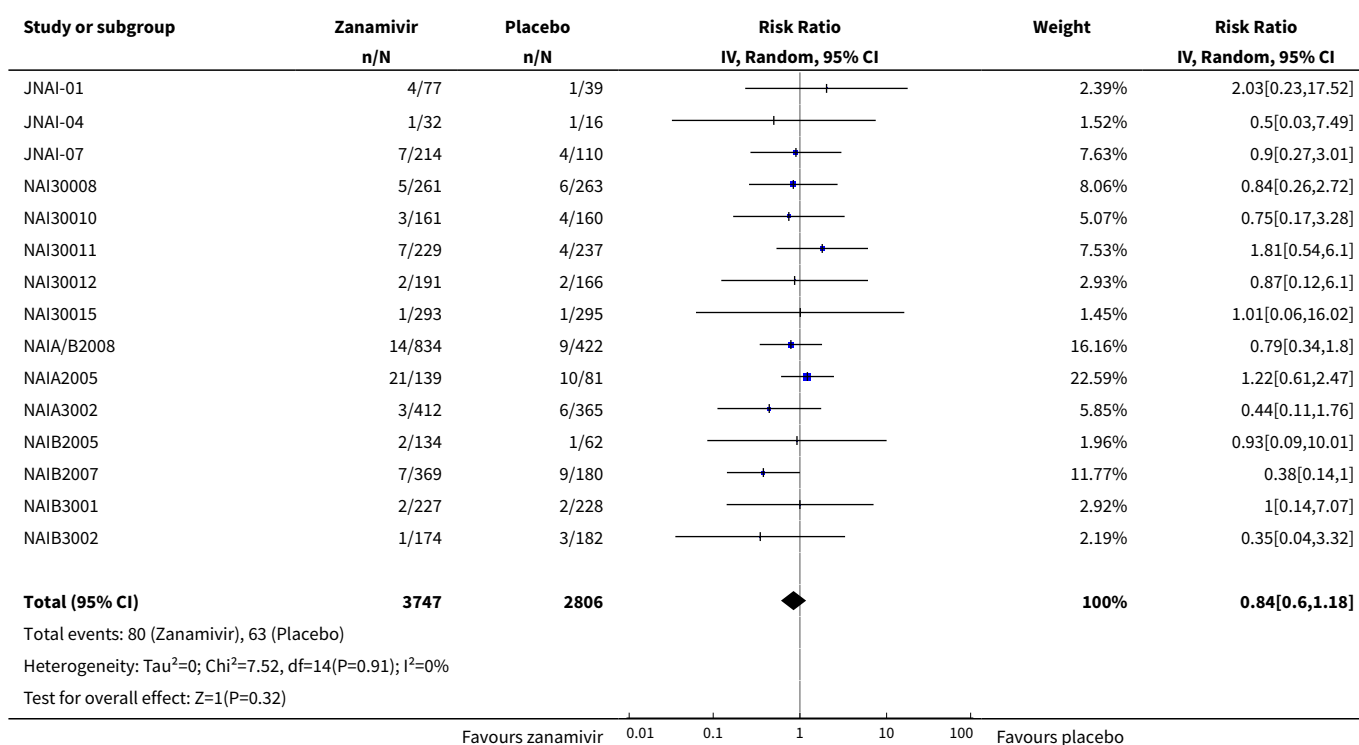


Analysis 3.34. Comparison 3 Zanamivir versus placebo for treatment, Outcome 34 Adverse events: dizziness in adult treatment (on-treatment).

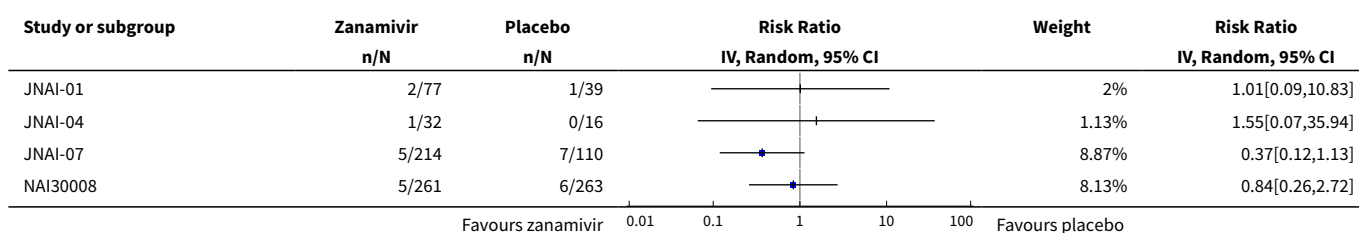


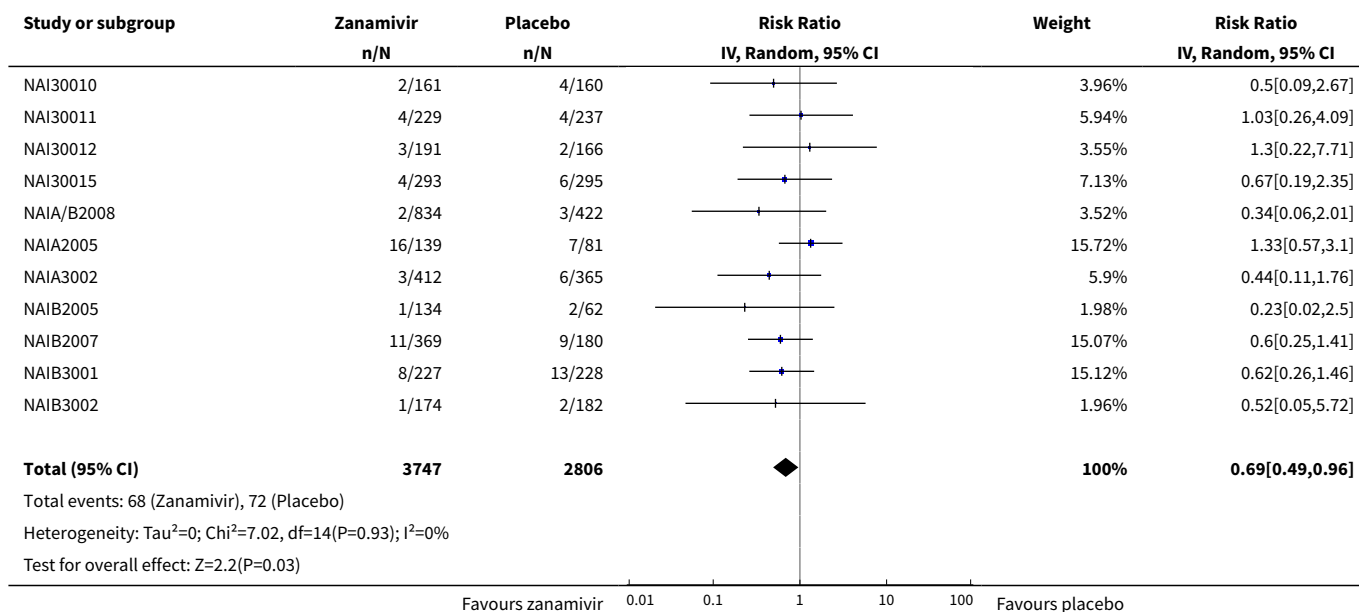


Analysis 3.35. Comparison 3 Zanamivir versus placebo for treatment, Outcome 35 Adverse events: headache in adult treatment (on-treatment).

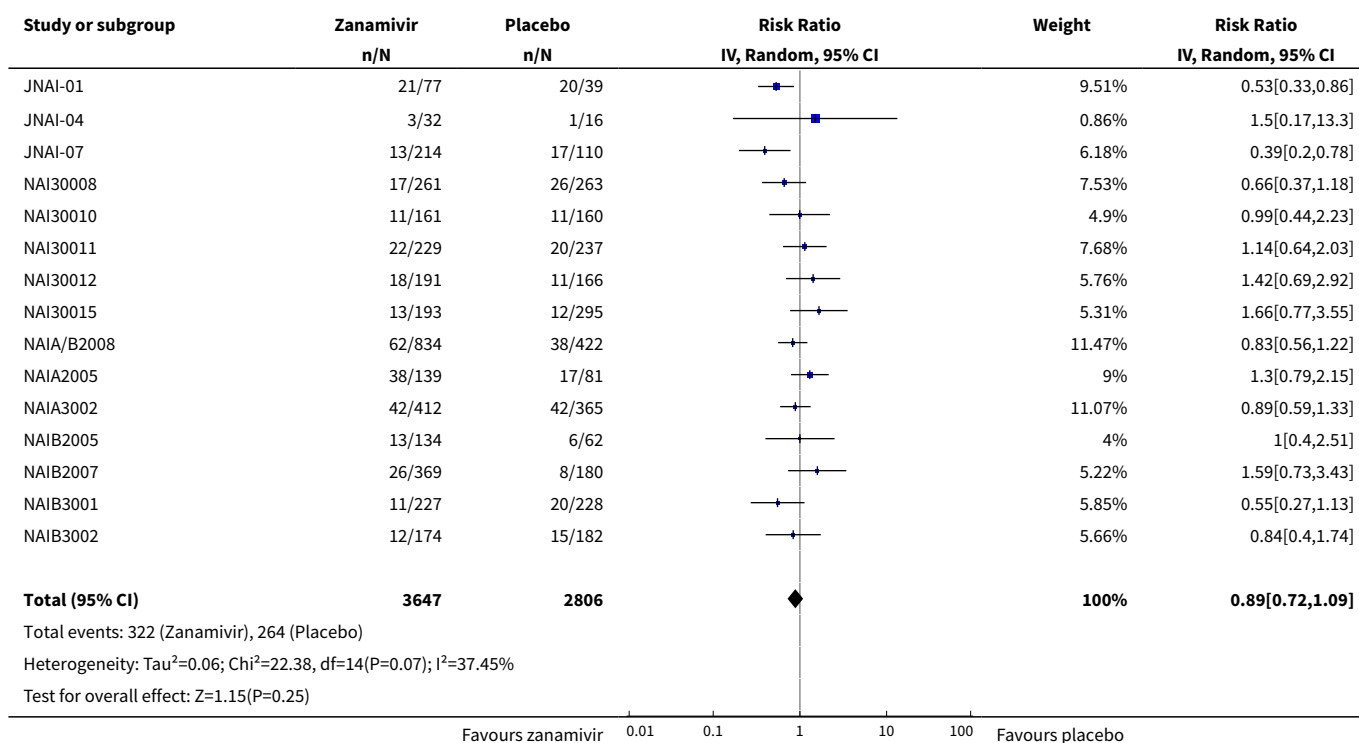


Analysis 3.36. Comparison 3 Zanamivir versus placebo for treatment, Outcome 36 Adverse events: cough in adult treatment (on-treatment).

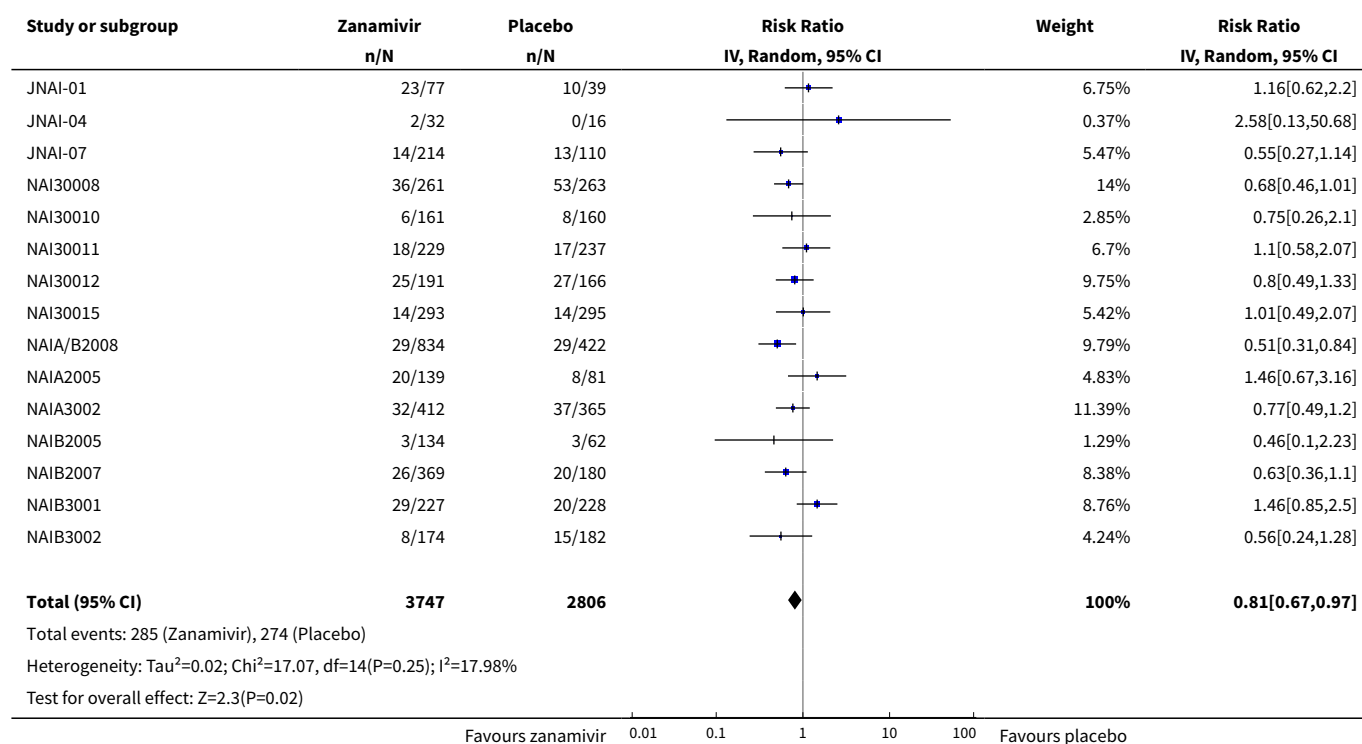




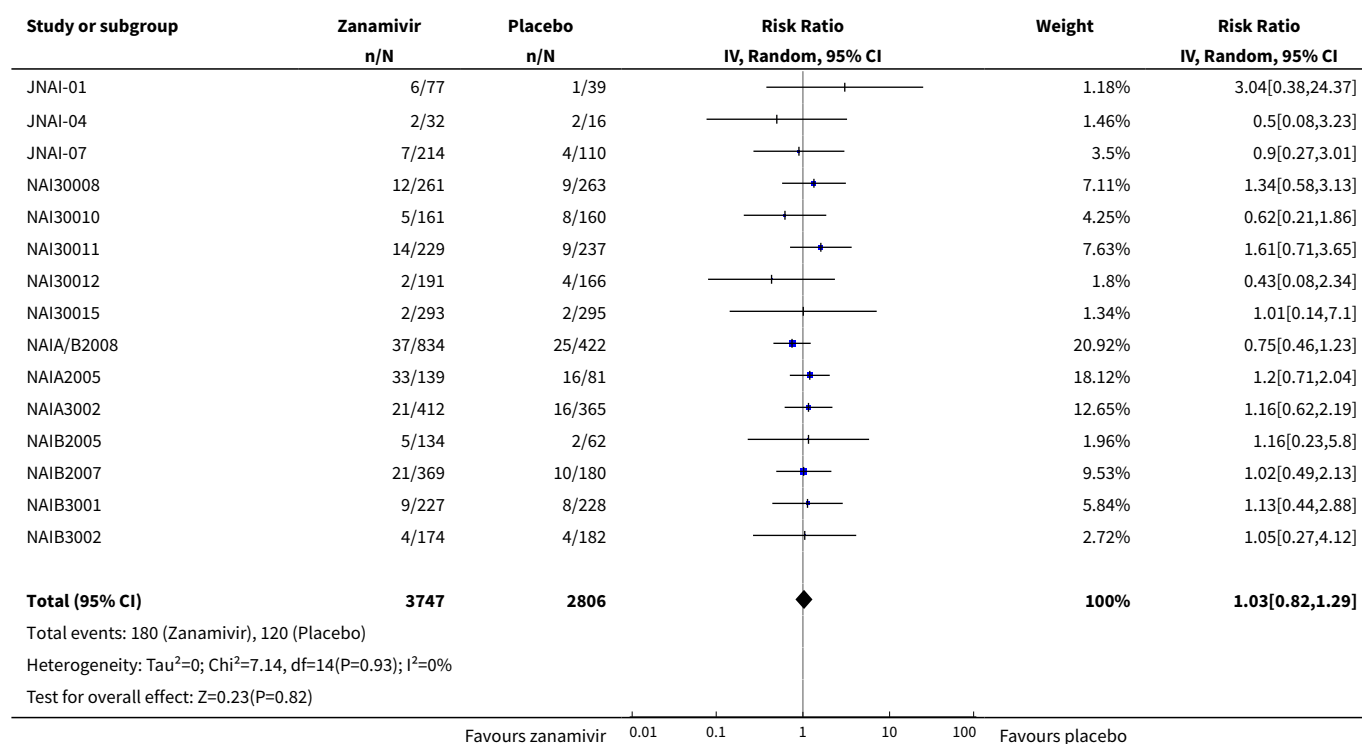
Analysis 3.37. Comparison 3 Zanamivir versus placebo for treatment, Outcome 37 Adverse events: gastrointestinal body system in adult treatment (on-treatment).

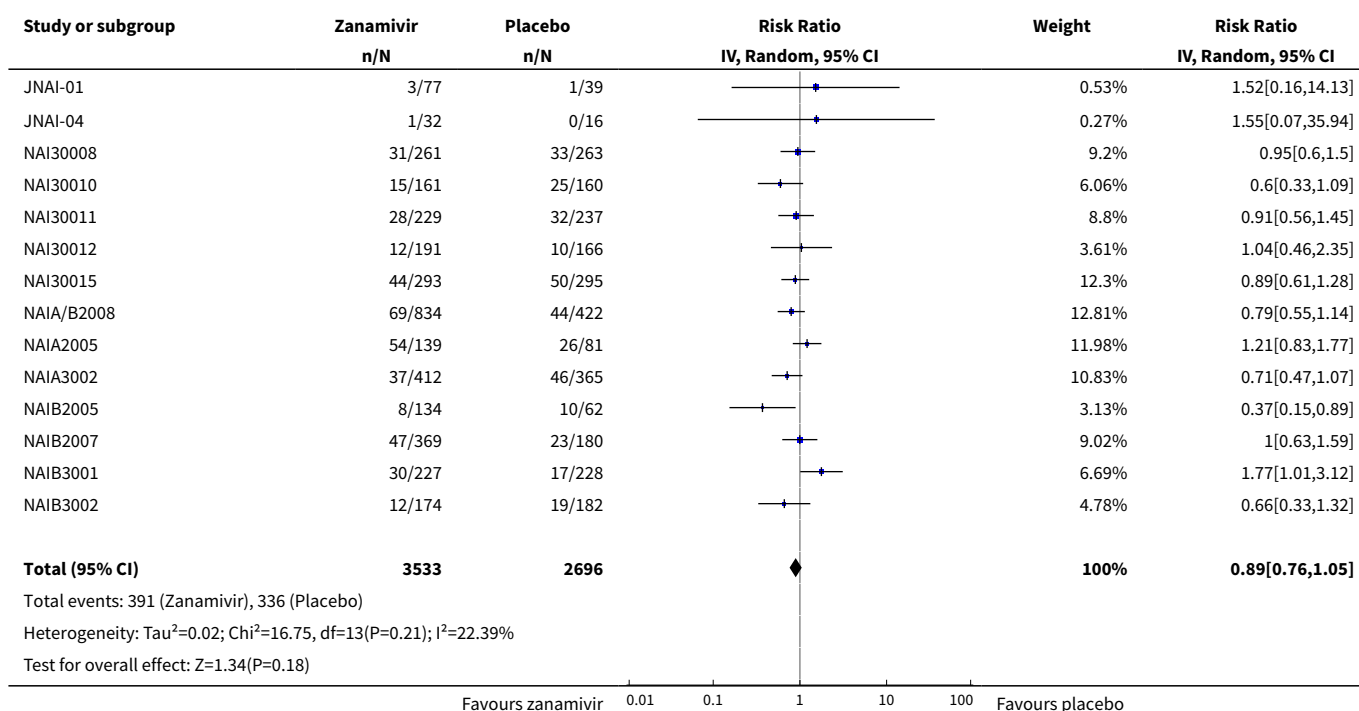
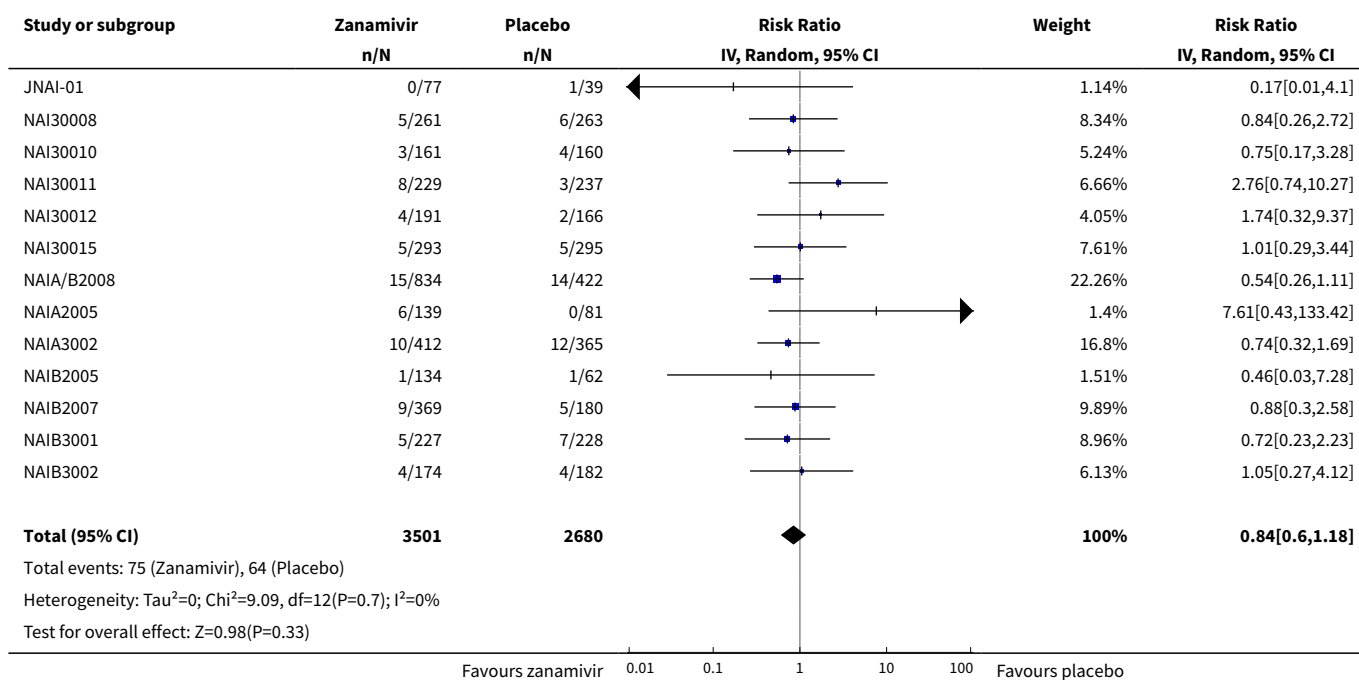


Analysis 3.38. Comparison 3 Zanamivir versus placebo for treatment, Outcome 38 Adverse events: respiratory body system in adult treatment (on-treatment).

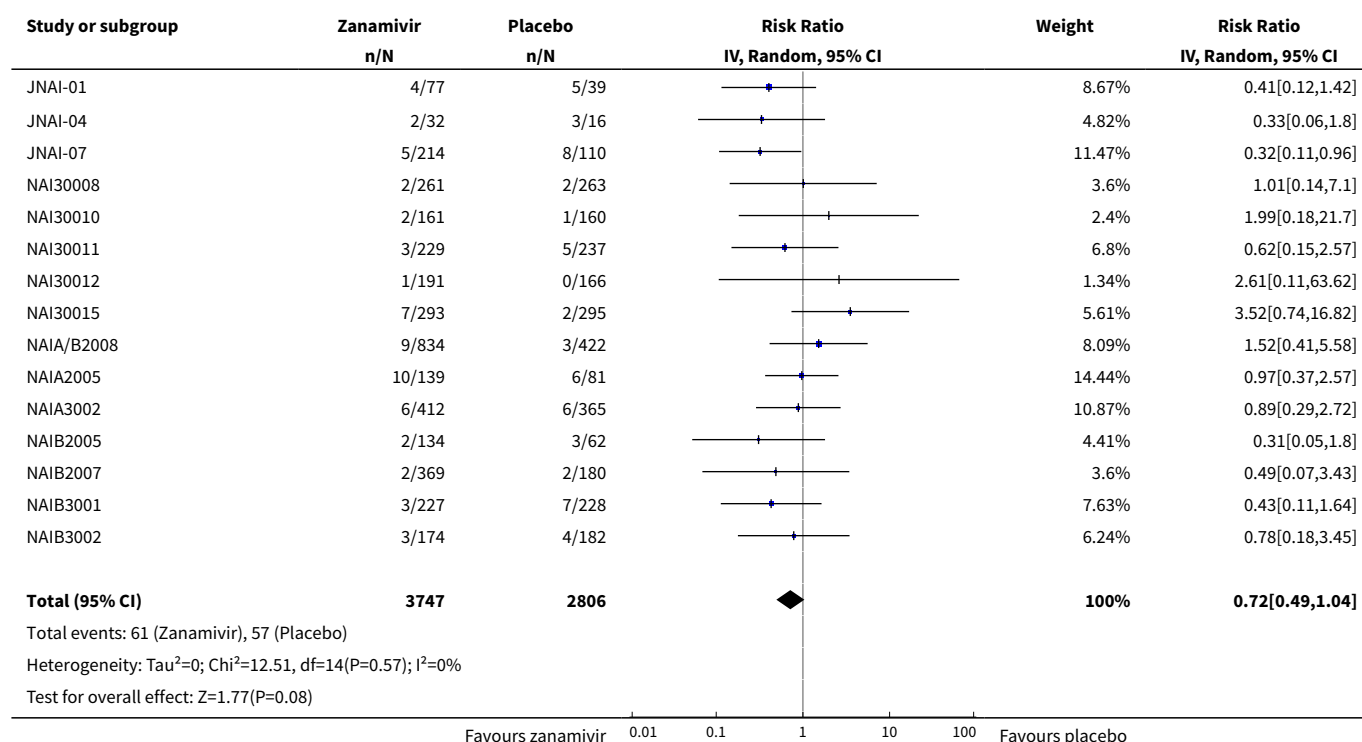


Analysis 3.39. Comparison 3 Zanamivir versus placebo for treatment, Outcome 39 Adverse events: neurological body system in adult treatment (on-treatment).

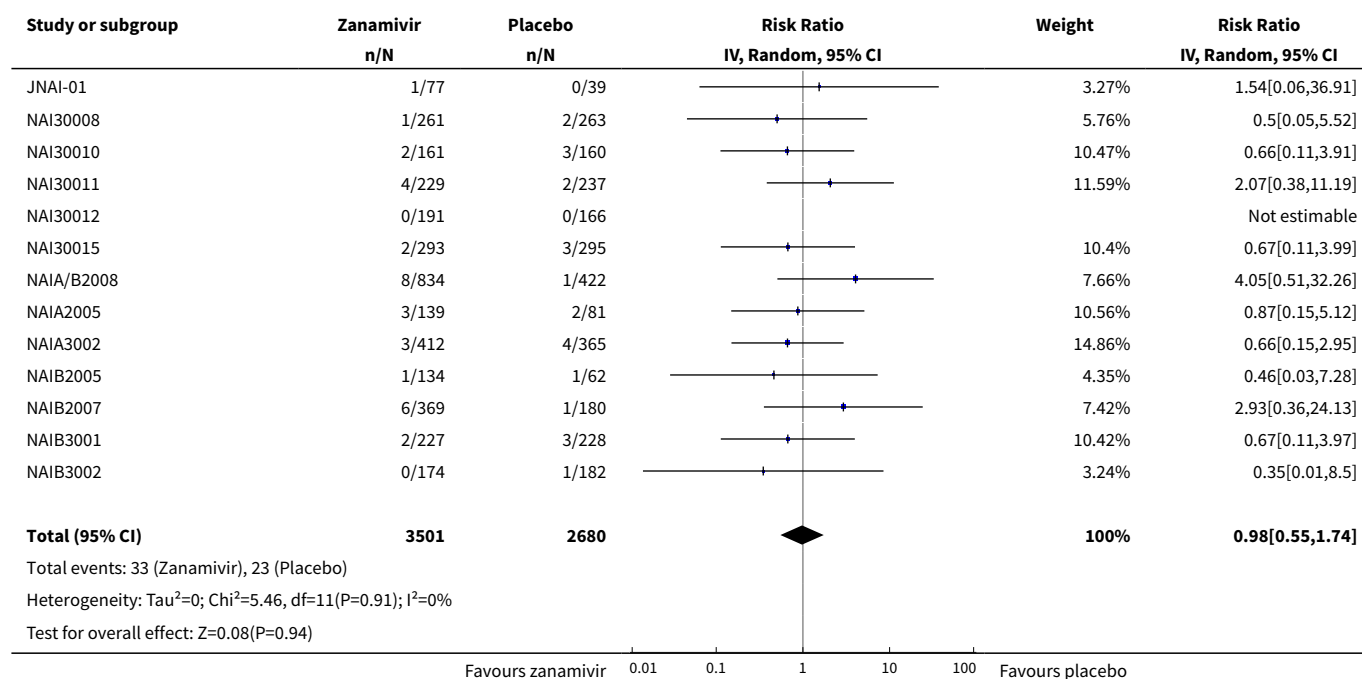


**Analysis 3.40. Comparison 3 Zanamivir versus placebo for treatment, Outcome 40
Adverse events: ear, nose and throat body system in adult treatment (on-treatment).****Analysis 3.41. Comparison 3 Zanamivir versus placebo for treatment, Outcome
41 Adverse events: skin body system in adult treatment (on-treatment).**

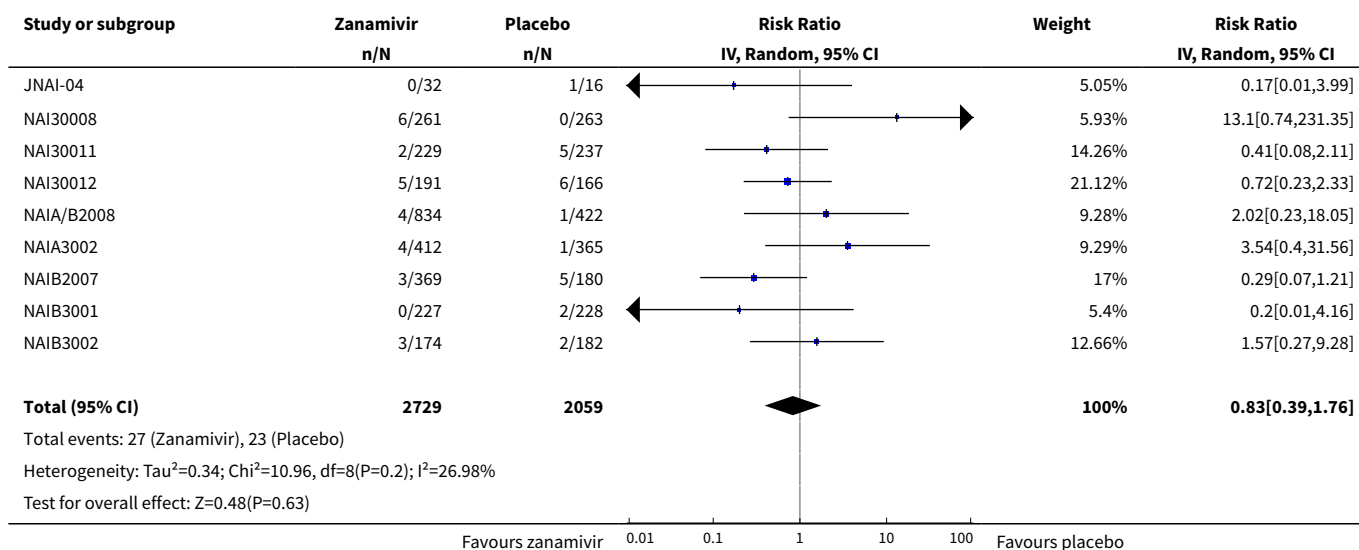
**Analysis 3.42. Comparison 3 Zanamivir versus placebo for treatment, Outcome 42
Adverse events: musculoskeletal body system in adult treatment (on-treatment).**



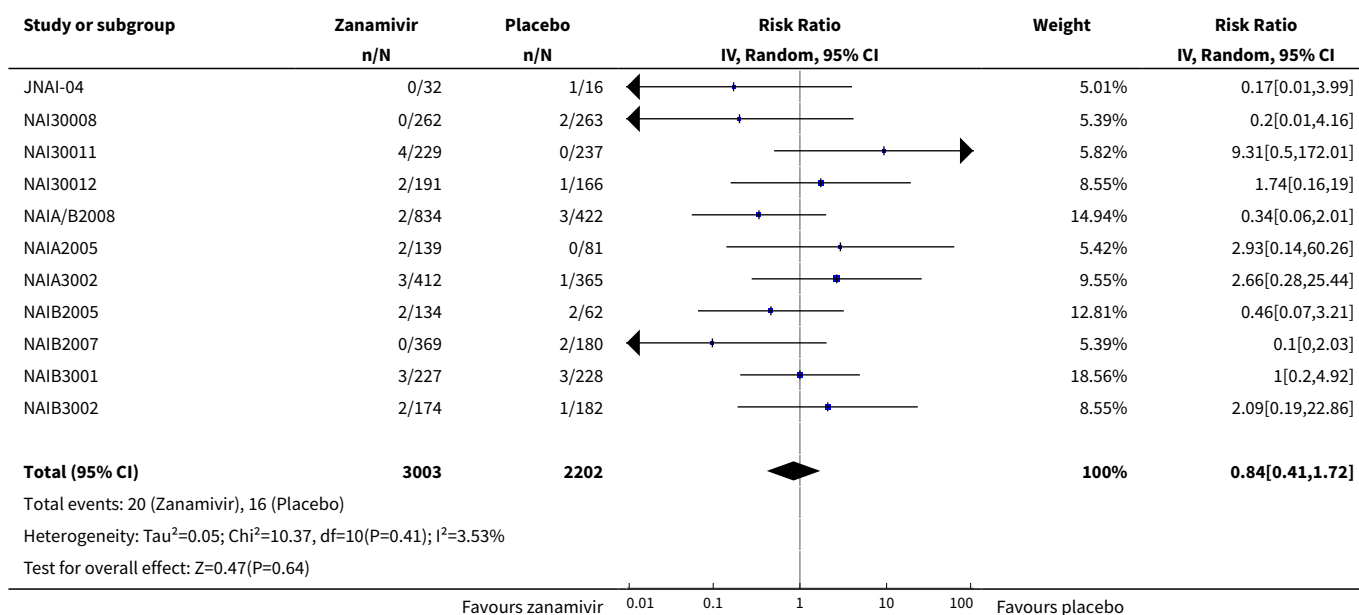
**Analysis 3.43. Comparison 3 Zanamivir versus placebo for treatment, Outcome
43 Adverse events: eye body system in adult treatment (on-treatment).**



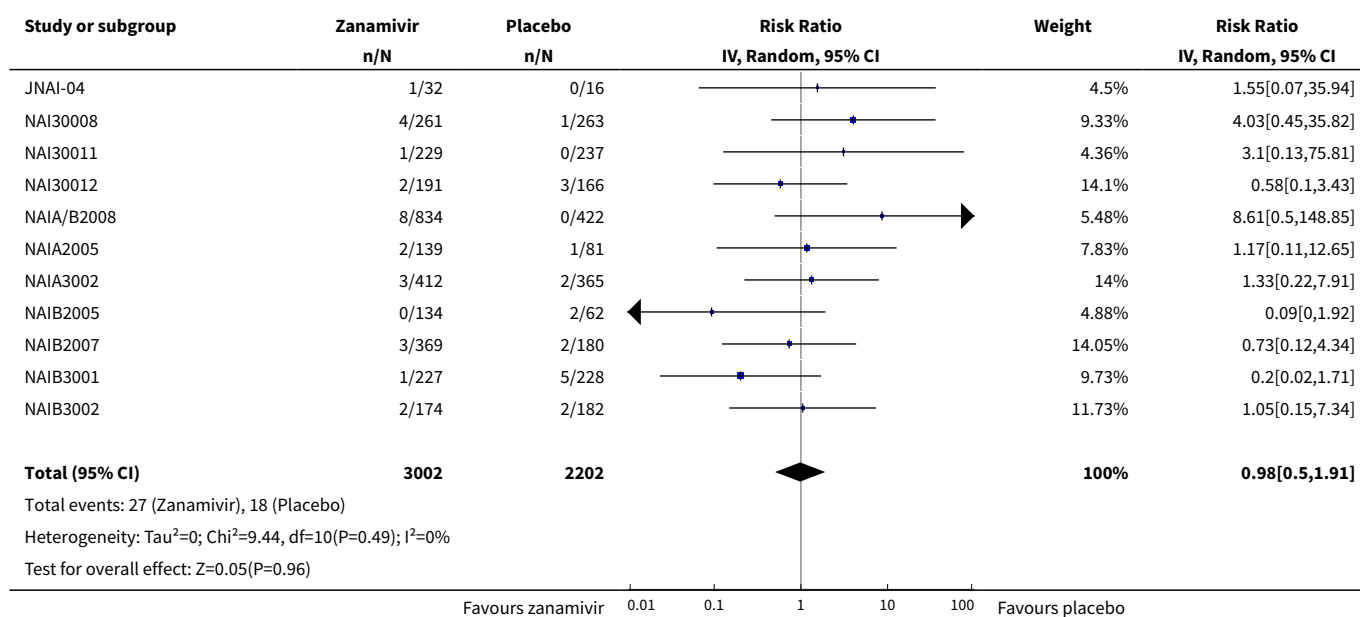
Analysis 3.44. Comparison 3 Zanamivir versus placebo for treatment, Outcome 44 Adverse events: hepato body system in adult treatment (on-treatment).



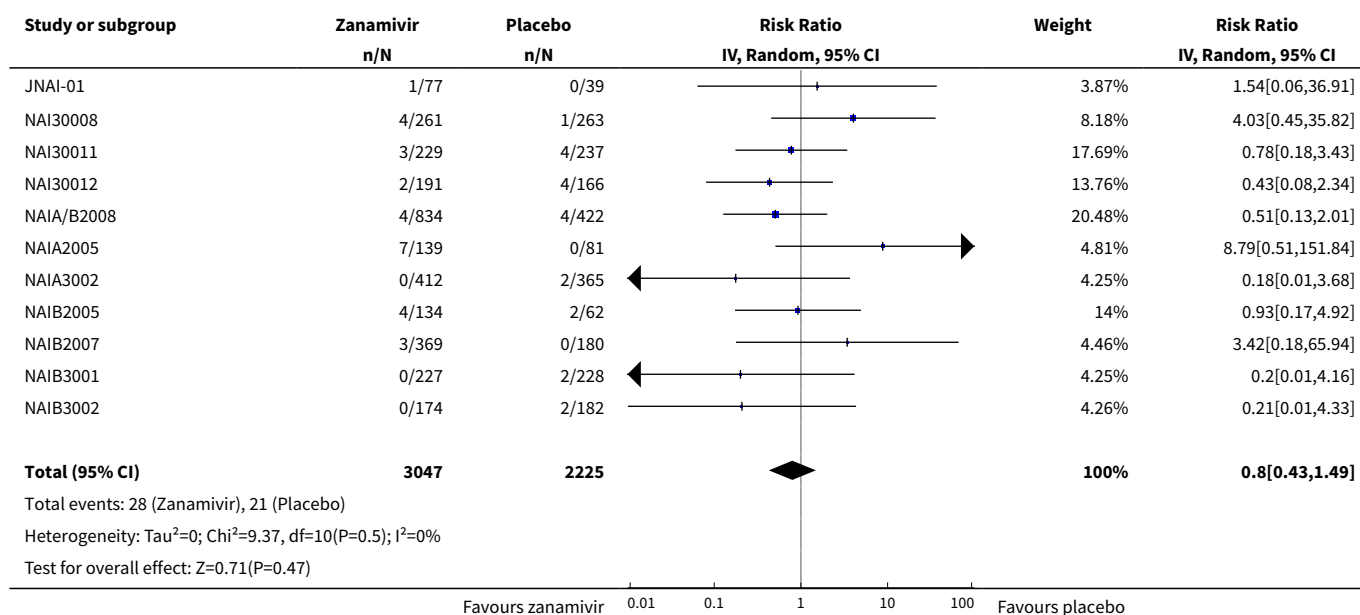
Analysis 3.45. Comparison 3 Zanamivir versus placebo for treatment, Outcome 45 Adverse events: renal body system in adult treatment (on-treatment).

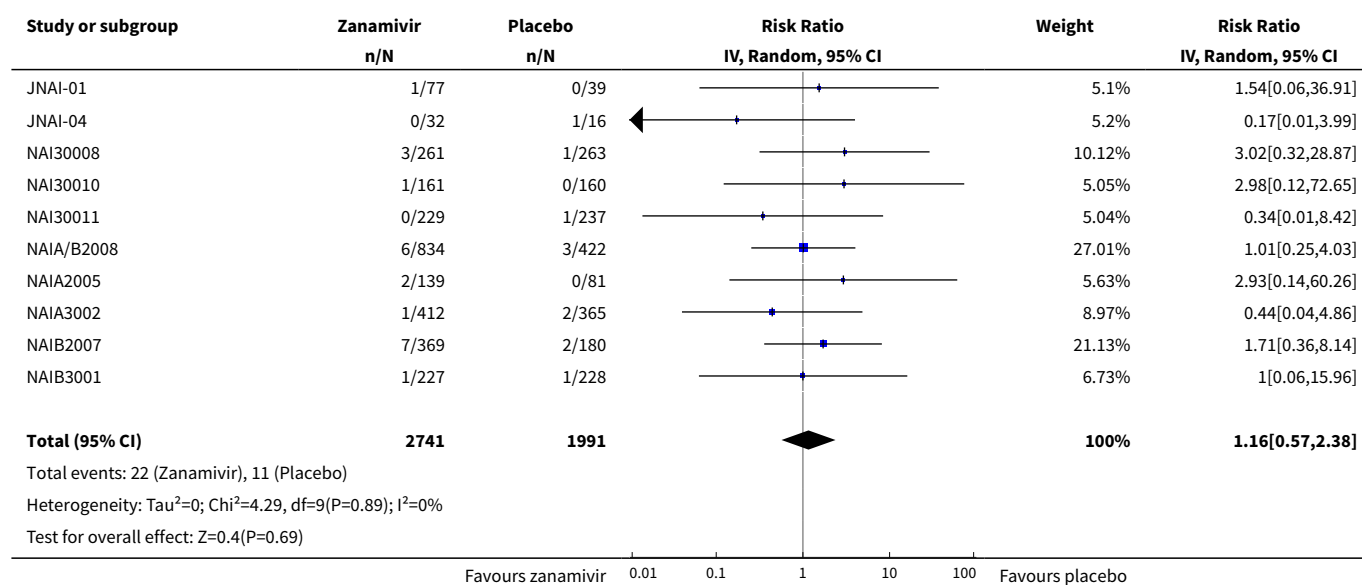
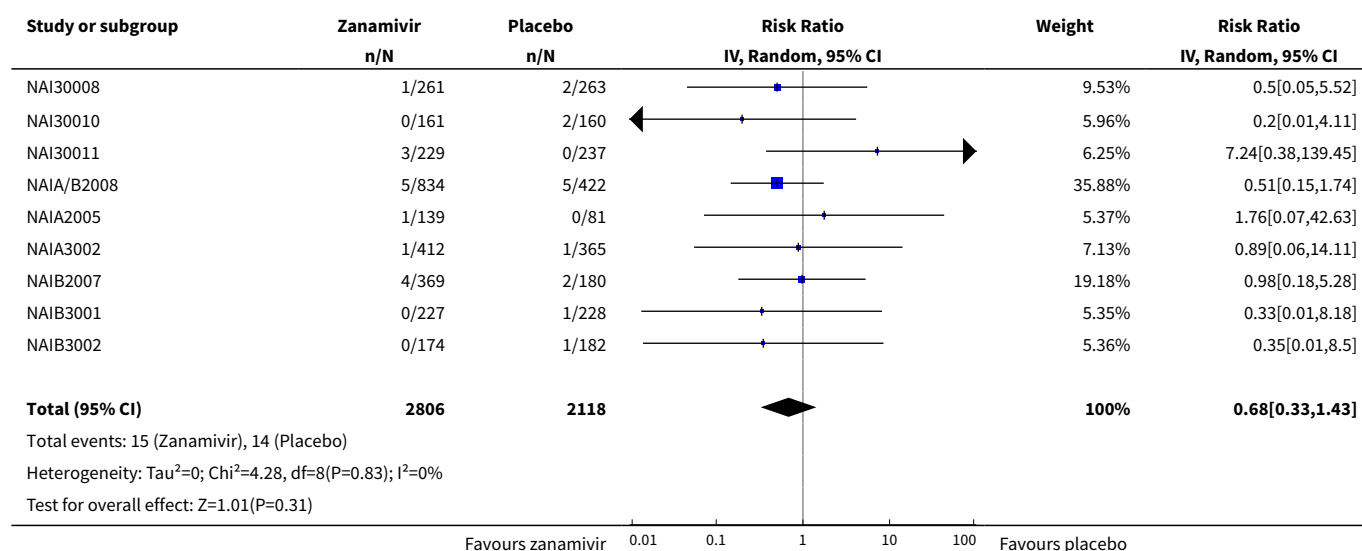
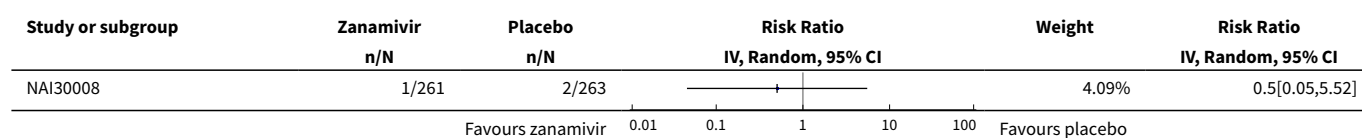


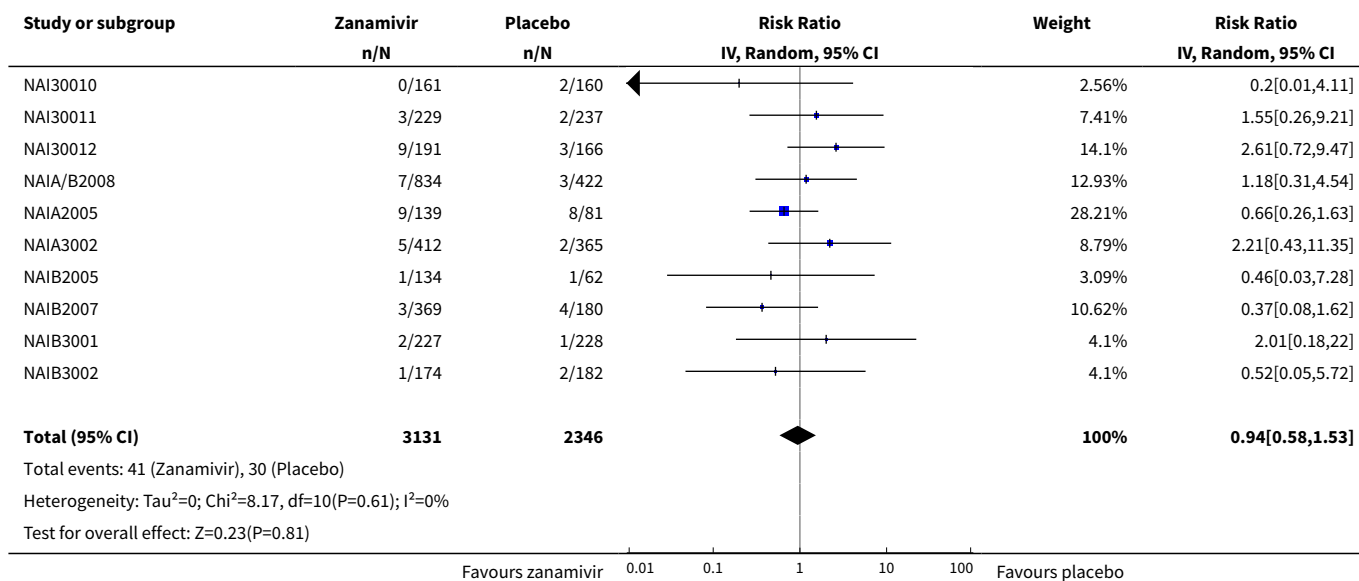
**Analysis 3.46. Comparison 3 Zanamivir versus placebo for treatment, Outcome 46
Adverse events: cardiovascular body system in adult treatment (on-treatment).**



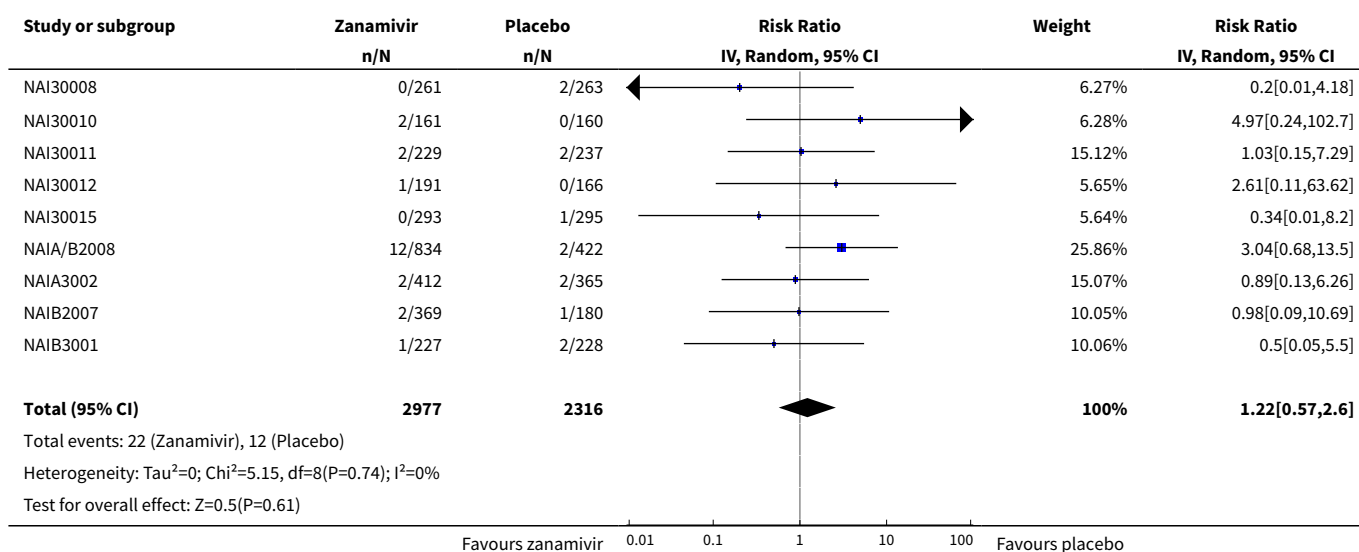
**Analysis 3.47. Comparison 3 Zanamivir versus placebo for treatment, Outcome 47
Adverse events: blood body system in adult treatment (on-treatment).**



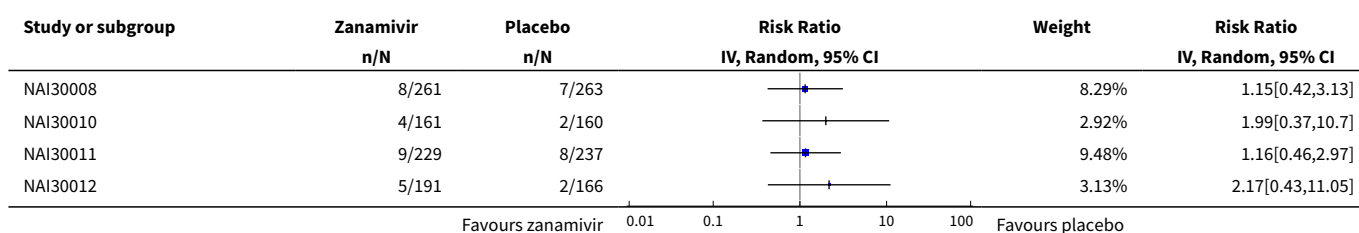
Analysis 3.48. Comparison 3 Zanamivir versus placebo for treatment, Outcome 48 Adverse events: psychiatric body system in adult treatment (on-treatment).**Analysis 3.49. Comparison 3 Zanamivir versus placebo for treatment, Outcome 49 Adverse events: reproduction body system in adult treatment (on-treatment).****Analysis 3.50. Comparison 3 Zanamivir versus placebo for treatment, Outcome 50 Adverse events: endocrine and metabolic body system in adult treatment (on-treatment).**

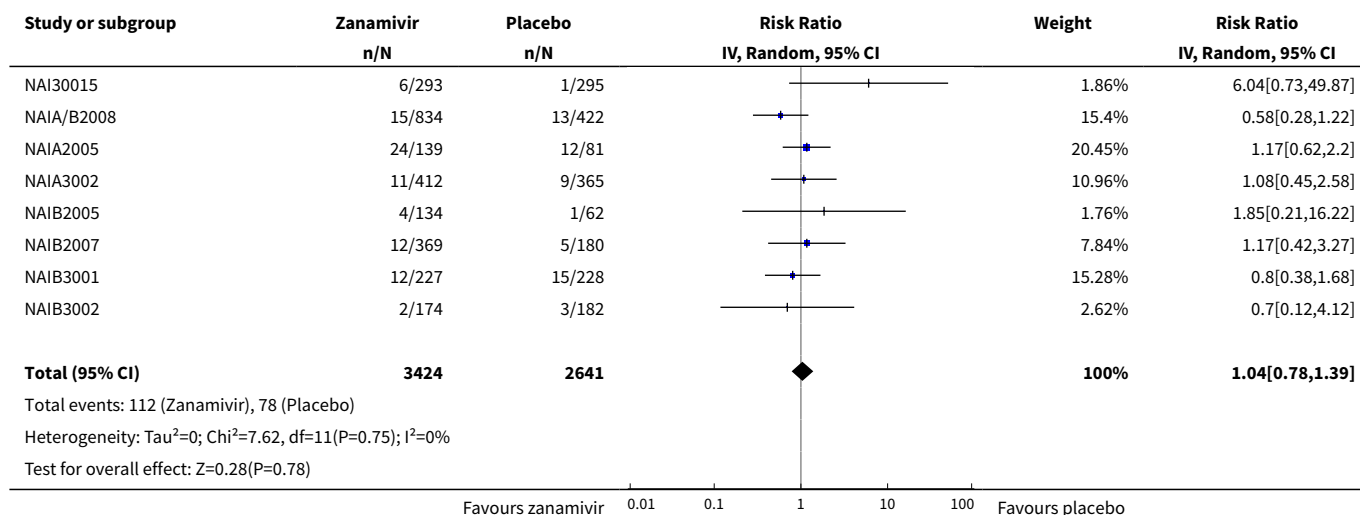


Analysis 3.51. Comparison 3 Zanamivir versus placebo for treatment, Outcome 51 Adverse events: injury body system in adult treatment (on-treatment).

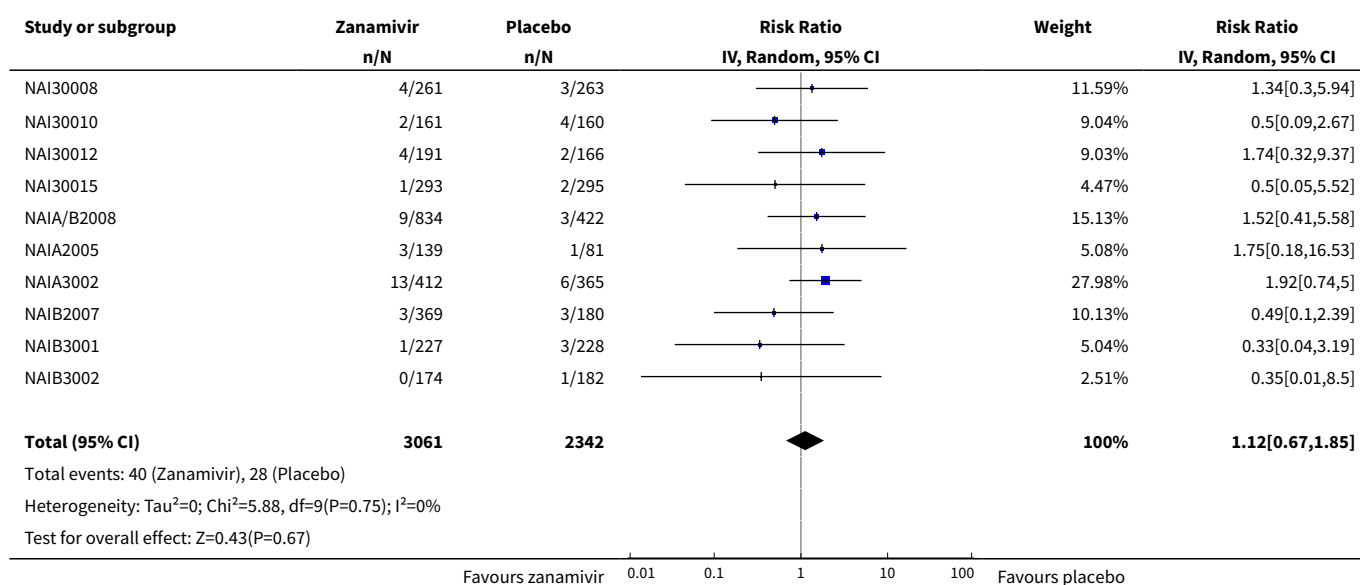


Analysis 3.52. Comparison 3 Zanamivir versus placebo for treatment, Outcome 52 Adverse events: non-site specific events in adult treatment (on-treatment).

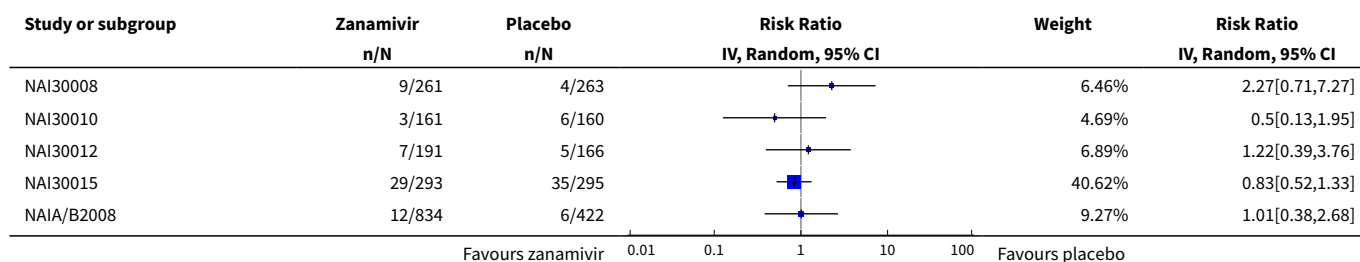


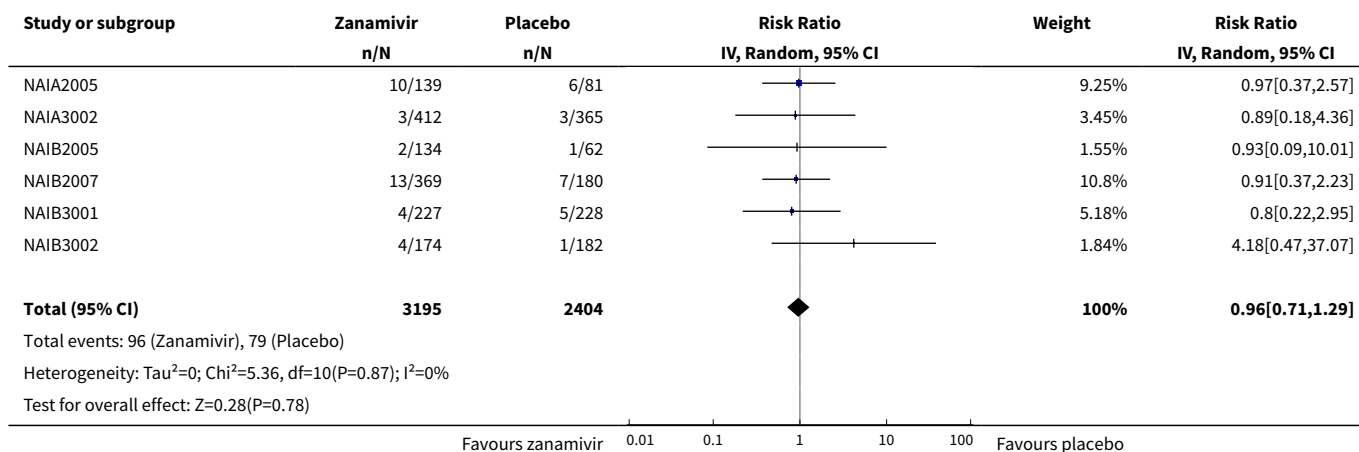


Analysis 3.53. Comparison 3 Zanamivir versus placebo for treatment, Outcome 53 Adverse events: nausea/vomiting in adult treatment (off-treatment).

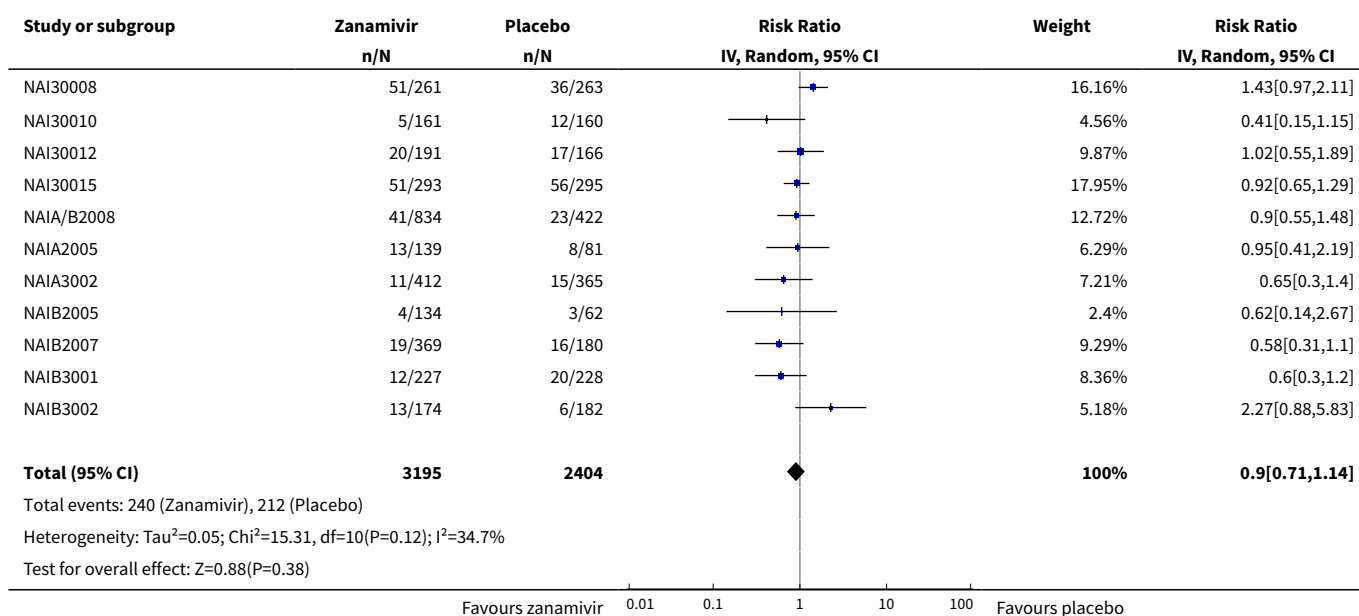


Analysis 3.54. Comparison 3 Zanamivir versus placebo for treatment, Outcome 54 Adverse events: cough in adult treatment (off-treatment).

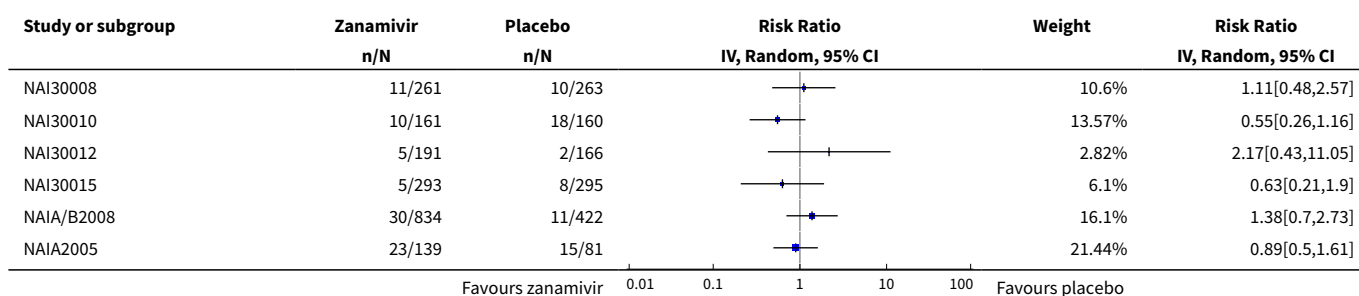


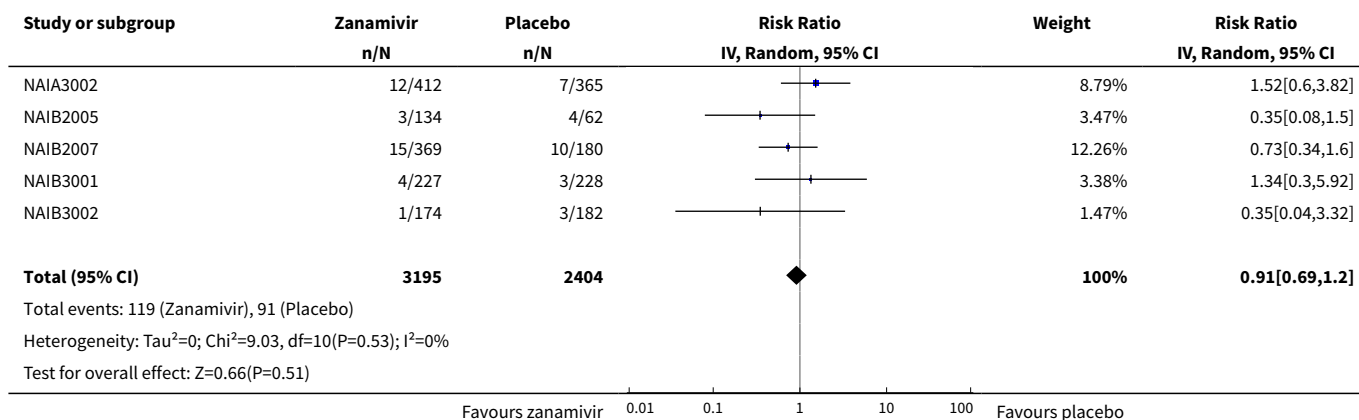


Analysis 3.55. Comparison 3 Zanamivir versus placebo for treatment, Outcome 55 Adverse events: respiratory body system in adult treatment (off-treatment).

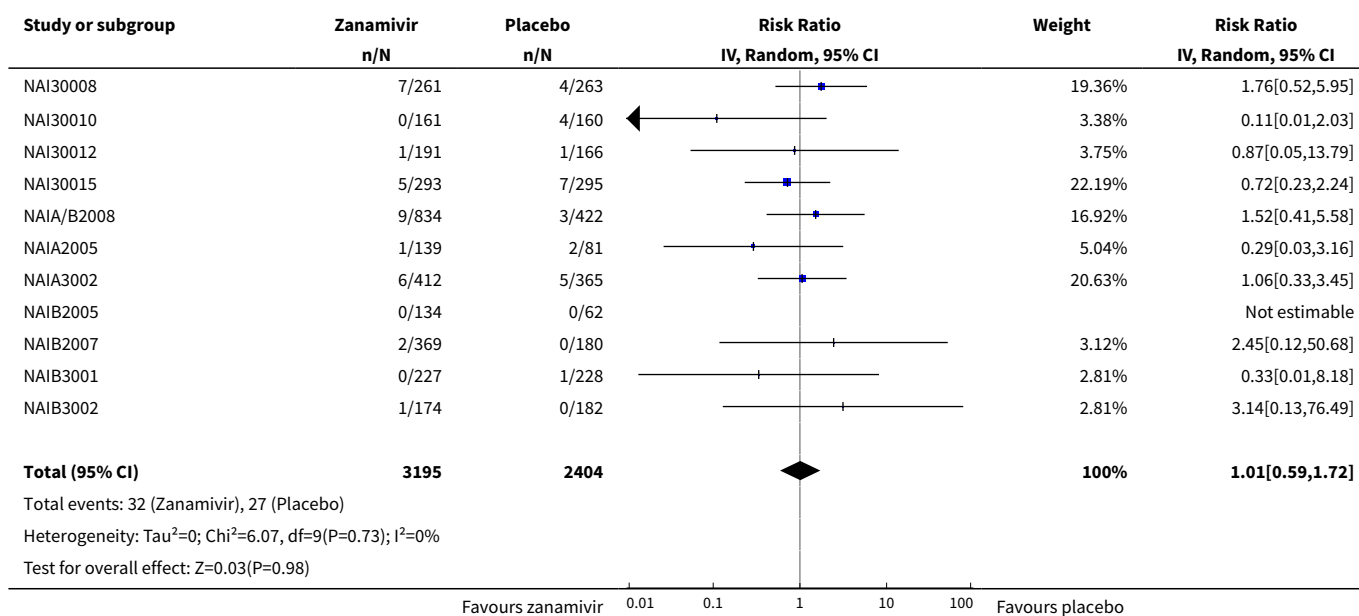


Analysis 3.56. Comparison 3 Zanamivir versus placebo for treatment, Outcome 56 Adverse events: headache in adult treatment (off-treatment).

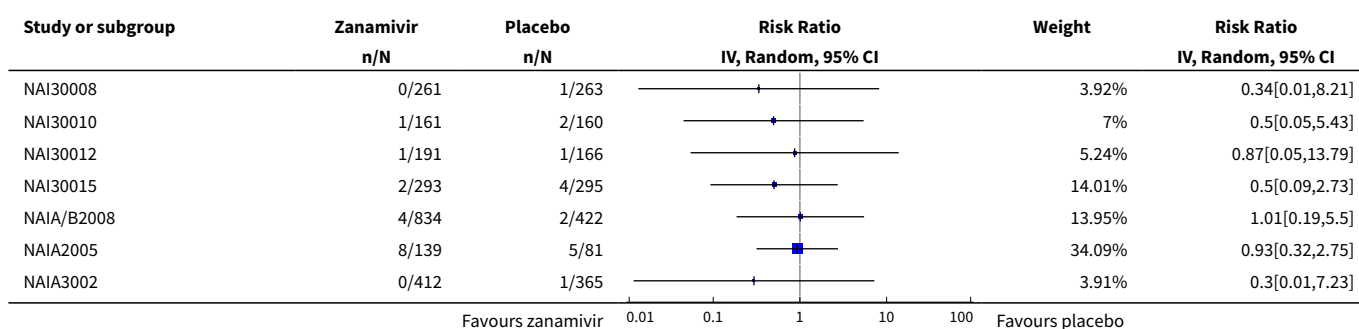


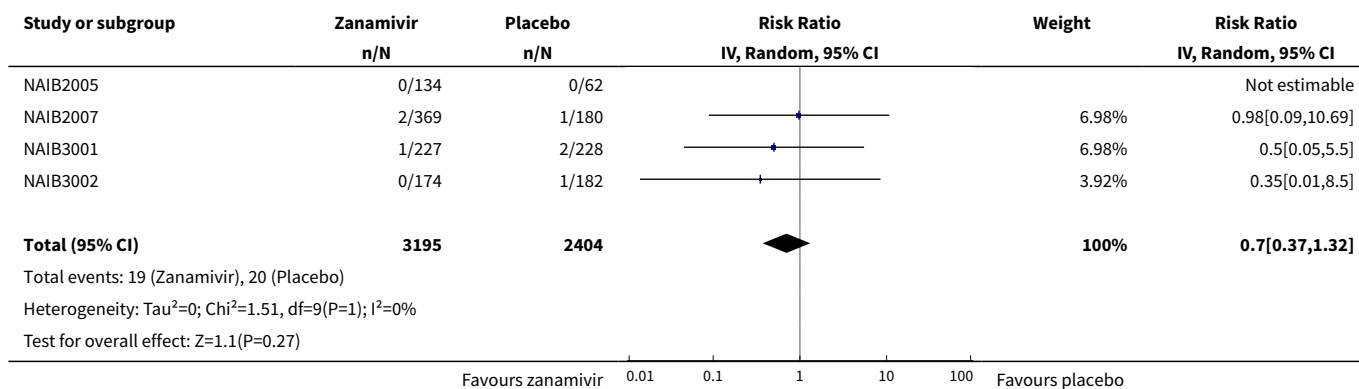


Analysis 3.57. Comparison 3 Zanamivir versus placebo for treatment, Outcome 57 Adverse events: diarrhoea in adult treatment (off-treatment).

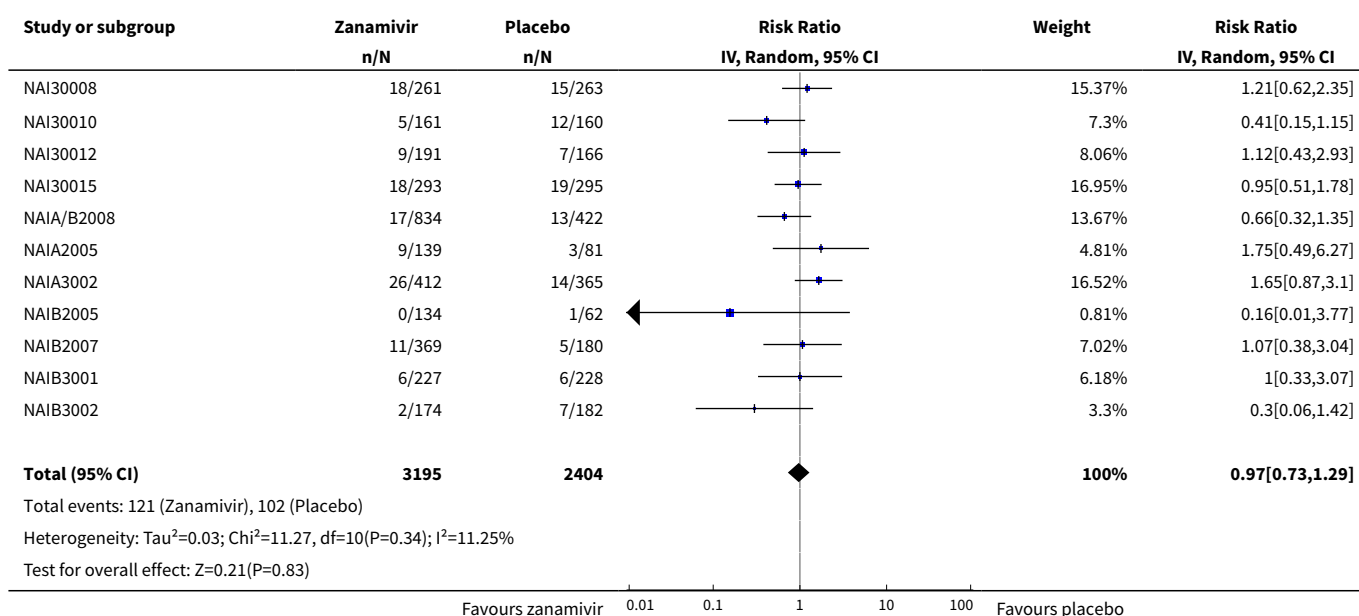


Analysis 3.58. Comparison 3 Zanamivir versus placebo for treatment, Outcome 58 Adverse events: fatigue in adult treatment (off-treatment).

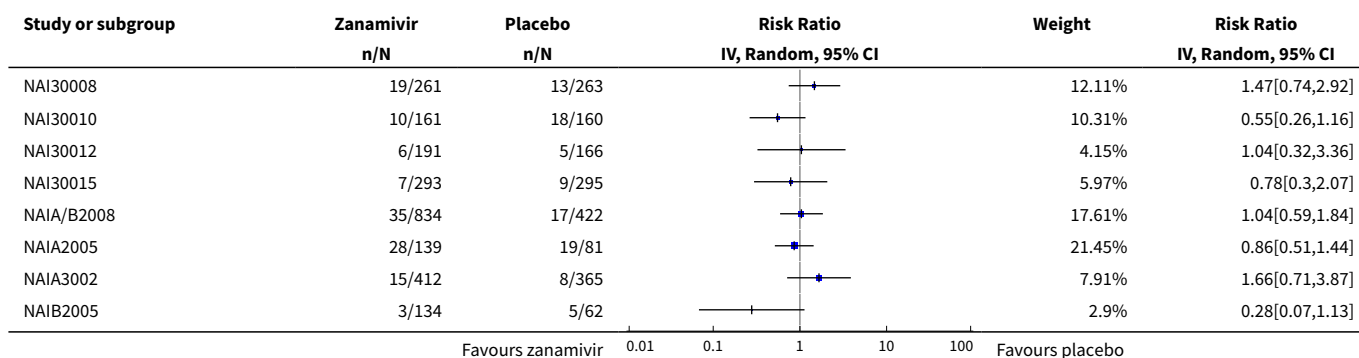


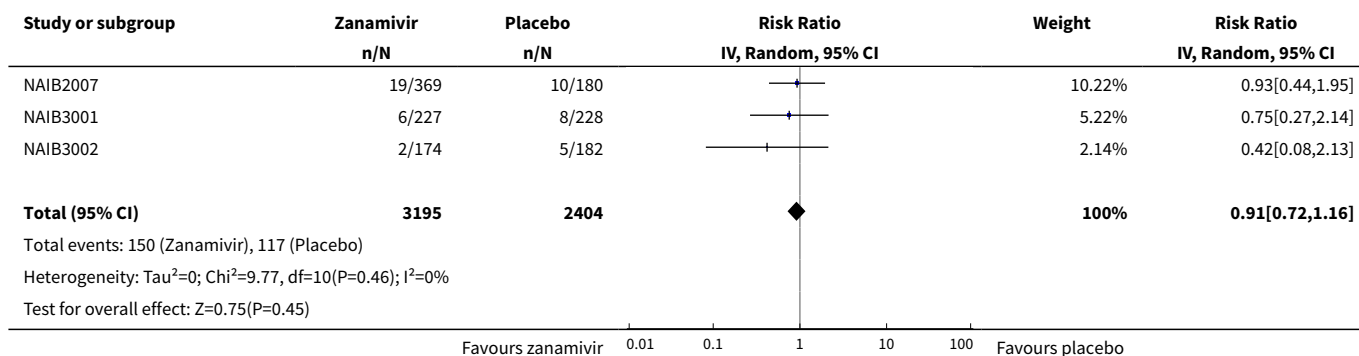


**Analysis 3.59. Comparison 3 Zanamivir versus placebo for treatment, Outcome 59
Adverse events: gastrointestinal body system in adult treatment (off-treatment).**

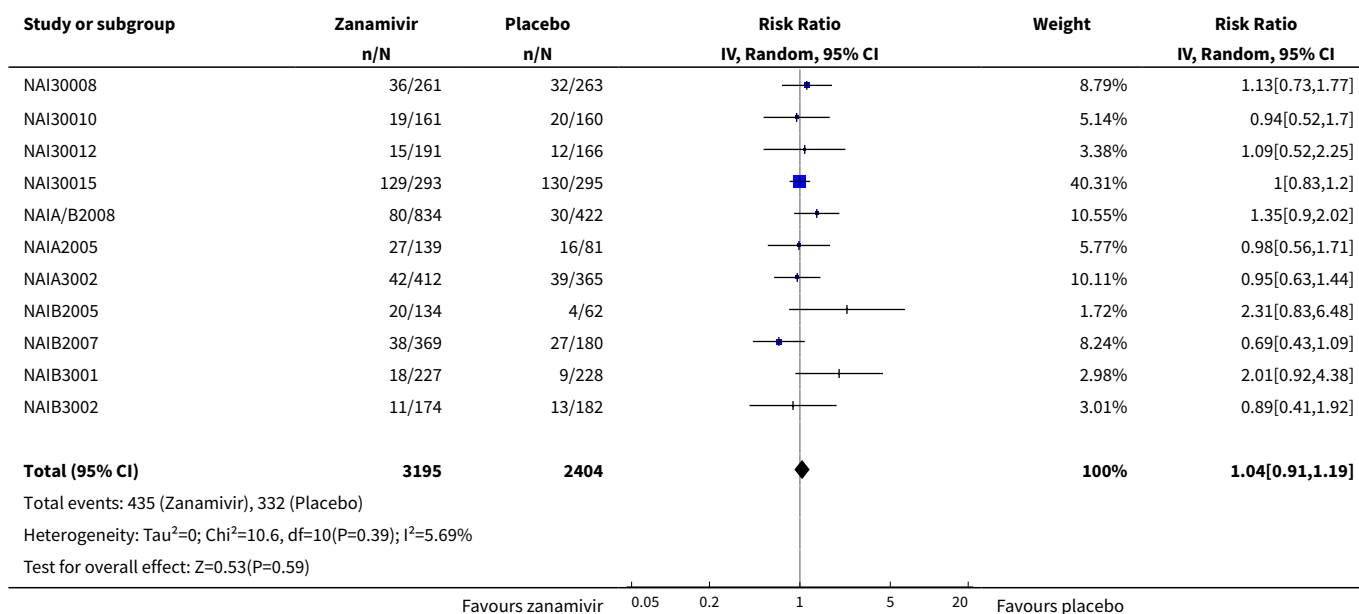


**Analysis 3.60. Comparison 3 Zanamivir versus placebo for treatment, Outcome 60
Adverse events: neurological body system in adult treatment (off-treatment).**

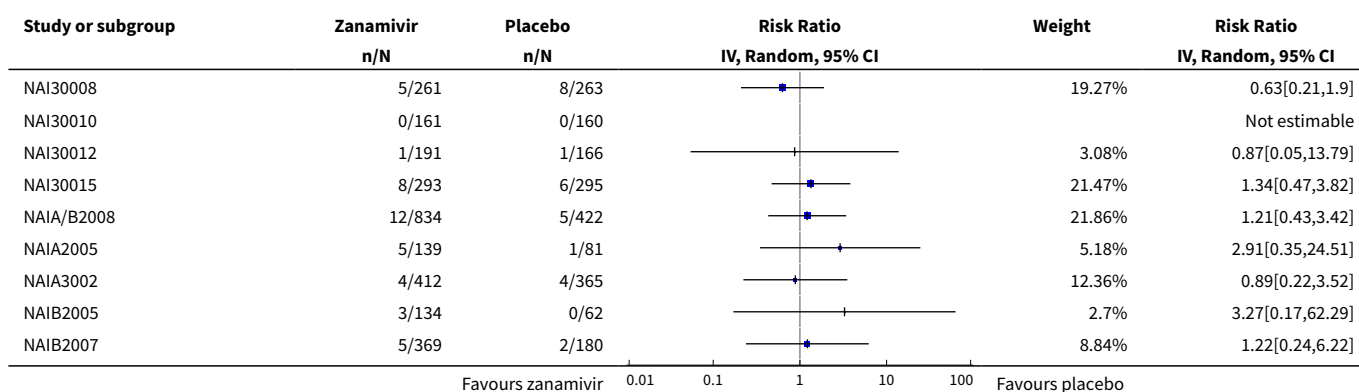


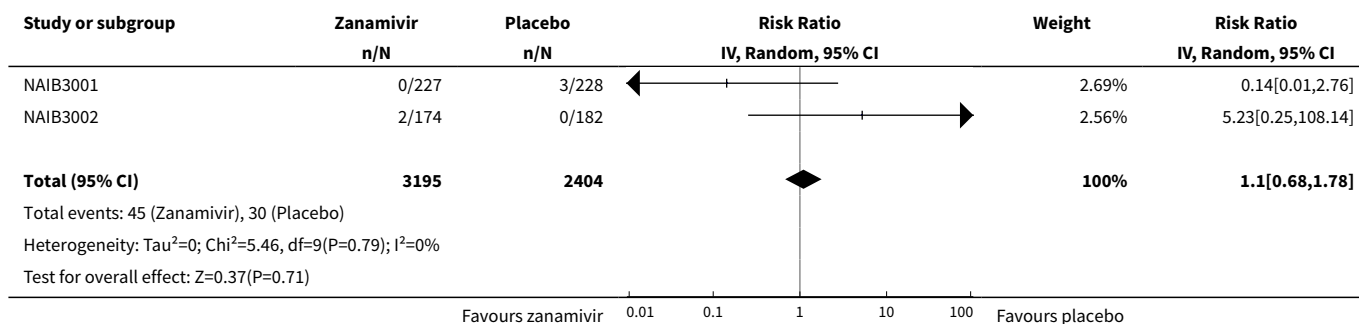


Analysis 3.61. Comparison 3 Zanamivir versus placebo for treatment, Outcome 61 Adverse events: ear, nose and throat in adult treatment (off-treatment).

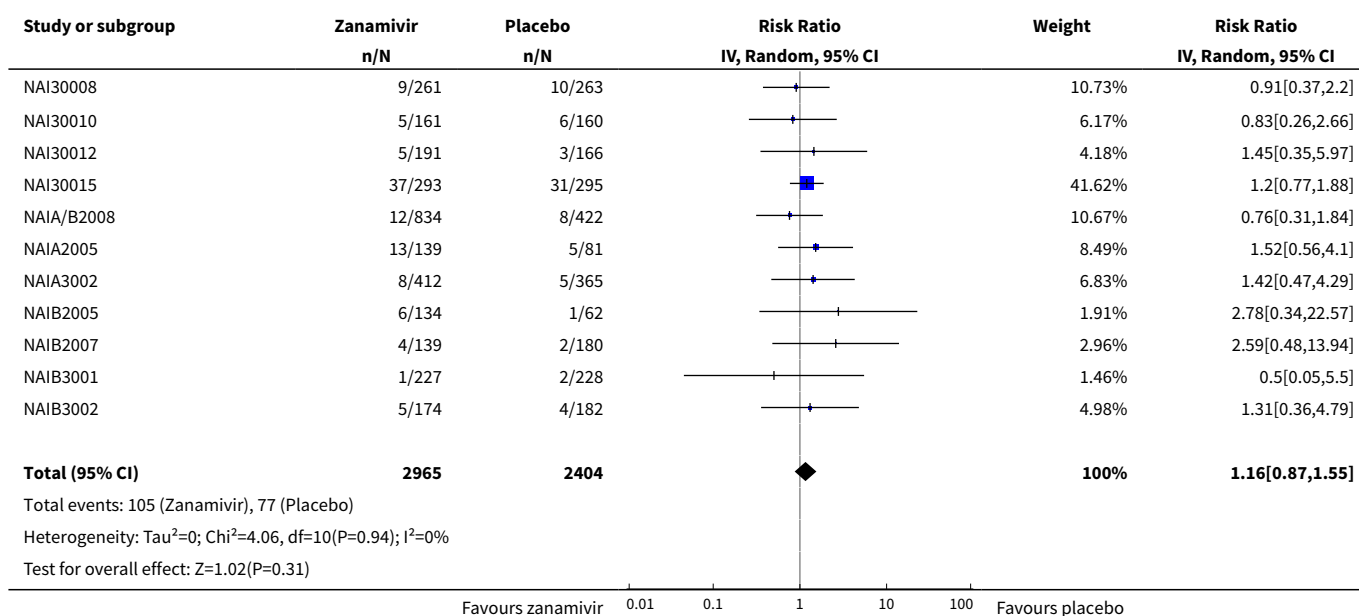


Analysis 3.62. Comparison 3 Zanamivir versus placebo for treatment, Outcome 62 Adverse events: skin body system in adult treatment (off-treatment).

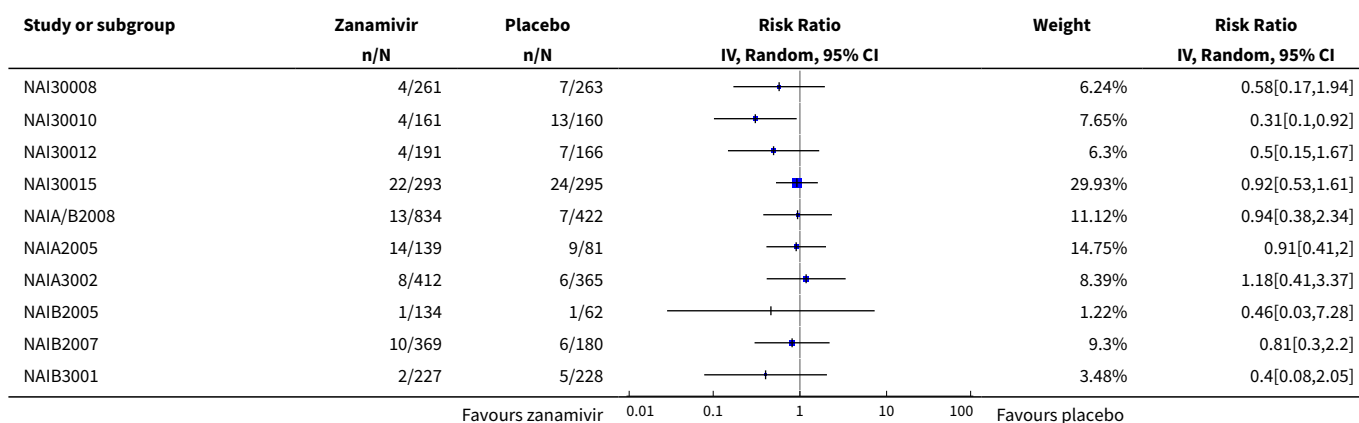


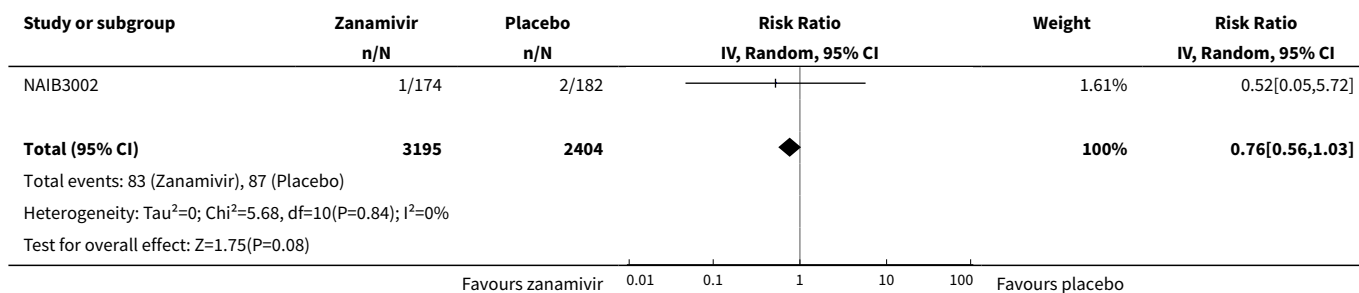


**Analysis 3.63. Comparison 3 Zanamivir versus placebo for treatment, Outcome 63
Adverse events: musculoskeletal body system in adult treatment (off-treatment).**

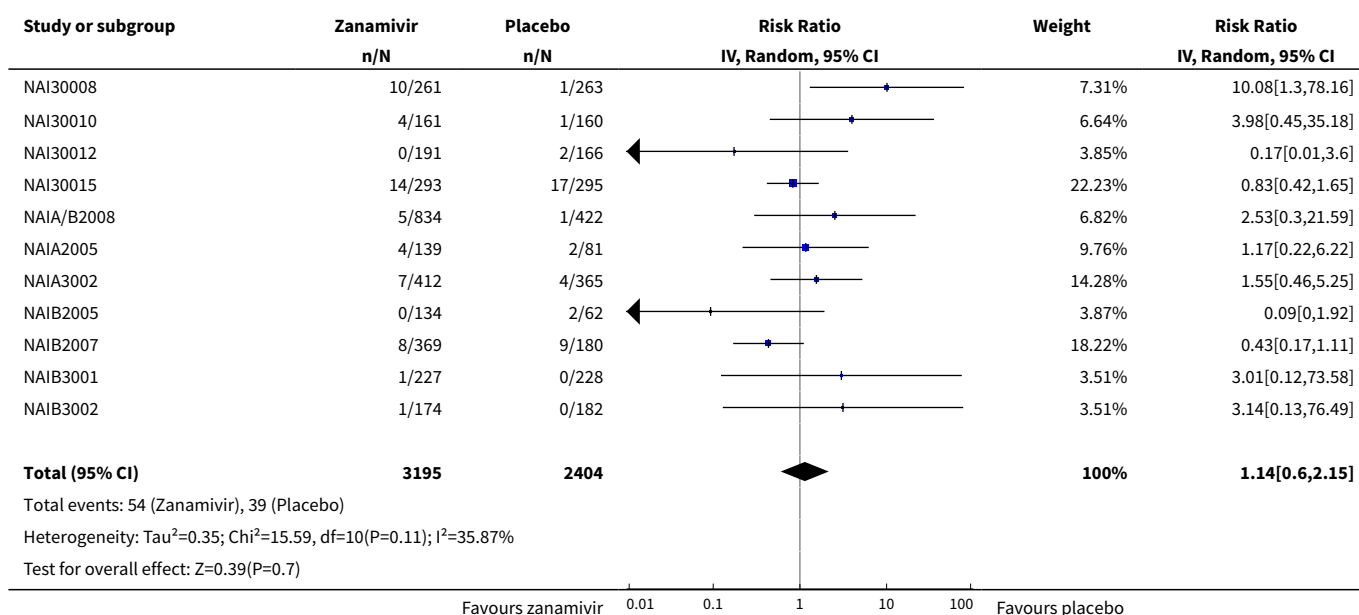


**Analysis 3.64. Comparison 3 Zanamivir versus placebo for treatment, Outcome
64 Adverse events: non-site specific in adult treatment (off-treatment).**

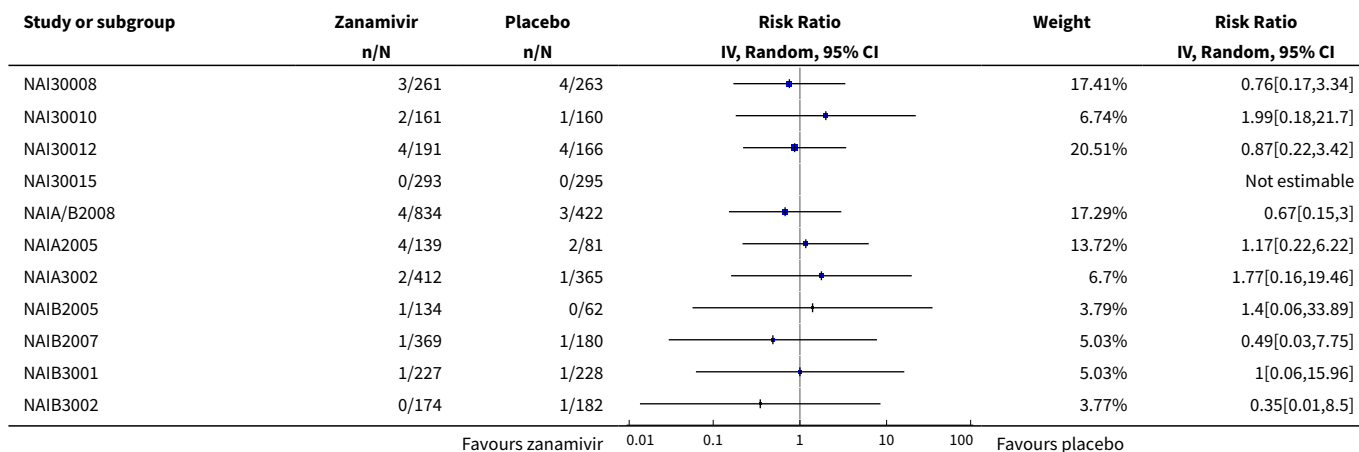


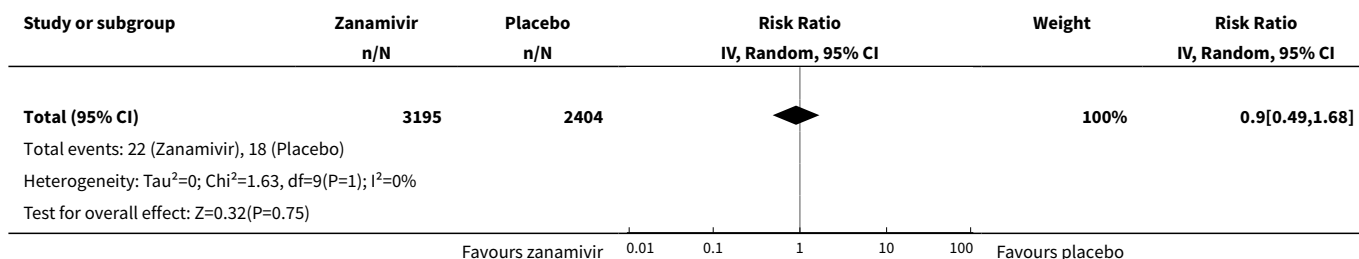


Analysis 3.65. Comparison 3 Zanamivir versus placebo for treatment, Outcome 65 Adverse events: injury body system in adult treatment (off-treatment).

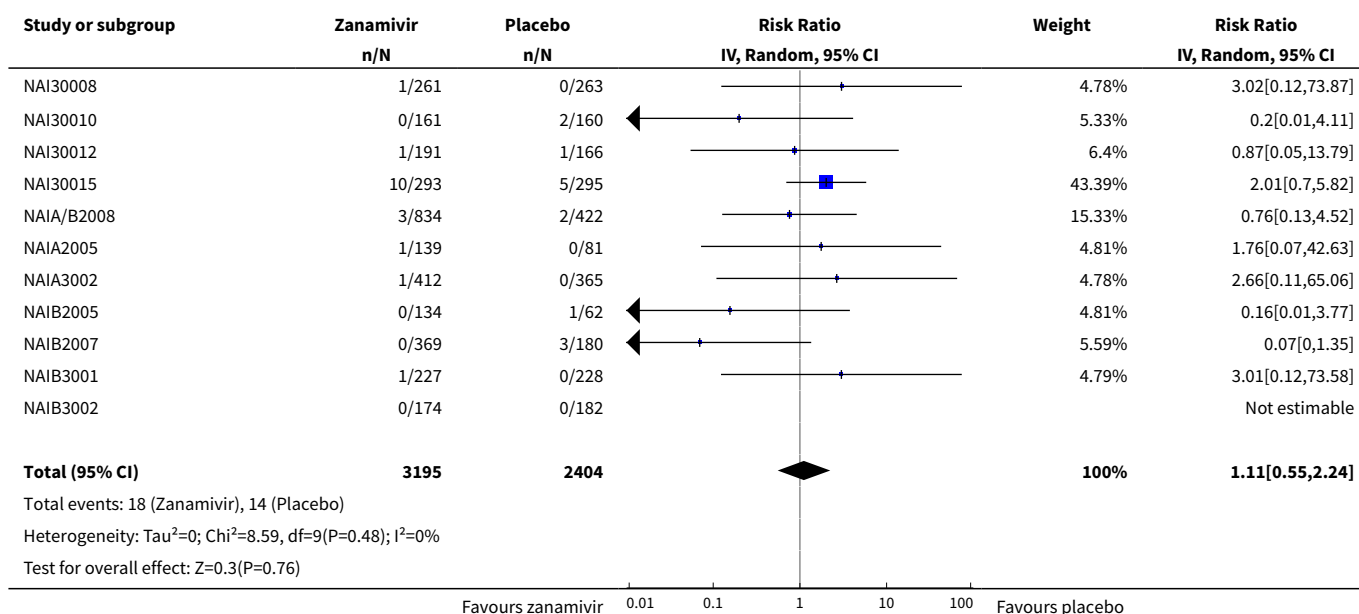


Analysis 3.66. Comparison 3 Zanamivir versus placebo for treatment, Outcome 66 Adverse events: endocrine and metabolic body system in adult treatment (off-treatment).

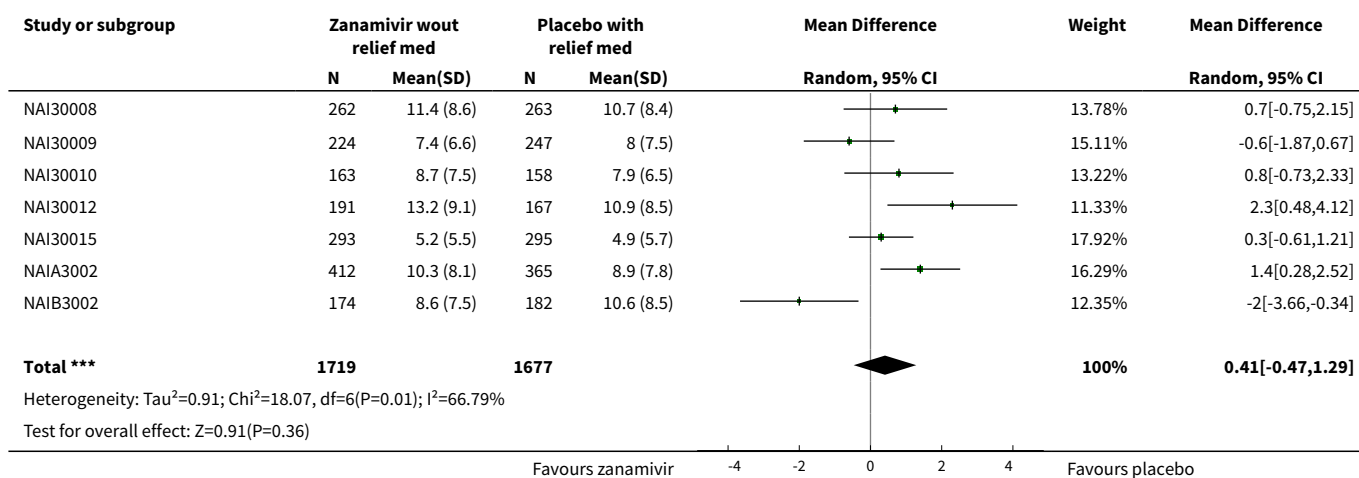




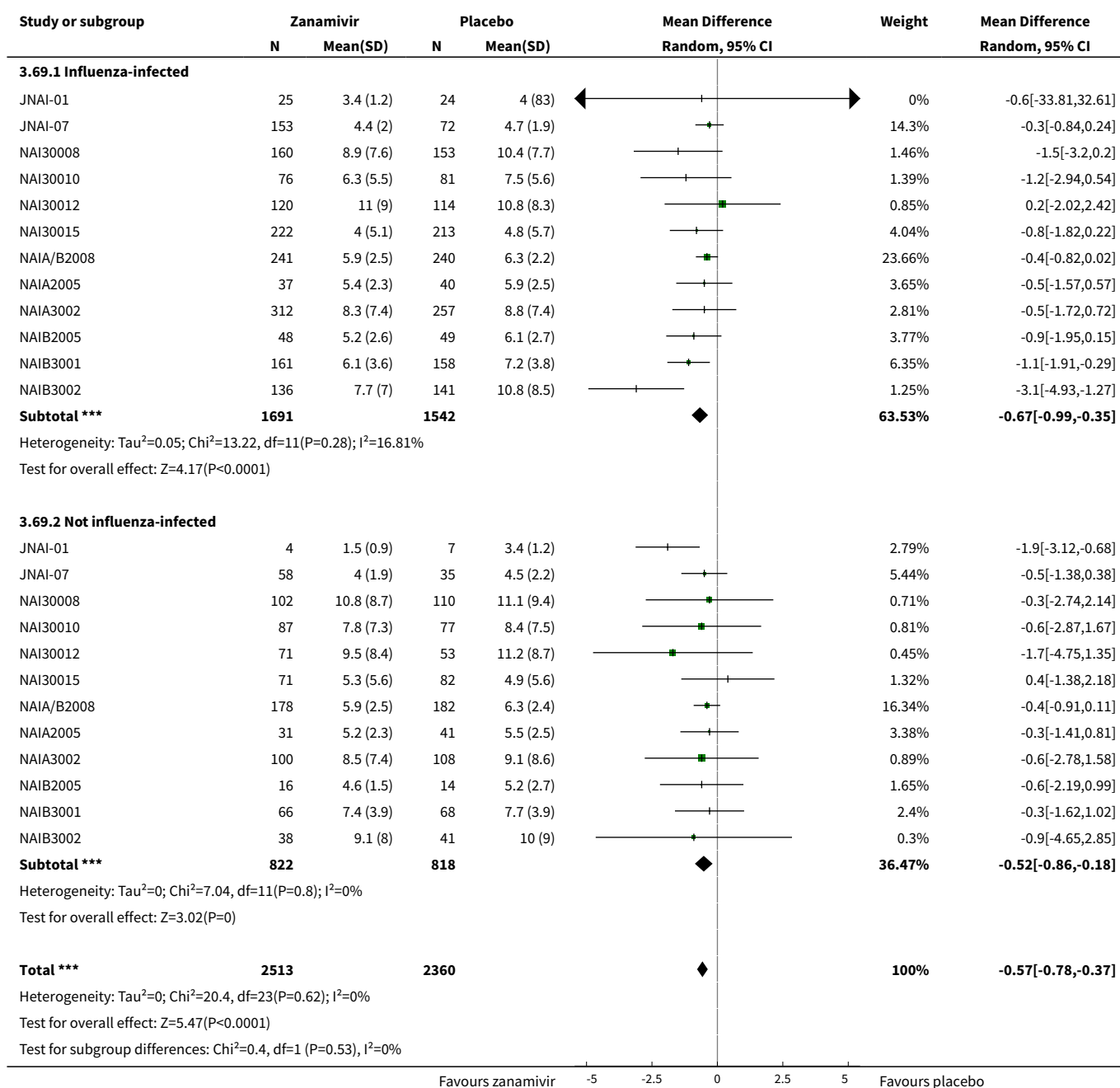
Analysis 3.67. Comparison 3 Zanamivir versus placebo for treatment, Outcome 67 Adverse events: eye body system in adult treatment (off-treatment).



Analysis 3.68. Comparison 3 Zanamivir versus placebo for treatment, Outcome 68 Time to first alleviation of symptoms in adults with/without relief medication [days].



Analysis 3.69. Comparison 3 Zanamivir versus placebo for treatment, Outcome 69 Time to first alleviation of symptoms in adults by infection status [days].



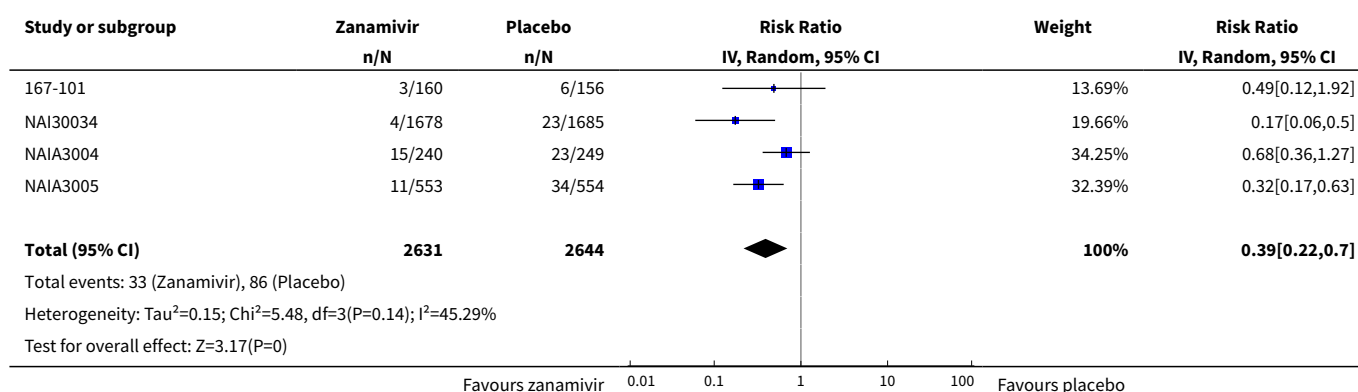
Comparison 4. Zanamivir versus placebo for prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic influenza in prophylaxis of individuals	4	5275	Risk Ratio (IV, Random, 95% CI)	0.39 [0.22, 0.70]
2 Asymptomatic influenza in prophylaxis of individuals	4	5275	Risk Ratio (IV, Random, 95% CI)	0.97 [0.76, 1.24]
3 Symptomatic influenza in post-exposure prophylaxis	5	1525	Risk Ratio (IV, Random, 95% CI)	0.33 [0.18, 0.58]
3.1 Household prophylaxis	2	824	Risk Ratio (IV, Random, 95% CI)	0.22 [0.13, 0.36]
3.2 Other prophylaxis	3	701	Risk Ratio (IV, Random, 95% CI)	0.59 [0.30, 1.16]
4 Asymptomatic influenza in post-exposure prophylaxis	5	1525	Risk Ratio (IV, Random, 95% CI)	0.88 [0.65, 1.20]
5 Complications: pneumonia in adult prophylaxis	6	7662	Risk Ratio (IV, Random, 95% CI)	0.30 [0.11, 0.80]
6 Complications: bronchitis in adult prophylaxis	6	7662	Risk Ratio (IV, Random, 95% CI)	0.49 [0.20, 1.19]
7 Complications: sinusitis in adult prophylaxis	6	7662	Risk Ratio (IV, Random, 95% CI)	0.93 [0.64, 1.36]
8 Complications classified as serious or leading to study withdrawal	5	6825	Risk Ratio (IV, Random, 95% CI)	1.09 [0.36, 3.26]
9 Serious adverse events in adult prophylaxis	10	8225	Risk Ratio (IV, Random, 95% CI)	1.12 [0.65, 1.91]
10 Adverse events leading to study withdrawal in adult prophylaxis	10	8225	Risk Ratio (IV, Random, 95% CI)	0.85 [0.60, 1.21]
11 All withdrawals in adult prophylaxis	8	7792	Risk Ratio (IV, Random, 95% CI)	0.81 [0.64, 1.03]
12 Adverse events: abdominal pain in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	1.28 [0.55, 2.99]
13 Adverse events: cough in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	0.91 [0.82, 1.01]
14 Adverse events: diarrhoea in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	1.01 [0.73, 1.40]
15 Adverse events: dizziness in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	1.07 [0.59, 1.96]
16 Adverse events: fatigue in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	1.01 [0.88, 1.16]

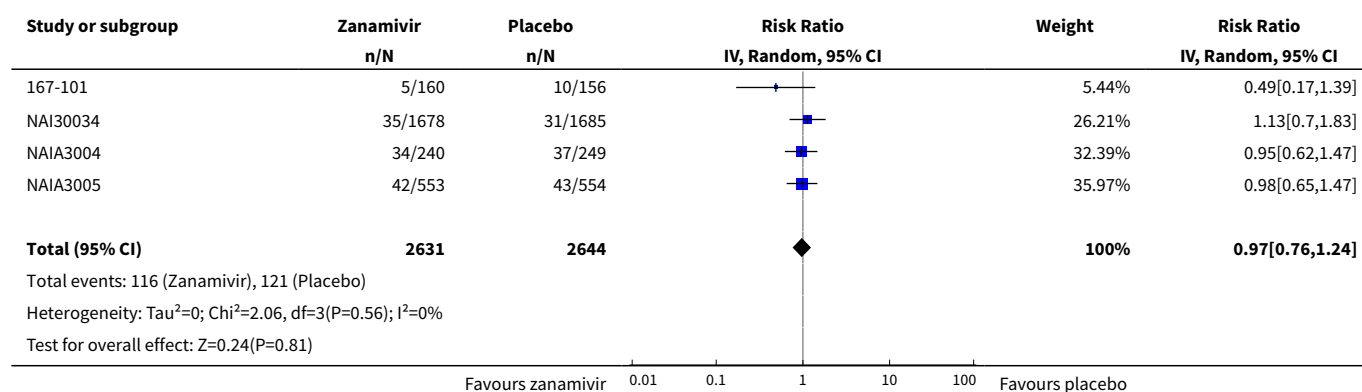
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Adverse events: headache in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	0.96 [0.89, 1.04]
18 Adverse events: blood body system in adult prophylaxis (on-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	1.18 [0.62, 2.25]
19 Adverse events: nausea/vomiting in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	0.88 [0.66, 1.18]
20 Adverse events: cardiovascular body system in adult prophylaxis (on-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	1.15 [0.77, 1.71]
21 Adverse events: ear, nose and throat body system in adult prophylaxis (on-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	0.94 [0.87, 1.01]
22 Adverse events: endocrine and metabolic body system in adult prophylaxis (on-treatment)	7	7730	Risk Ratio (IV, Random, 95% CI)	0.86 [0.69, 1.08]
23 Adverse events: eye body system in adult prophylaxis (on-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	0.79 [0.51, 1.21]
24 Adverse events: gastrointestinal body system in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	0.83 [0.72, 0.97]
25 Adverse events: injury body system in adult prophylaxis (on-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	0.92 [0.62, 1.35]
26 Adverse events: musculoskeletal body system in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	1.05 [0.93, 1.19]
27 Adverse events: neurological body system in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	0.96 [0.89, 1.03]
28 Adverse events: non-site specific in adult prophylaxis (on-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	0.99 [0.85, 1.16]
29 Adverse events: psychiatric body system in adult prophylaxis (on-treatment)	7	7730	Risk Ratio (IV, Random, 95% CI)	1.05 [0.48, 2.29]
30 Adverse events: renal body system in adult prophylaxis (on-treatment)	7	7730	Risk Ratio (IV, Random, 95% CI)	0.67 [0.35, 1.26]
31 Adverse events: reproductive body system in adult prophylaxis (on-treatment)	10	8153	Risk Ratio (IV, Random, 95% CI)	0.77 [0.55, 1.09]
32 Adverse events: respiratory body system in adult prophylaxis (on-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	0.87 [0.80, 0.94]
33 Adverse events: skin body system in adult prophylaxis (on-treatment)	8	7774	Risk Ratio (IV, Random, 95% CI)	0.92 [0.58, 1.45]
34 Adverse events: gastrointestinal body system in adult prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	0.84 [0.63, 1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35 Adverse events: respiratory body system in adult prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	0.79 [0.54, 1.15]
36 Adverse events: nausea/vomiting in prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	0.80 [0.39, 1.67]
37 Adverse events: diarrhoea in prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	0.92 [0.54, 1.57]
38 Adverse events: headache in prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	0.95 [0.76, 1.19]
39 Adverse events: cough in prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	1.31 [0.99, 1.73]
40 Adverse events: fatigue in prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	0.74 [0.47, 1.16]
41 Adverse events: neurological body system in prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	1.01 [0.82, 1.24]
42 Adverse events: ear, nose and throat in prophylaxis (off-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	0.99 [0.84, 1.17]
43 Adverse events: musculoskeletal body system in prophylaxis (off-treatment)	9	8109	Risk Ratio (IV, Random, 95% CI)	1.03 [0.77, 1.39]
44 Adverse events: non-site specific in prophylaxis (off-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	0.99 [0.74, 1.32]
45 Adverse events: injury in prophylaxis (off-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	0.61 [0.34, 1.10]
46 Adverse events: endocrine and metabolic in prophylaxis (off-treatment)	8	7792	Risk Ratio (IV, Random, 95% CI)	1.04 [0.60, 1.83]

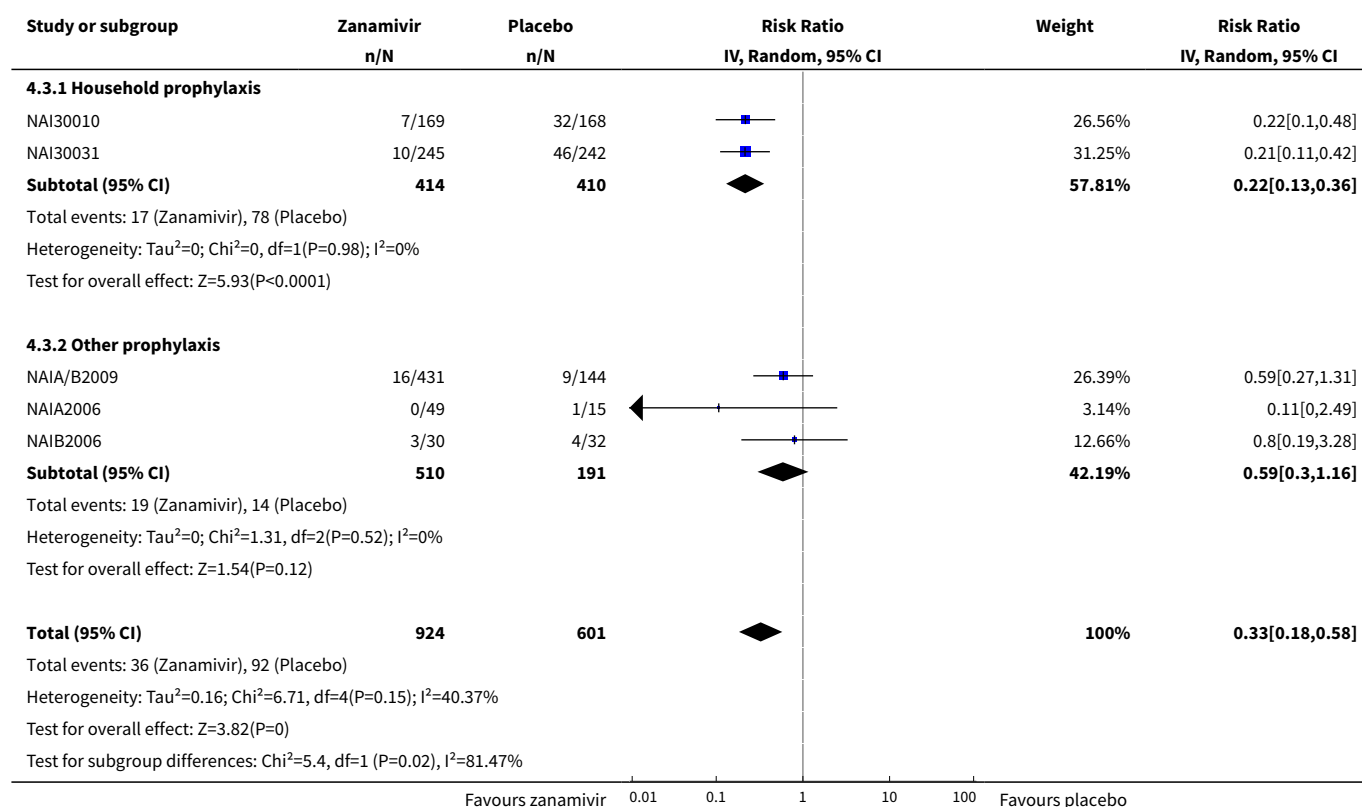
Analysis 4.1. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 1 Symptomatic influenza in prophylaxis of individuals.



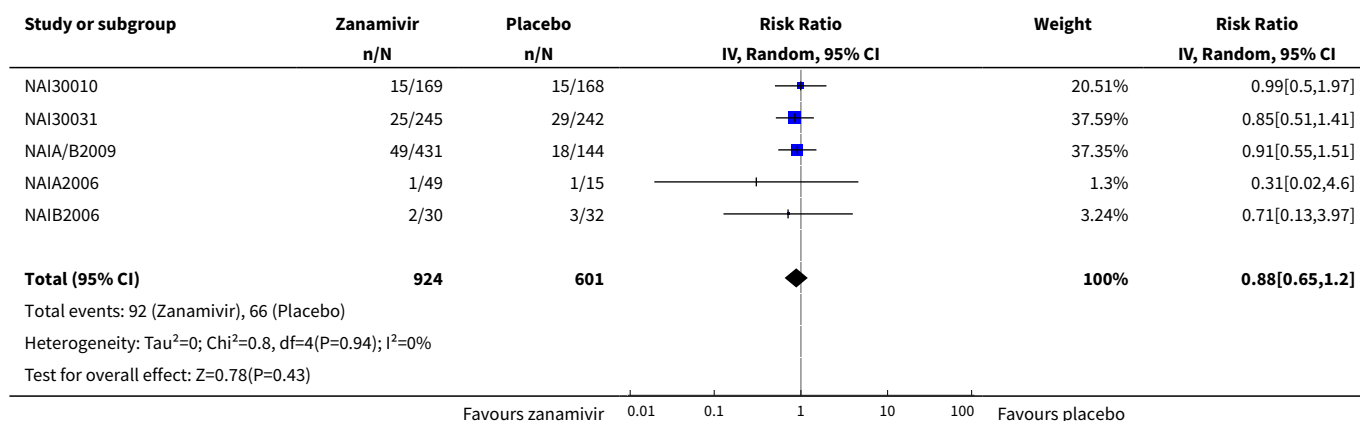
Analysis 4.2. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 2 Asymptomatic influenza in prophylaxis of individuals.



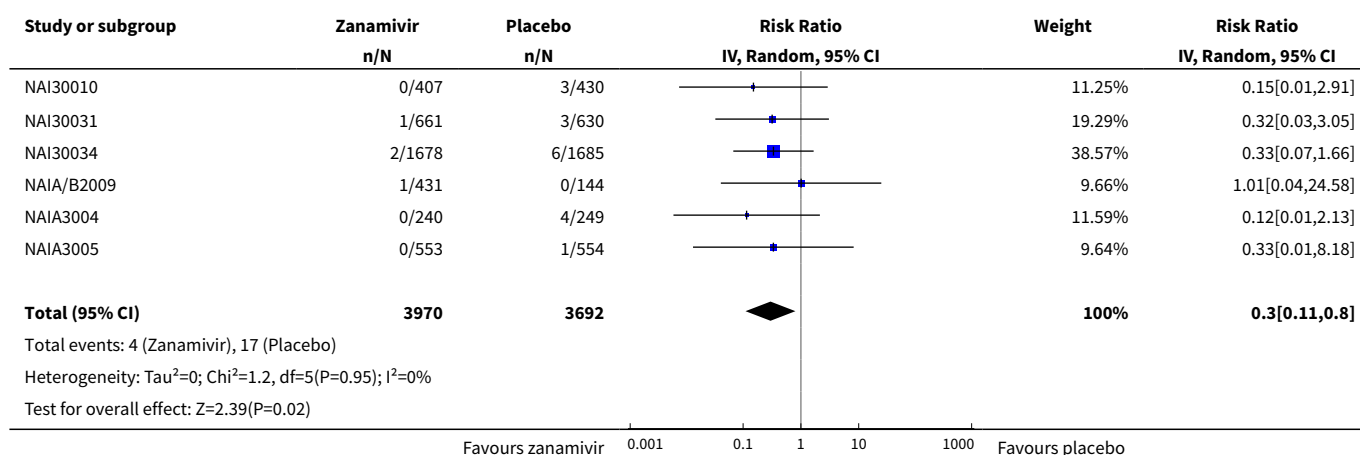
Analysis 4.3. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 3 Symptomatic influenza in post-exposure prophylaxis.



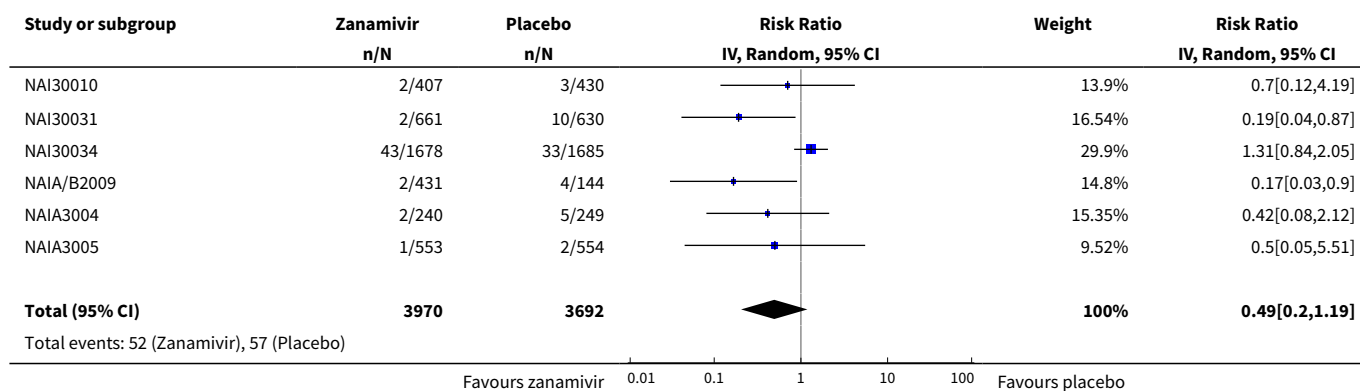
Analysis 4.4. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 4 Asymptomatic influenza in post-exposure prophylaxis.

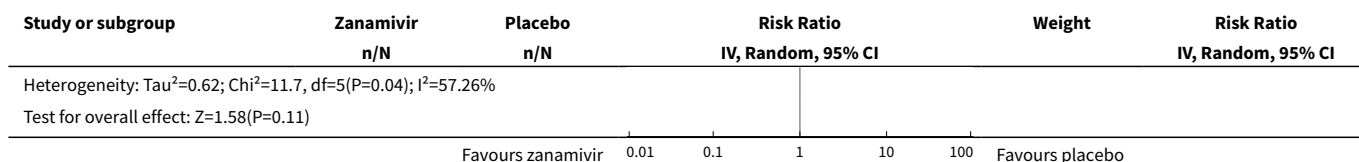


Analysis 4.5. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 5 Complications: pneumonia in adult prophylaxis.

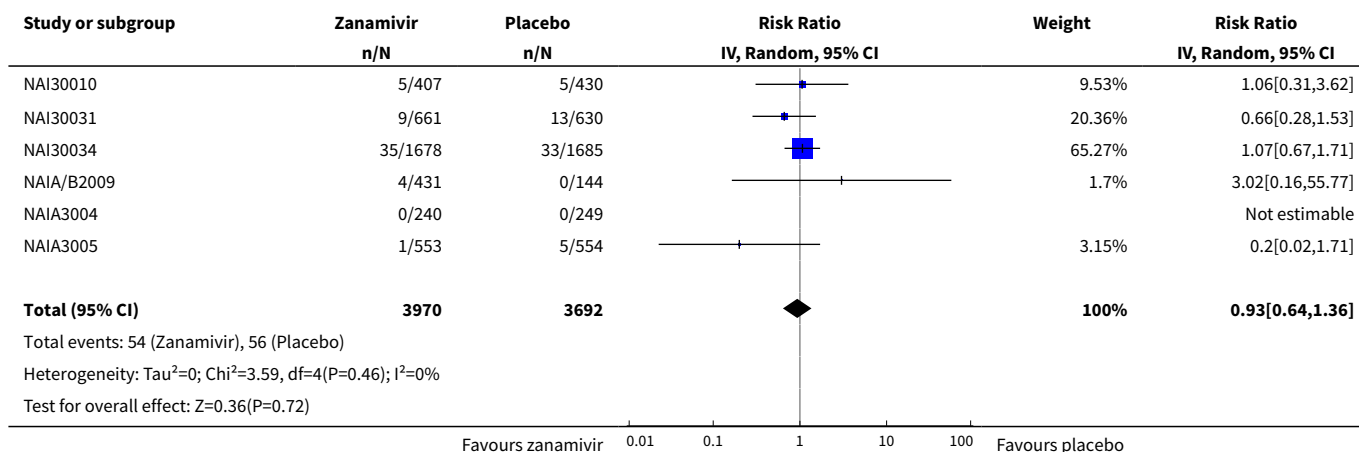


Analysis 4.6. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 6 Complications: bronchitis in adult prophylaxis.

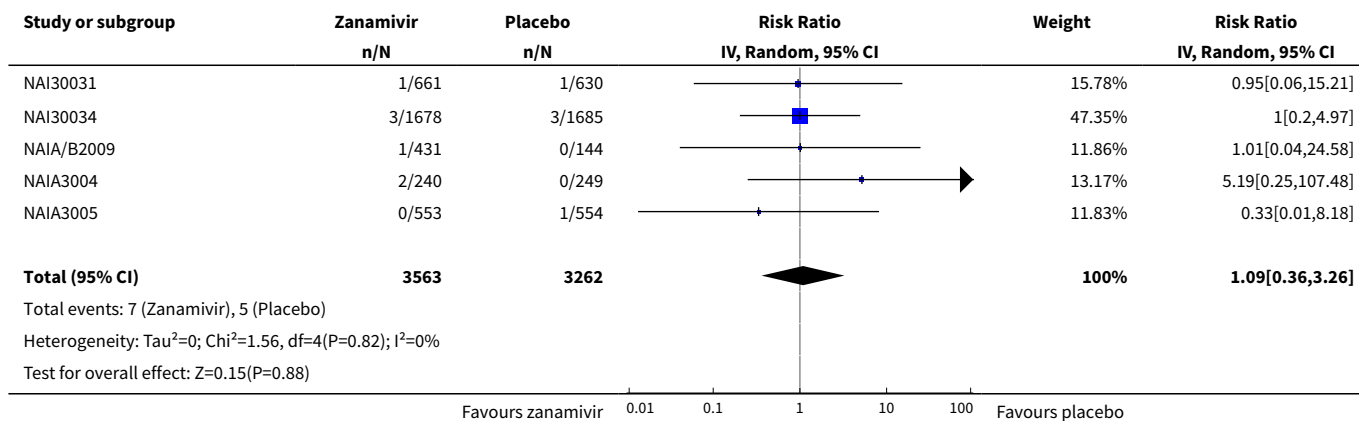




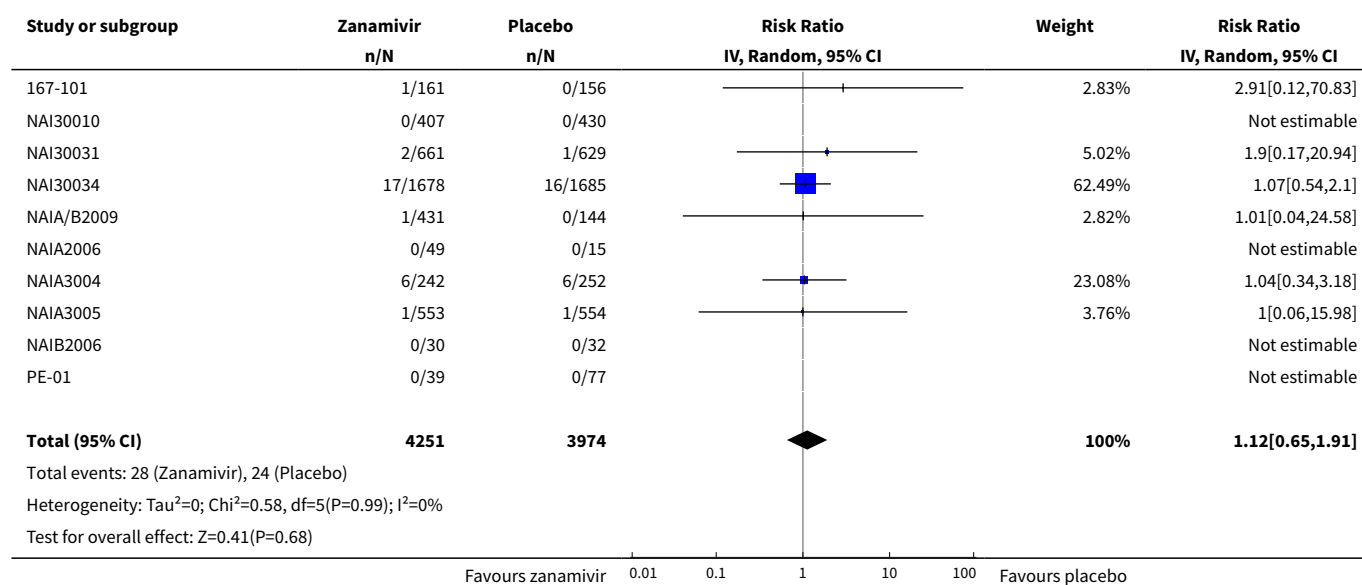
Analysis 4.7. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 7 Complications: sinusitis in adult prophylaxis.



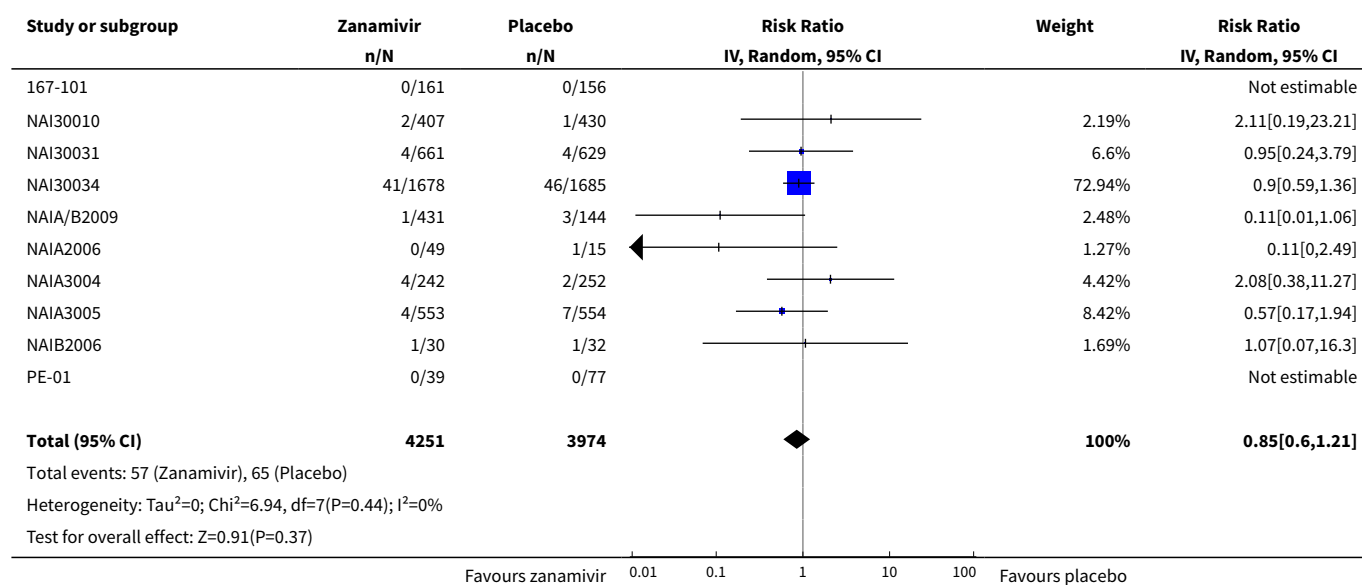
Analysis 4.8. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 8 Complications classified as serious or leading to study withdrawal.



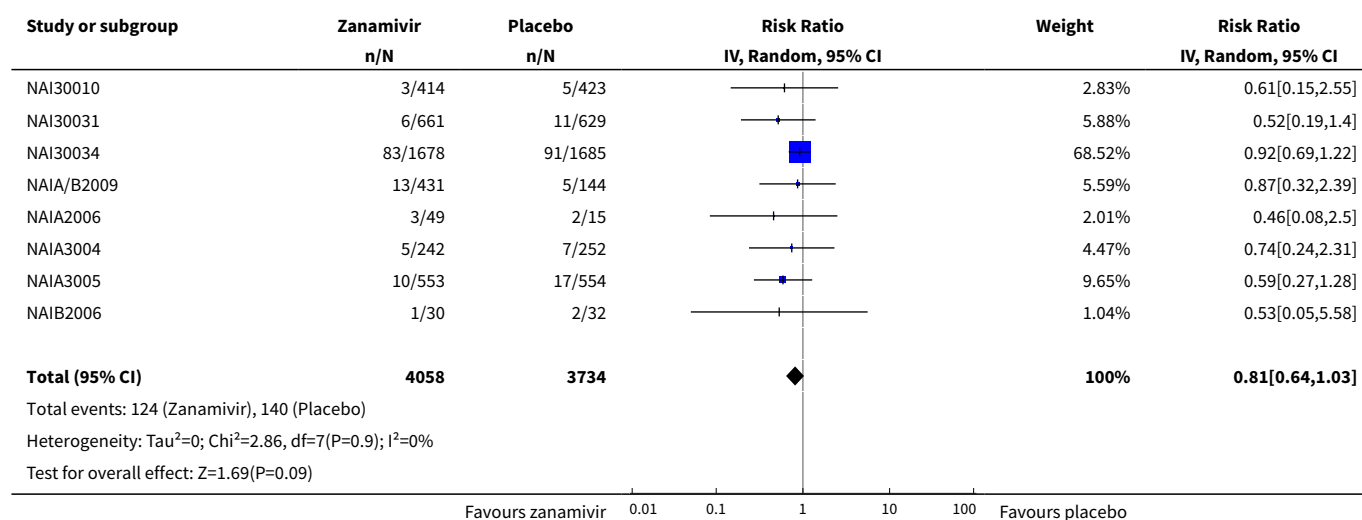
Analysis 4.9. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 9 Serious adverse events in adult prophylaxis.



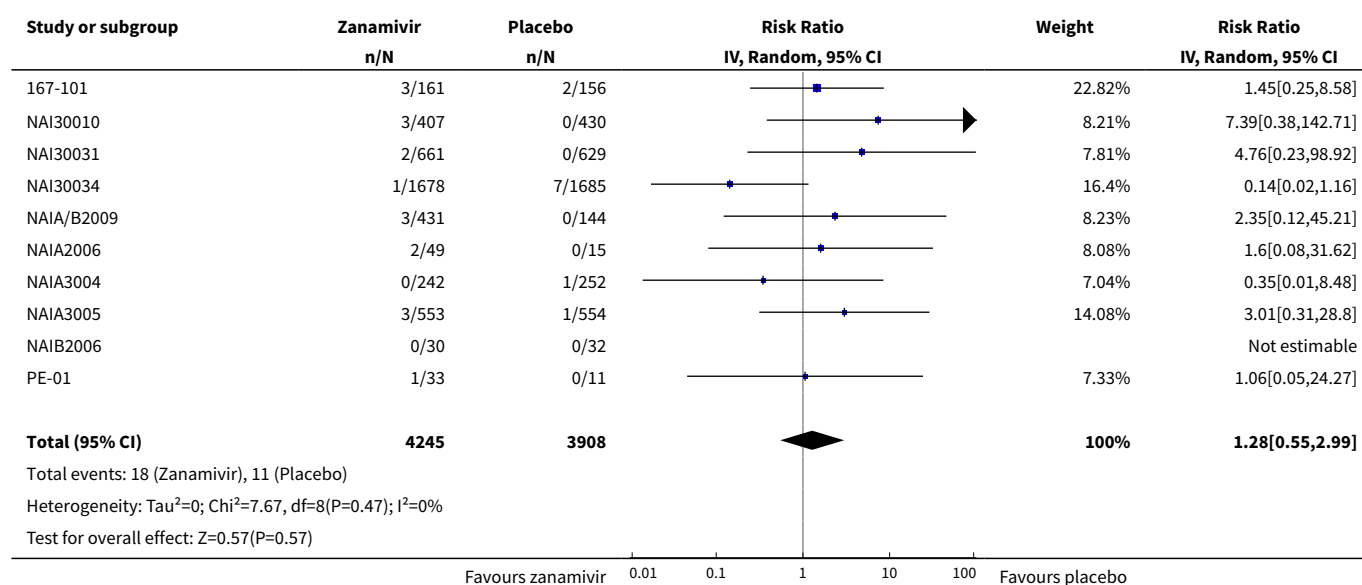
Analysis 4.10. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 10 Adverse events leading to study withdrawal in adult prophylaxis.



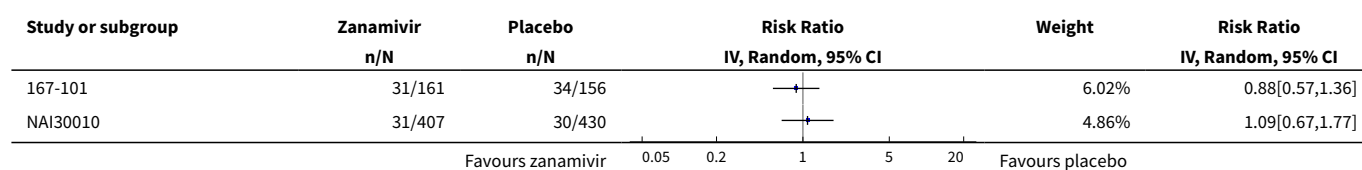
Analysis 4.11. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 11 All withdrawals in adult prophylaxis.

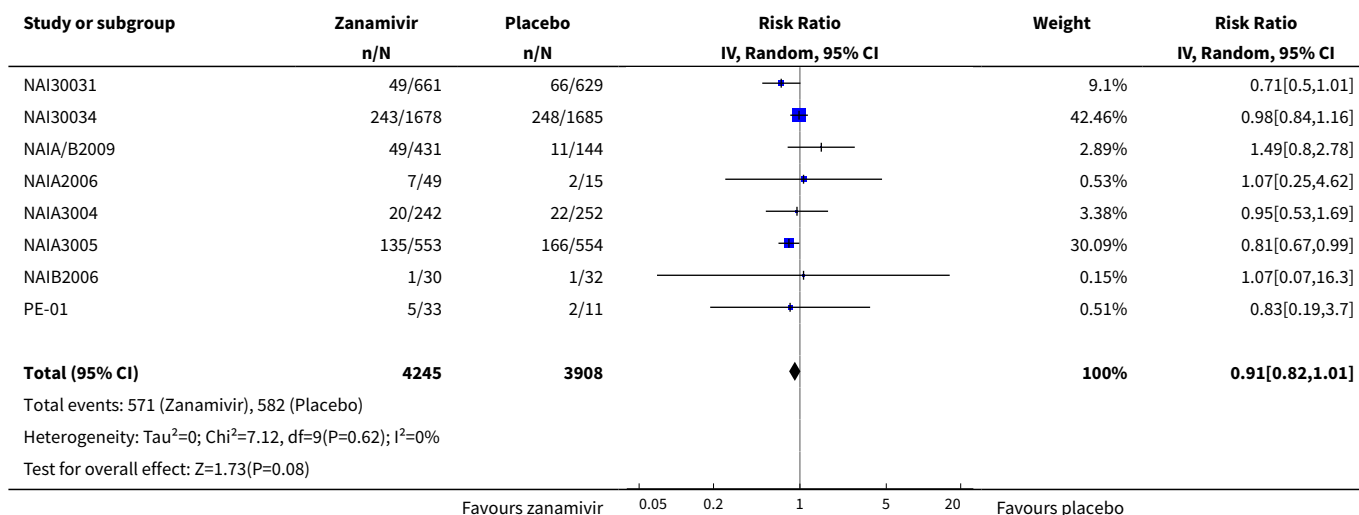


Analysis 4.12. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 12 Adverse events: abdominal pain in adult prophylaxis (on-treatment).

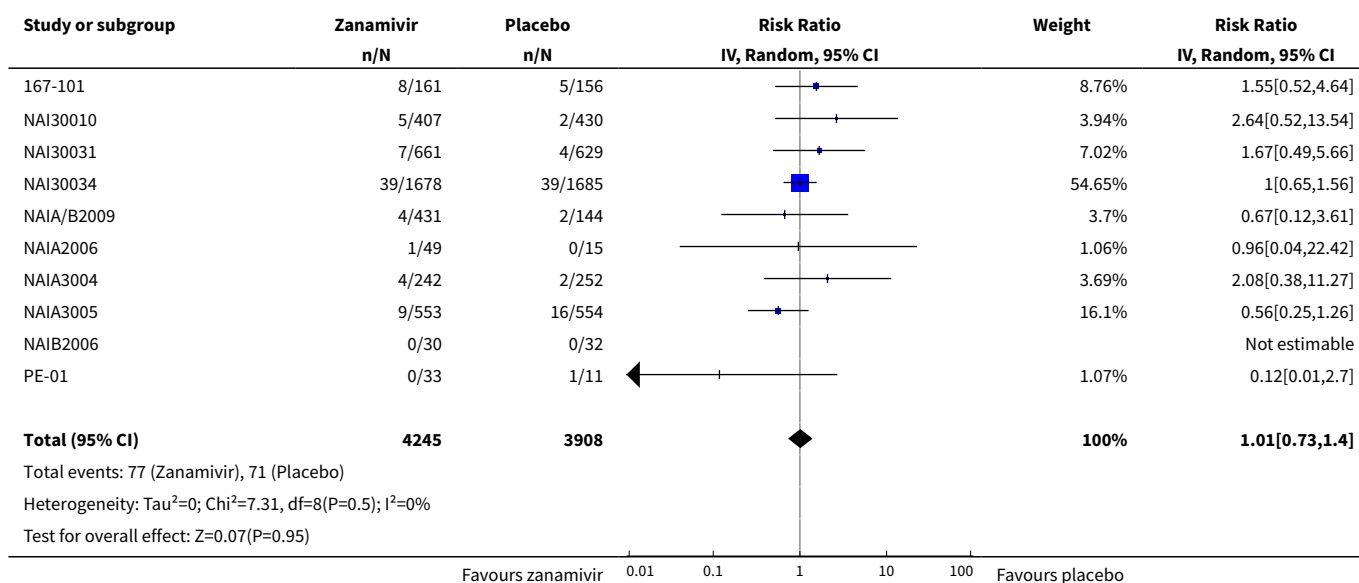


Analysis 4.13. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 13 Adverse events: cough in adult prophylaxis (on-treatment).

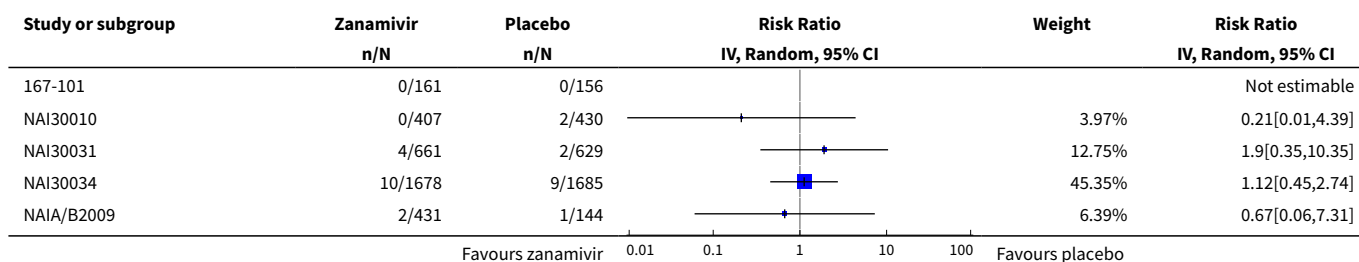


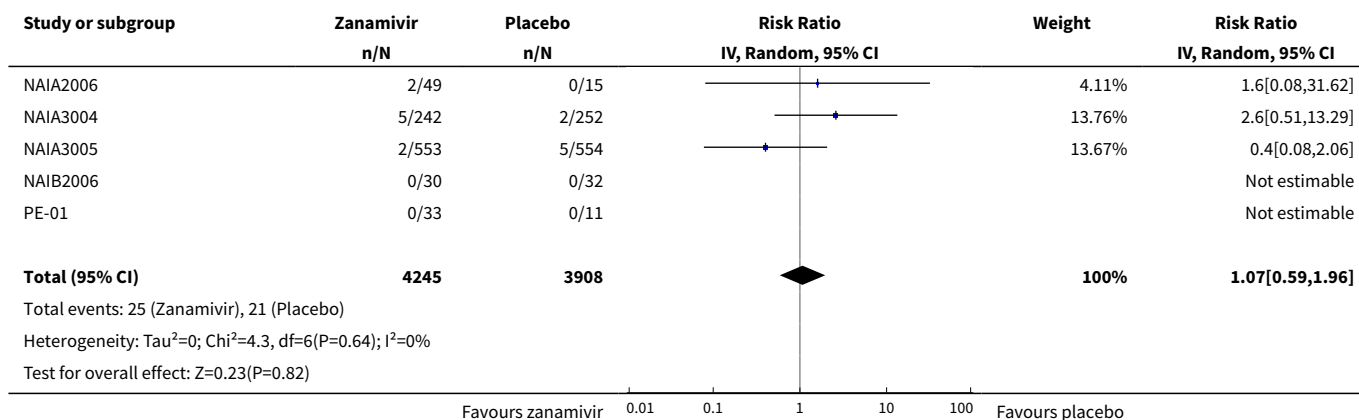


Analysis 4.14. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 14 Adverse events: diarrhoea in adult prophylaxis (on-treatment).

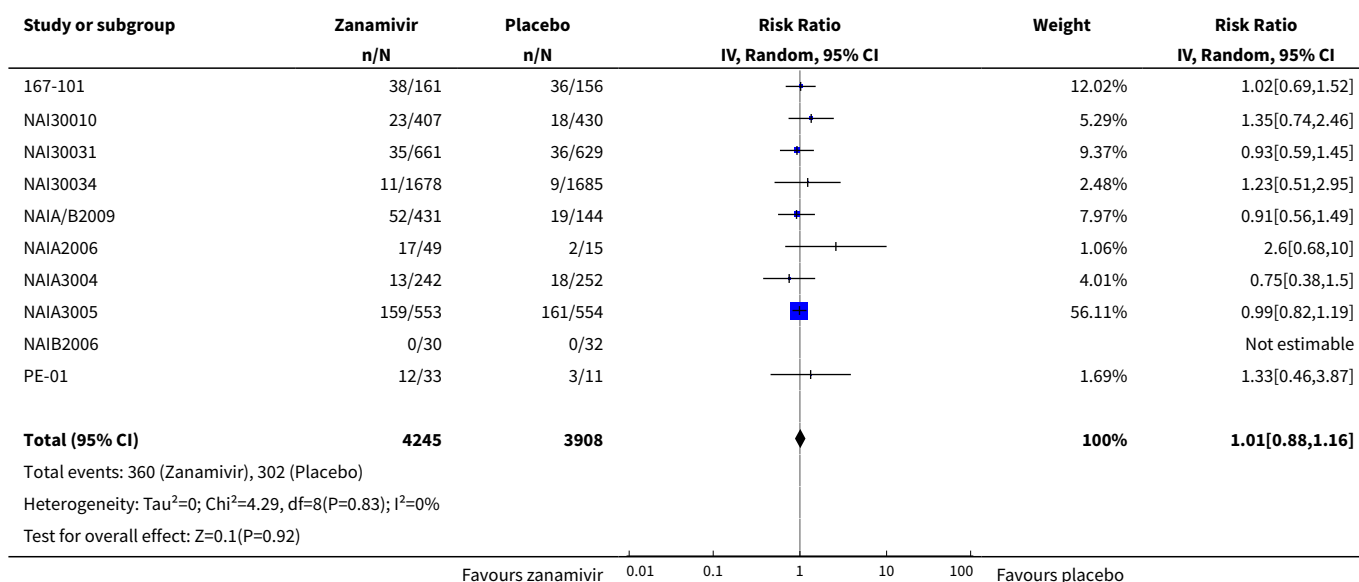


Analysis 4.15. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 15 Adverse events: dizziness in adult prophylaxis (on-treatment).

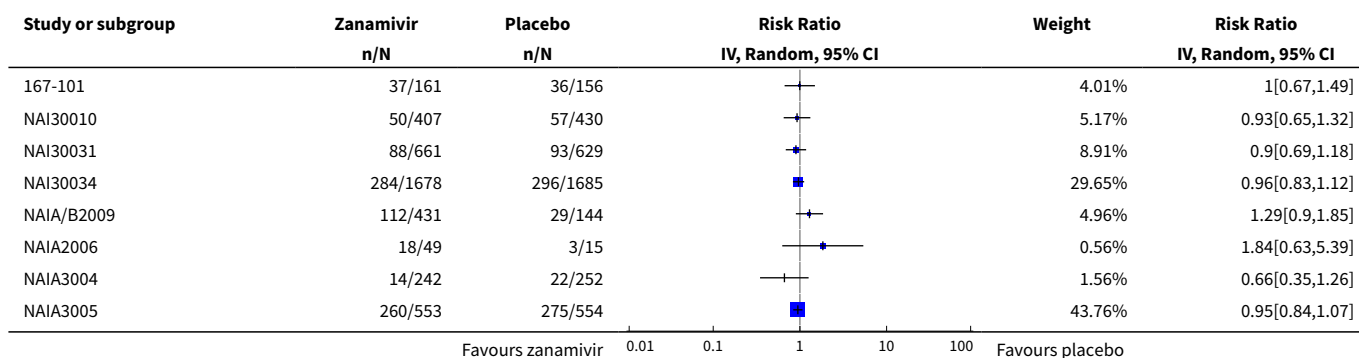


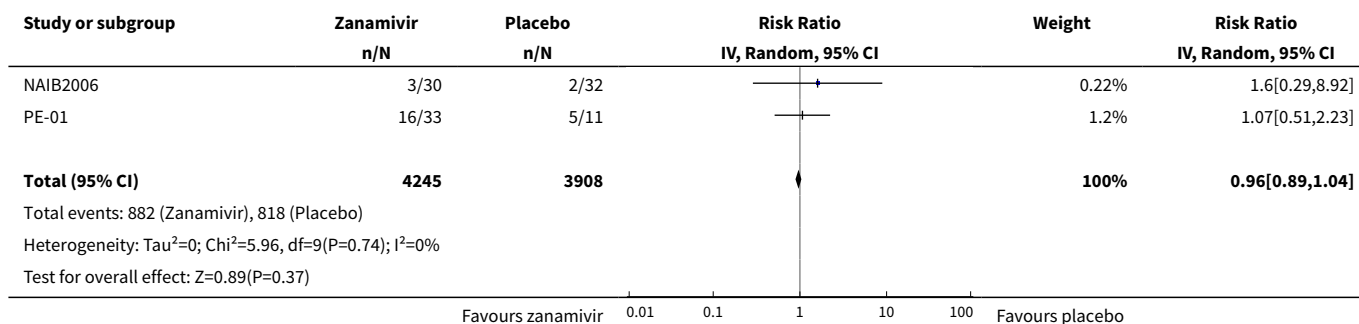


Analysis 4.16. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 16 Adverse events: fatigue in adult prophylaxis (on-treatment).

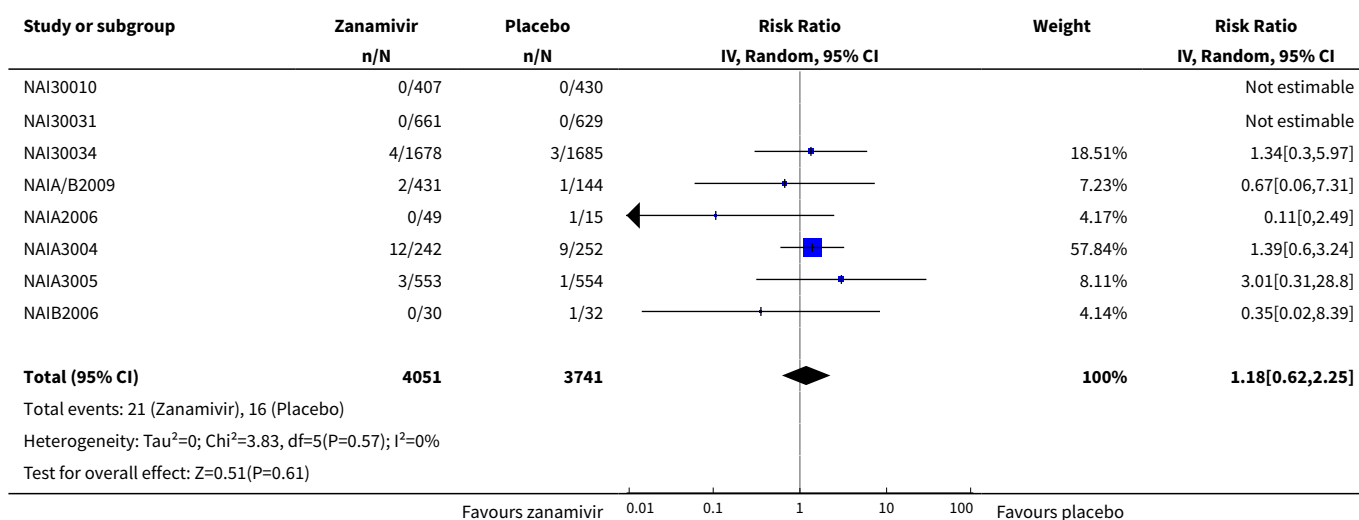


Analysis 4.17. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 17 Adverse events: headache in adult prophylaxis (on-treatment).

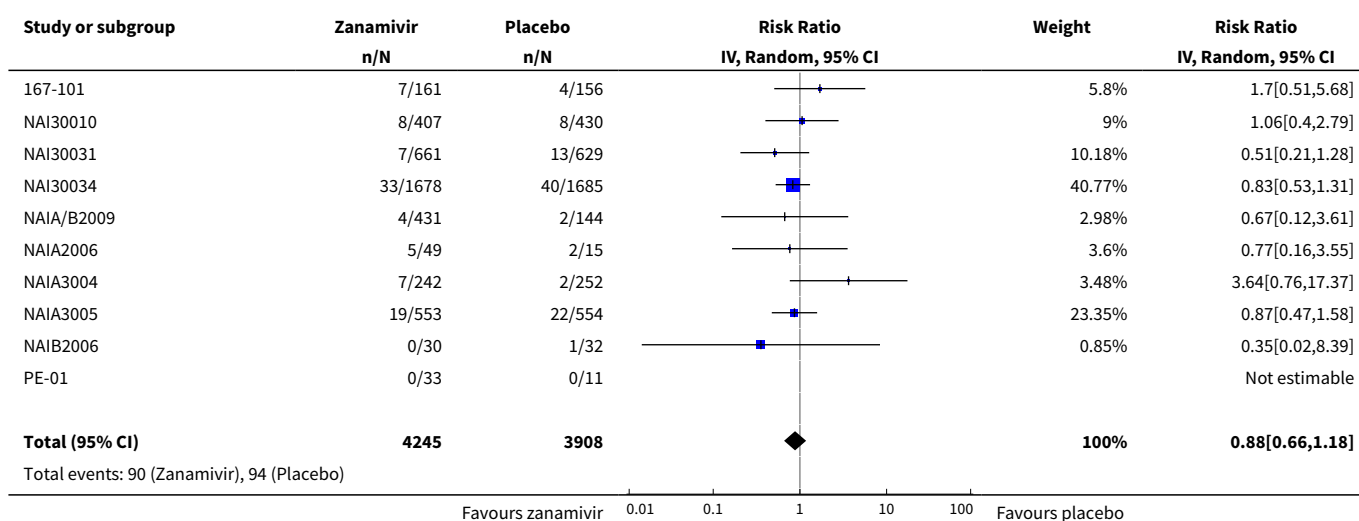


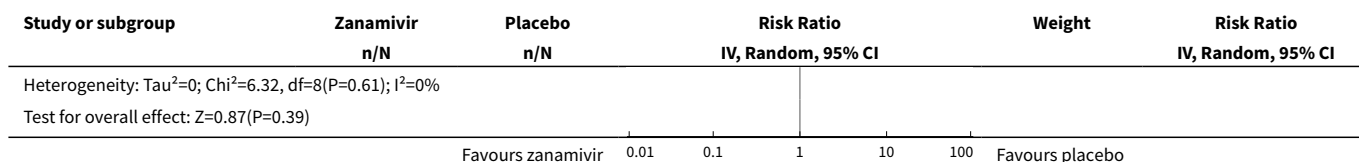


Analysis 4.18. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 18 Adverse events: blood body system in adult prophylaxis (on-treatment).

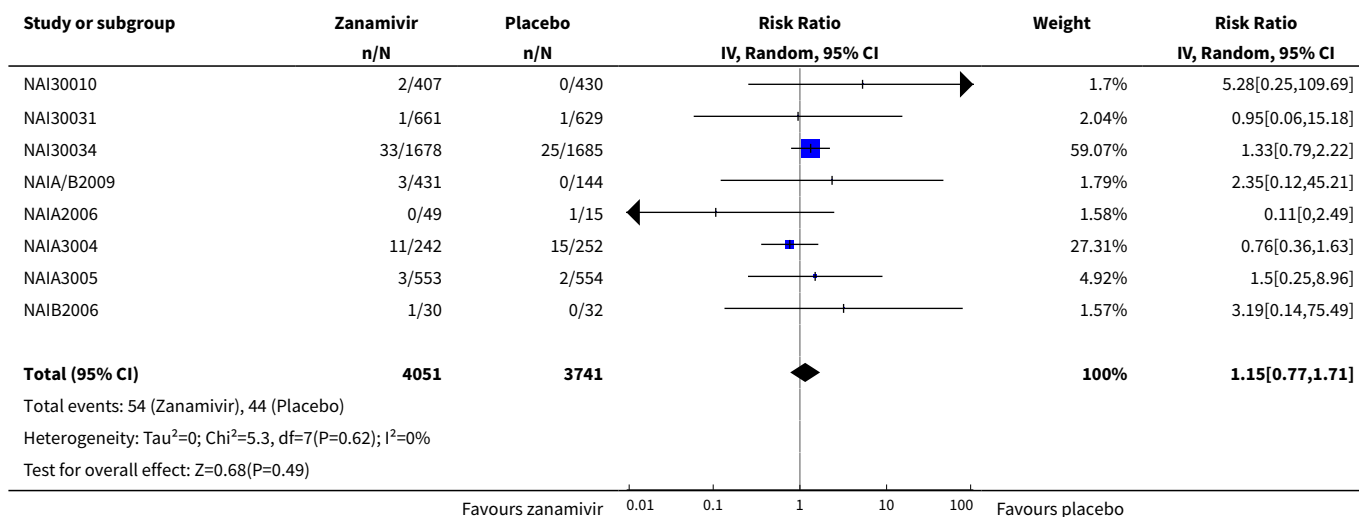


Analysis 4.19. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 19 Adverse events: nausea/vomiting in adult prophylaxis (on-treatment).

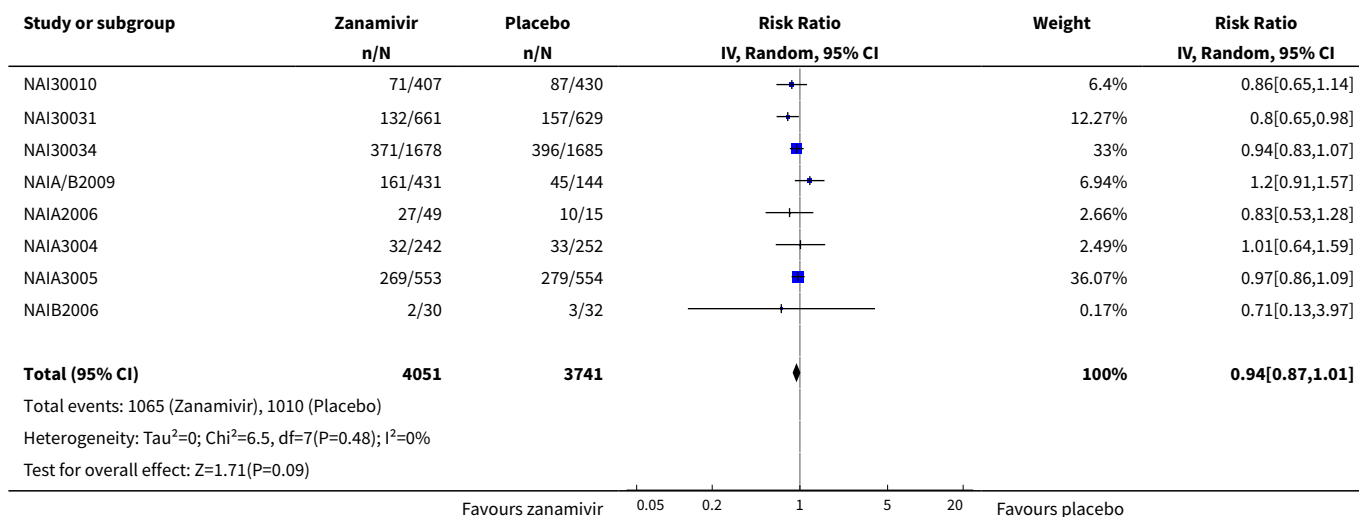




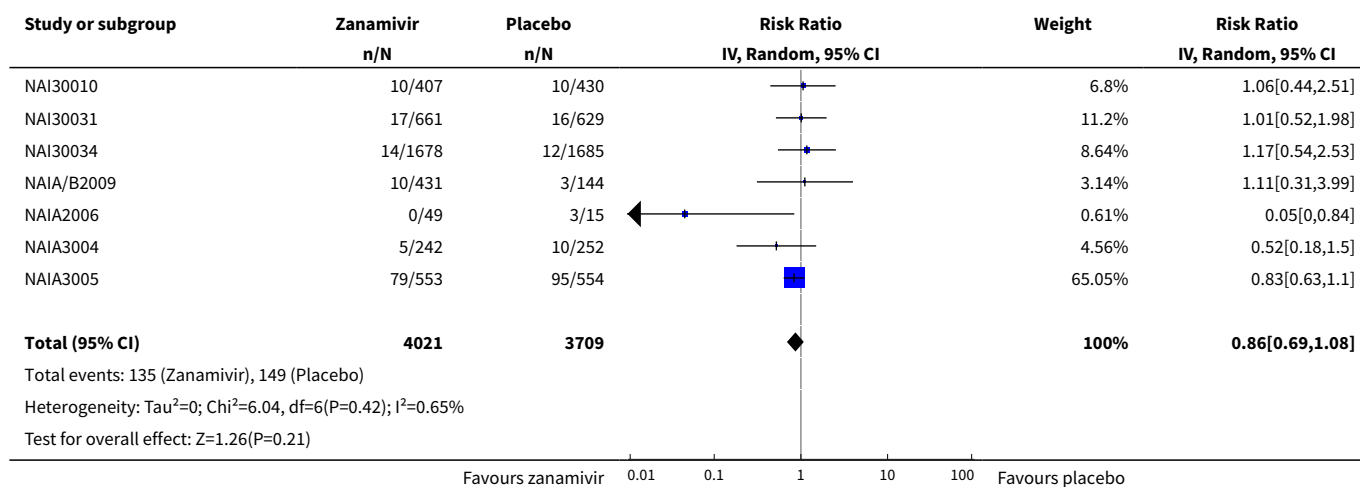
Analysis 4.20. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 20
Adverse events: cardiovascular body system in adult prophylaxis (on-treatment).



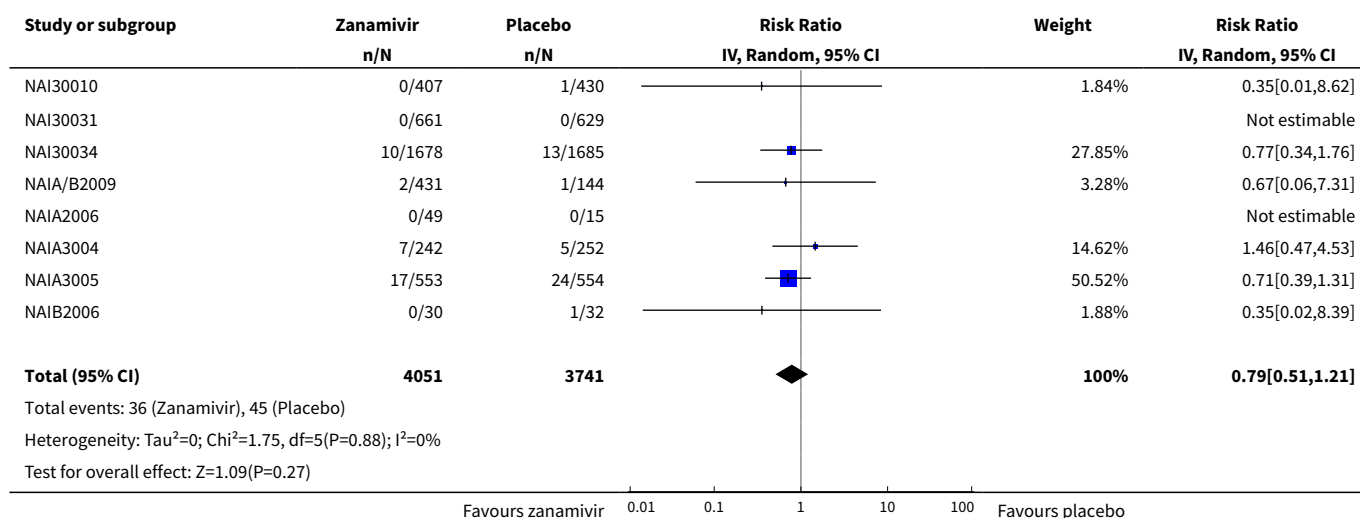
Analysis 4.21. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 21
Adverse events: ear, nose and throat body system in adult prophylaxis (on-treatment).



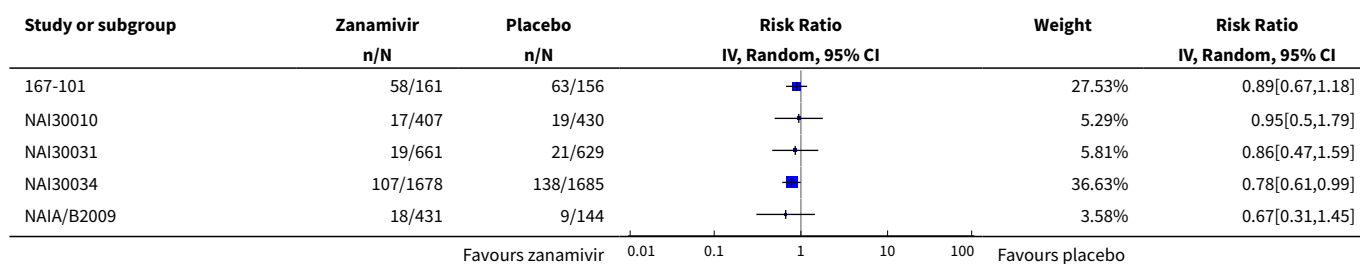
Analysis 4.22. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 22 Adverse events: endocrine and metabolic body system in adult prophylaxis (on-treatment).

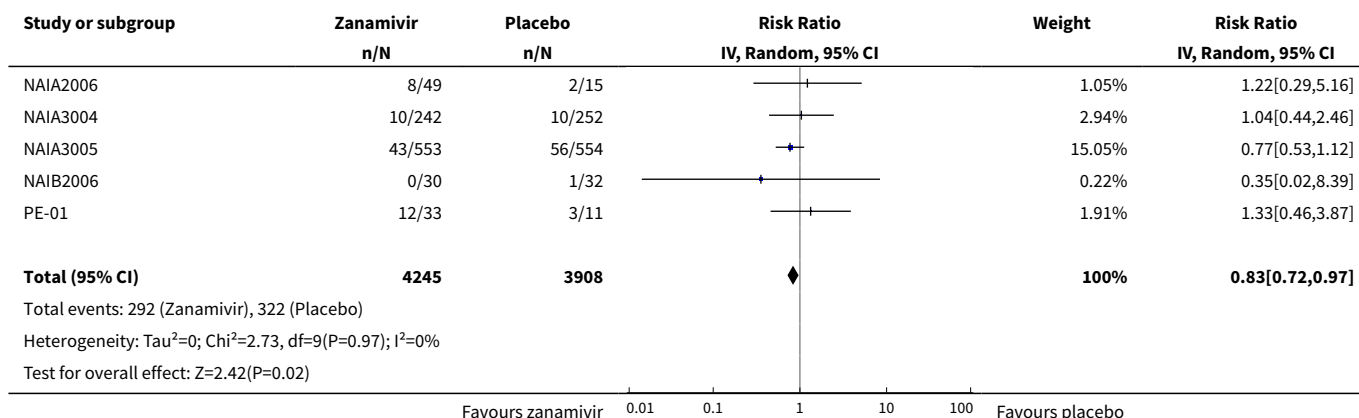


Analysis 4.23. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 23 Adverse events: eye body system in adult prophylaxis (on-treatment).

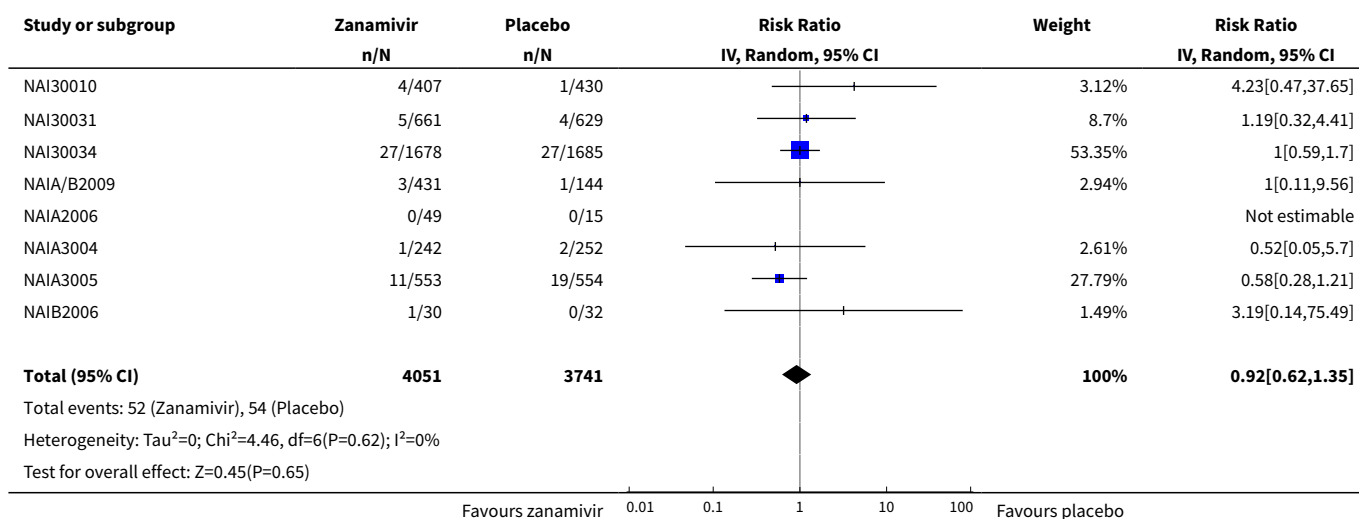


Analysis 4.24. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 24 Adverse events: gastrointestinal body system in adult prophylaxis (on-treatment).

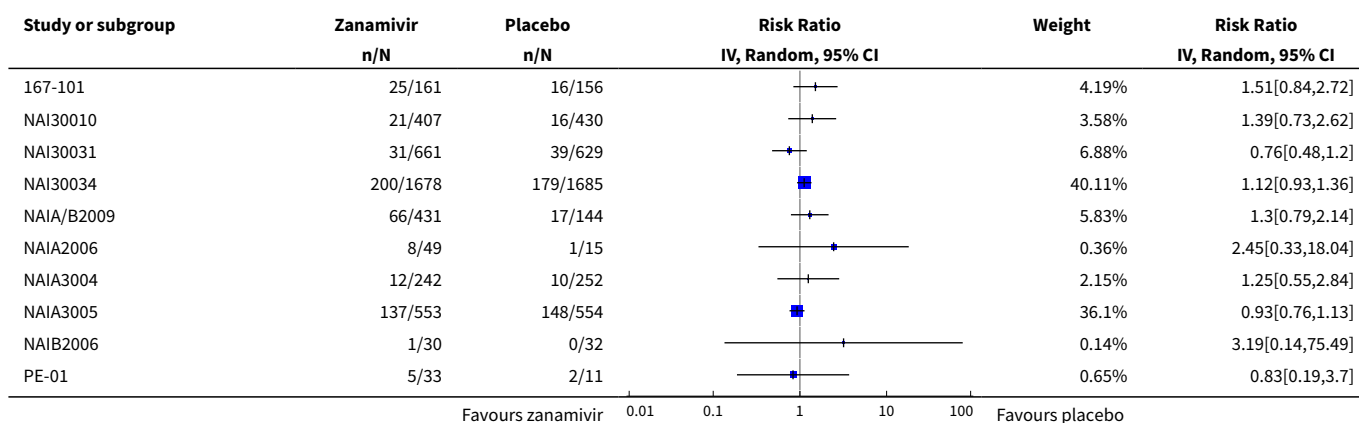


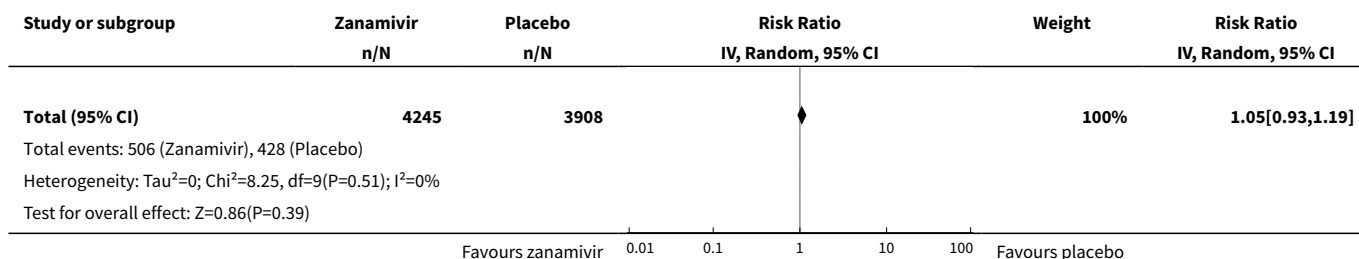


Analysis 4.25. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 25 Adverse events: injury body system in adult prophylaxis (on-treatment).

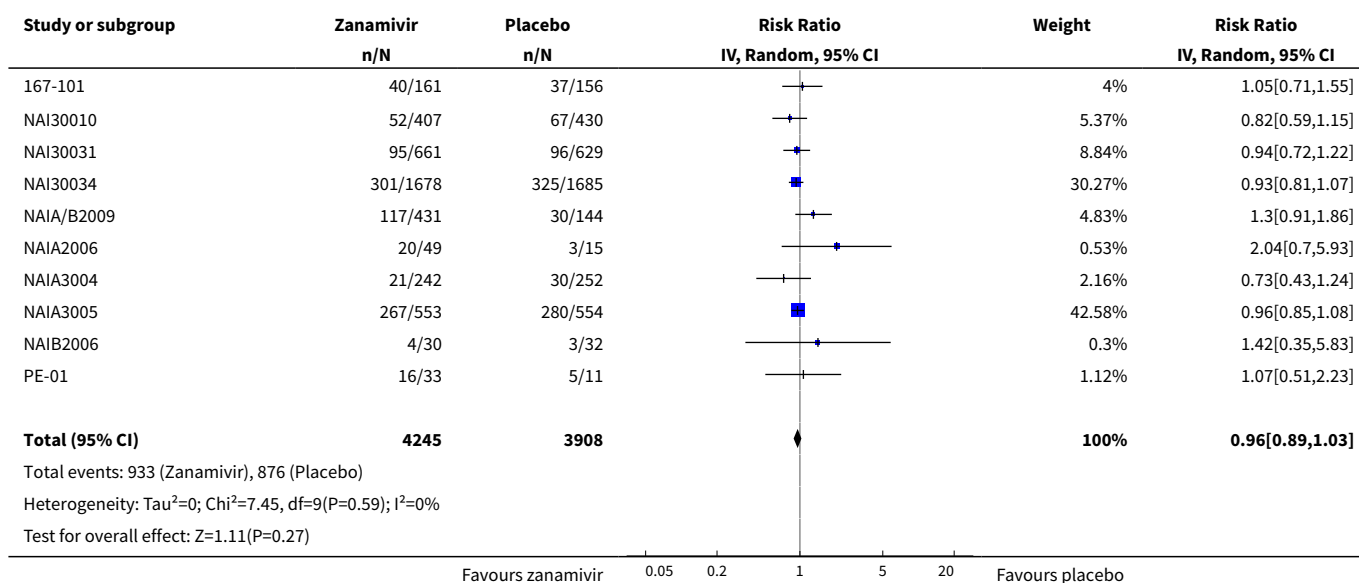


Analysis 4.26. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 26 Adverse events: musculoskeletal body system in adult prophylaxis (on-treatment).

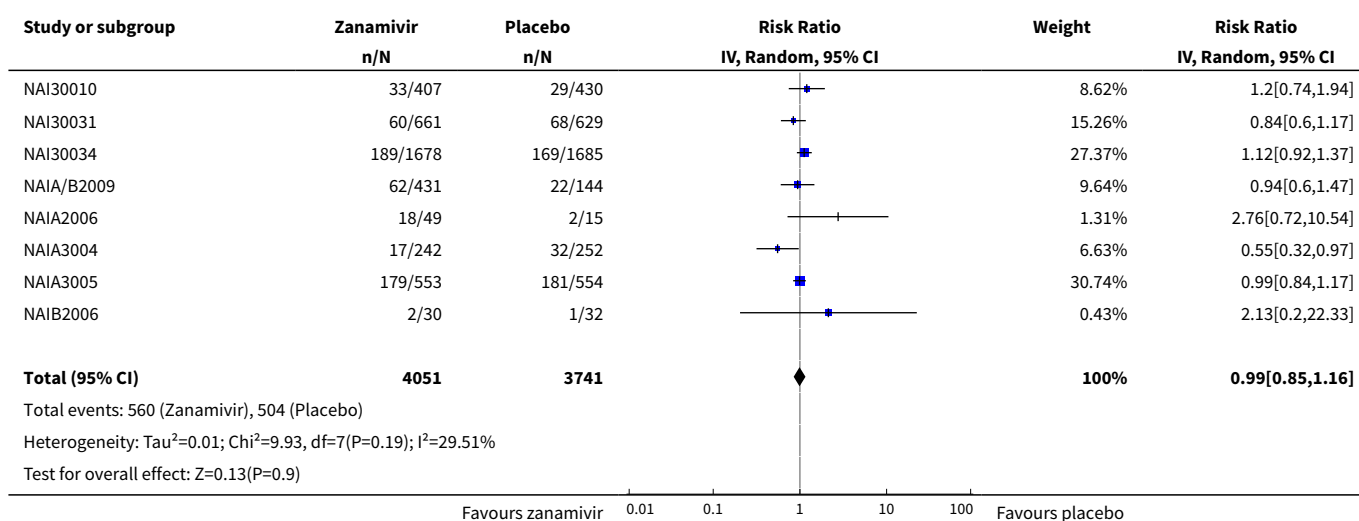




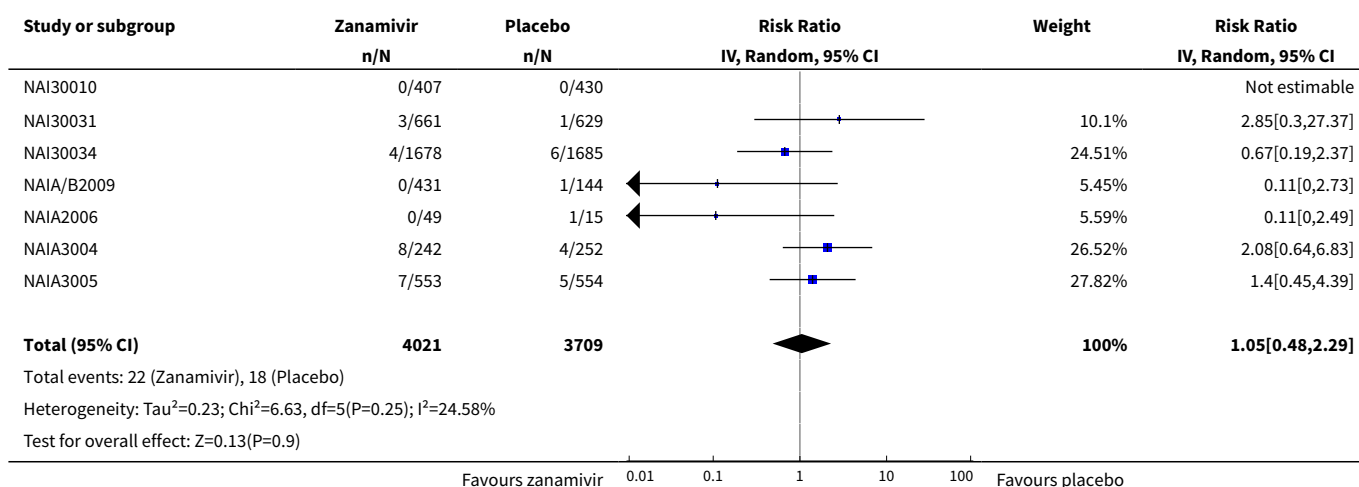
Analysis 4.27. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 27 Adverse events: neurological body system in adult prophylaxis (on-treatment).



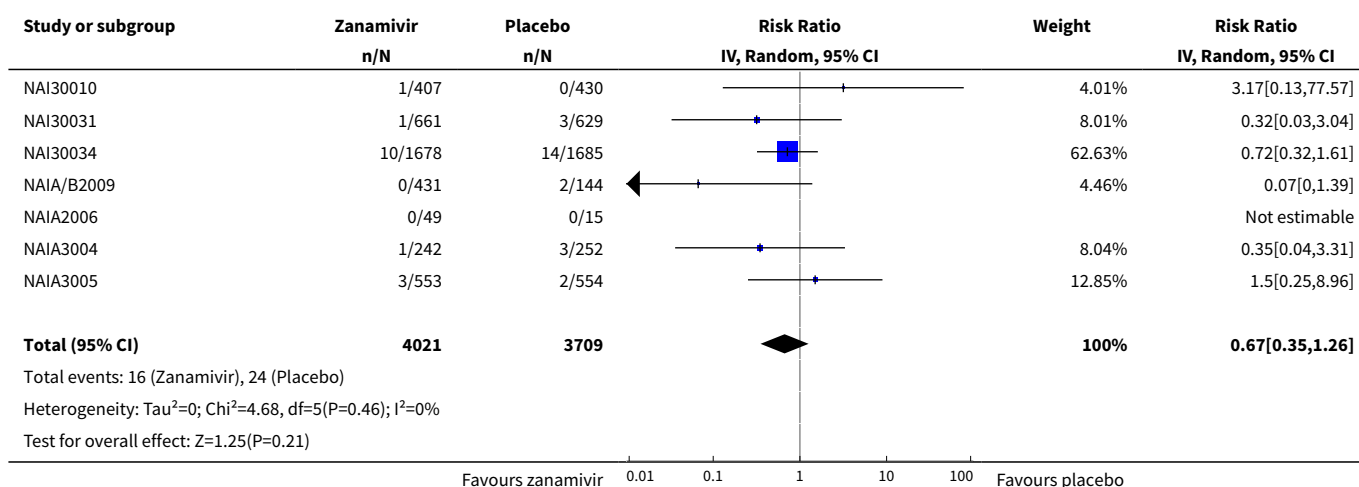
Analysis 4.28. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 28 Adverse events: non-site specific in adult prophylaxis (on-treatment).



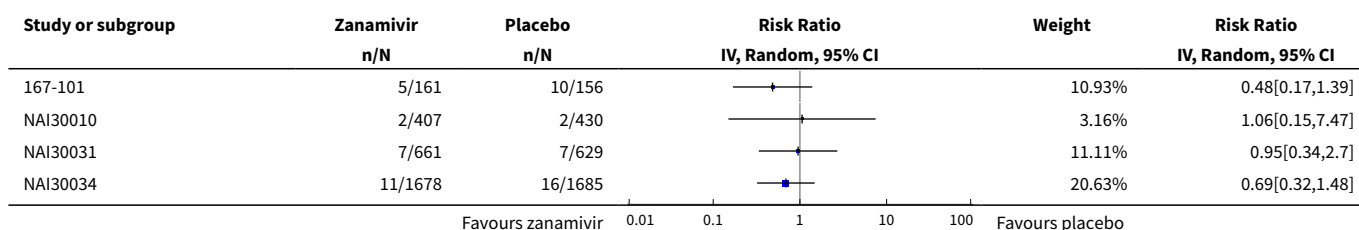
Analysis 4.29. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 29 Adverse events: psychiatric body system in adult prophylaxis (on-treatment).

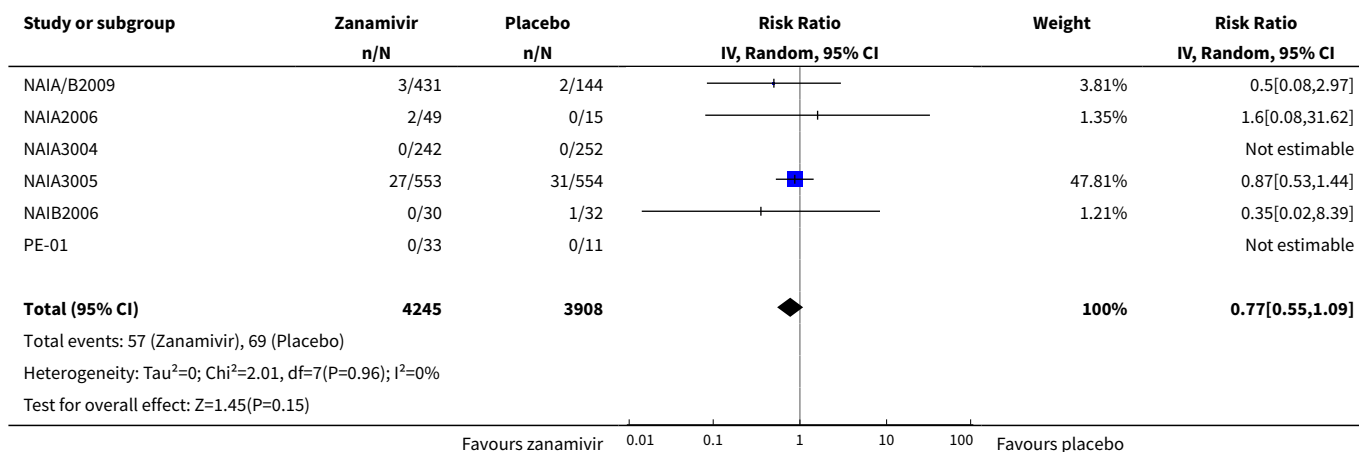


Analysis 4.30. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 30 Adverse events: renal body system in adult prophylaxis (on-treatment).

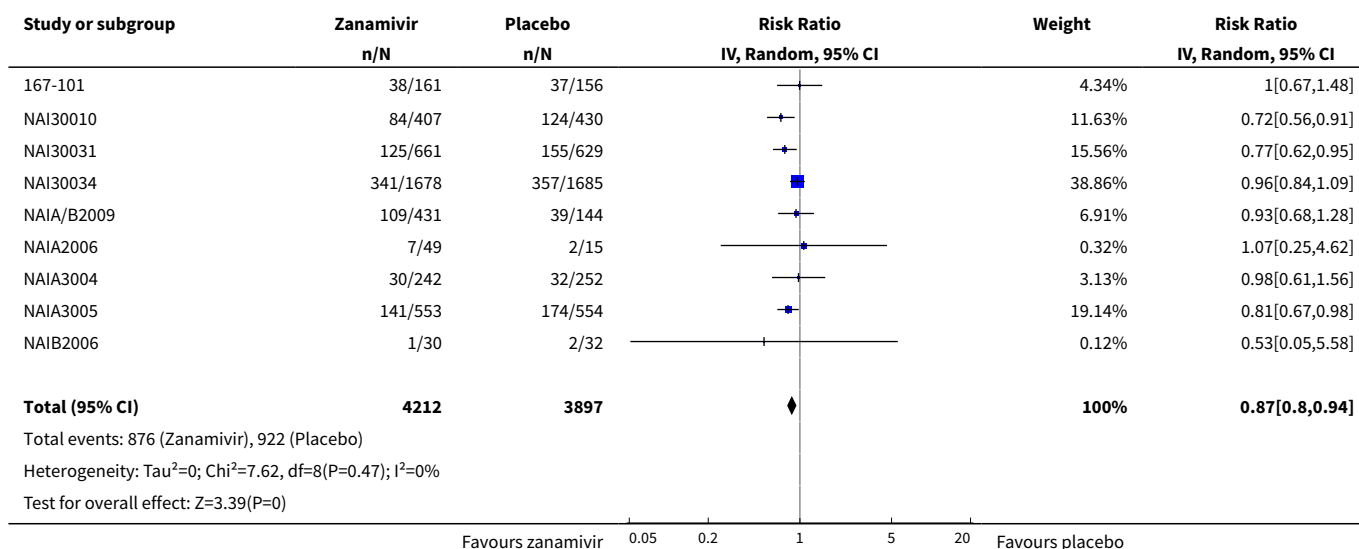


Analysis 4.31. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 31 Adverse events: reproductive body system in adult prophylaxis (on-treatment).

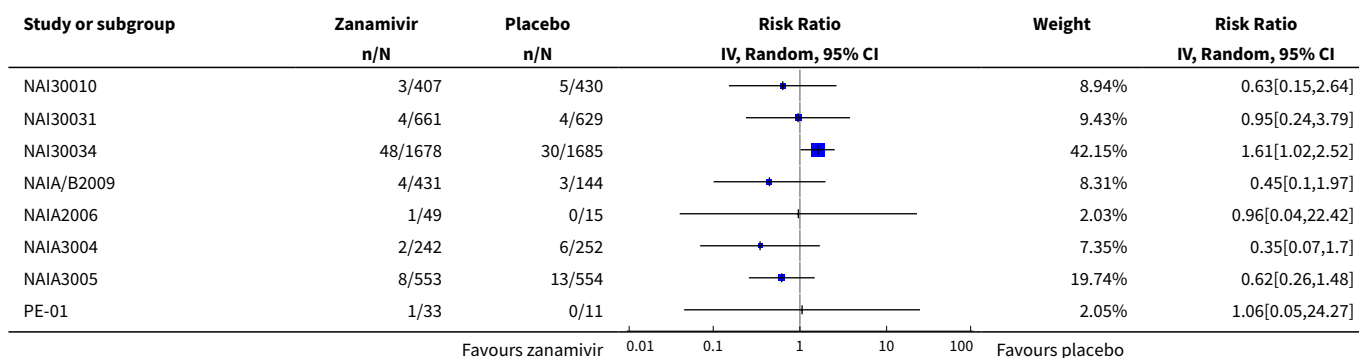


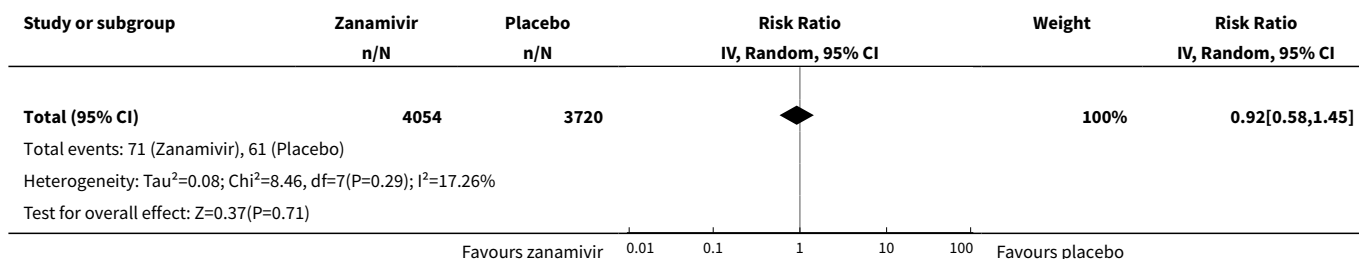


Analysis 4.32. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 32 Adverse events: respiratory body system in adult prophylaxis (on-treatment).

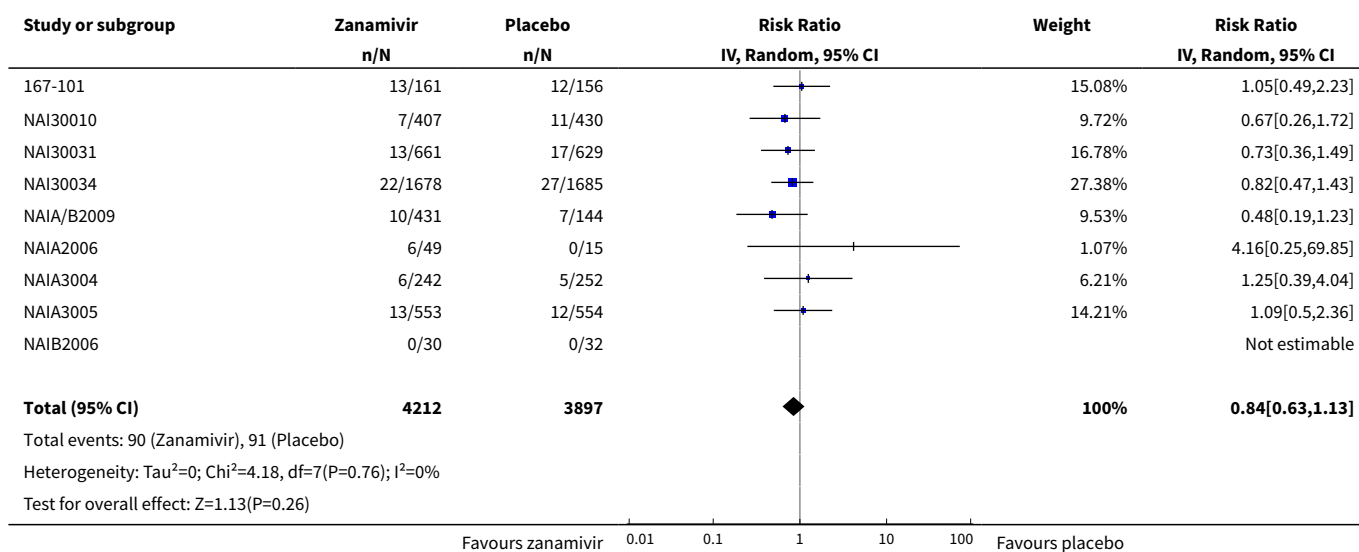


Analysis 4.33. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 33 Adverse events: skin body system in adult prophylaxis (on-treatment).

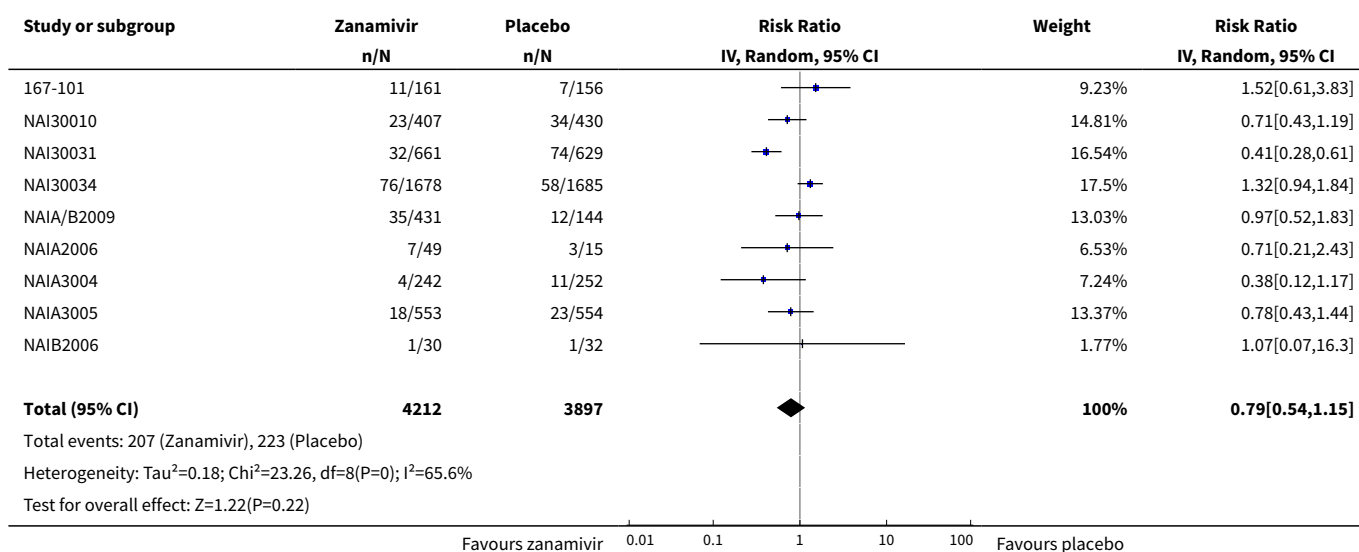




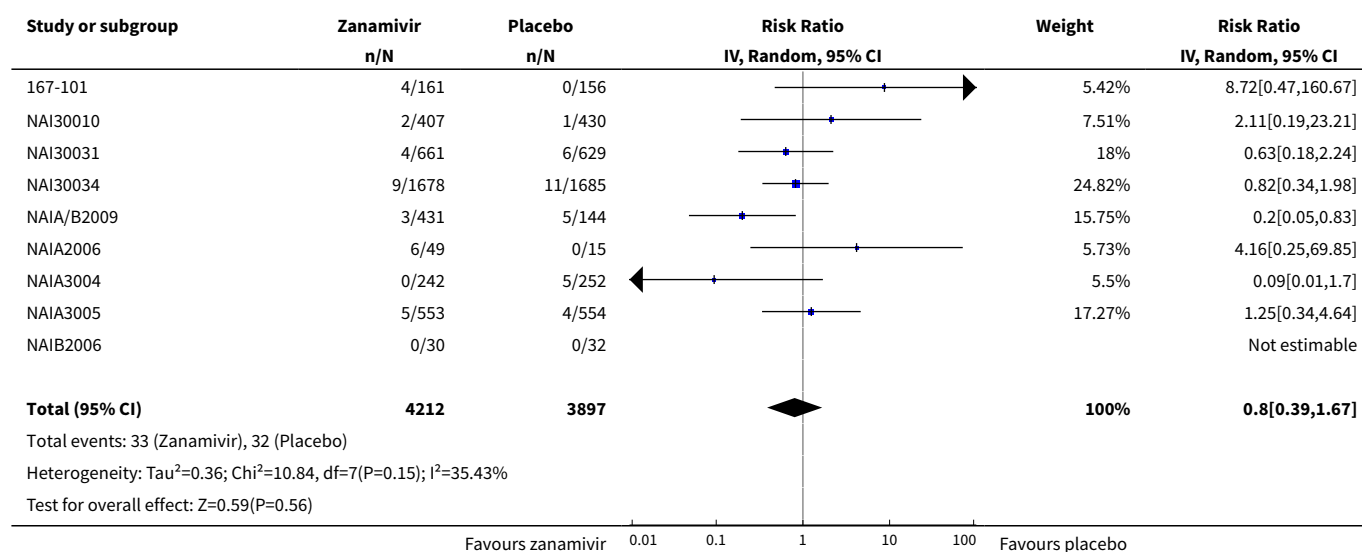
Analysis 4.34. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 34 Adverse events: gastrointestinal body system in adult prophylaxis (off-treatment).



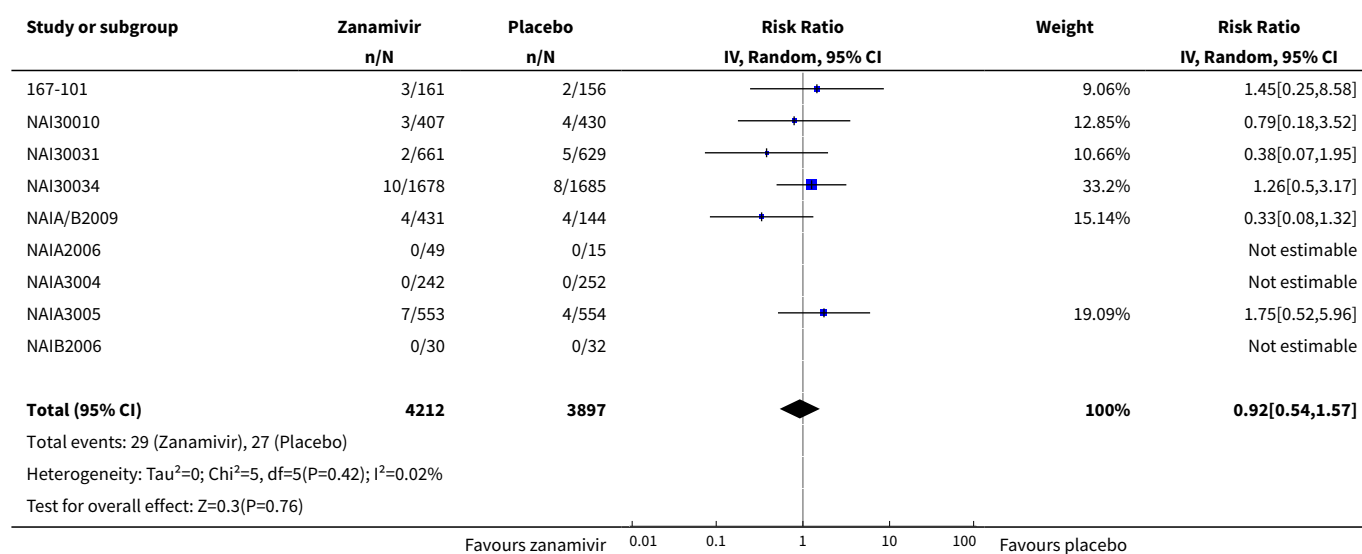
Analysis 4.35. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 35 Adverse events: respiratory body system in adult prophylaxis (off-treatment).



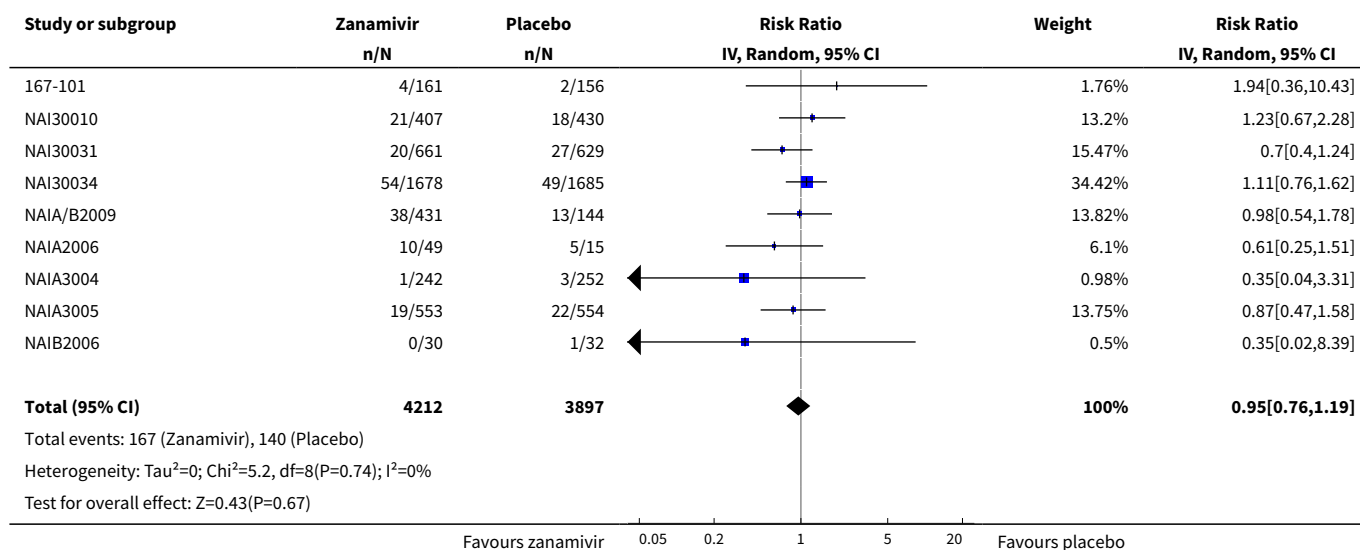
**Analysis 4.36. Comparison 4 Zanamivir versus placebo for prophylaxis,
Outcome 36 Adverse events: nausea/vomiting in prophylaxis (off-treatment).**



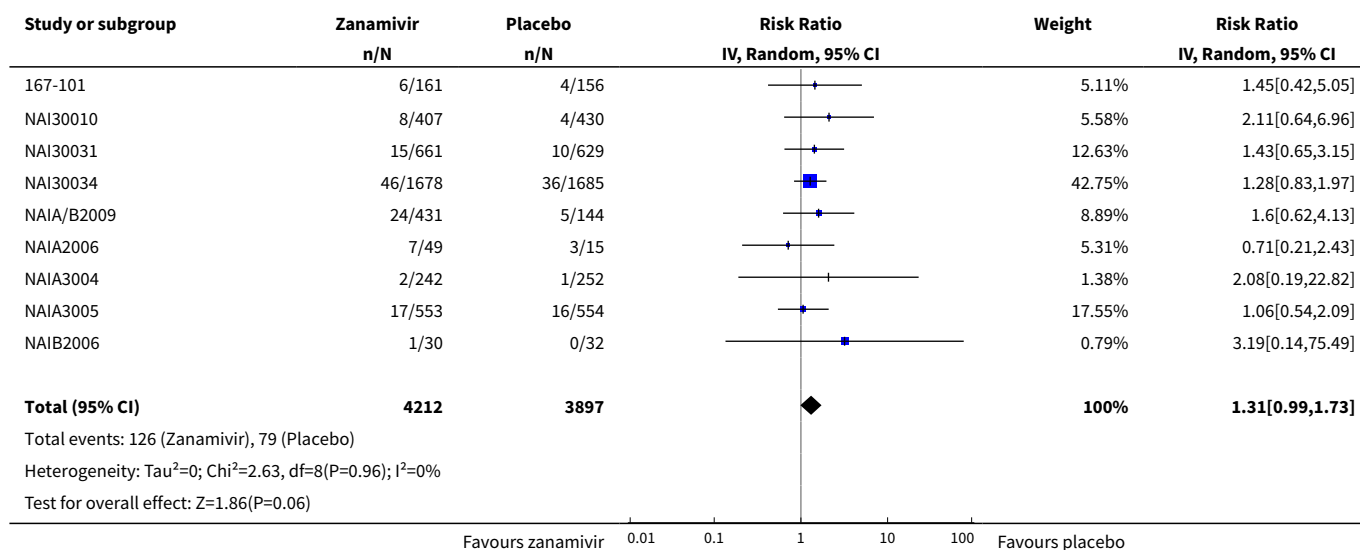
**Analysis 4.37. Comparison 4 Zanamivir versus placebo for prophylaxis,
Outcome 37 Adverse events: diarrhoea in prophylaxis (off-treatment).**



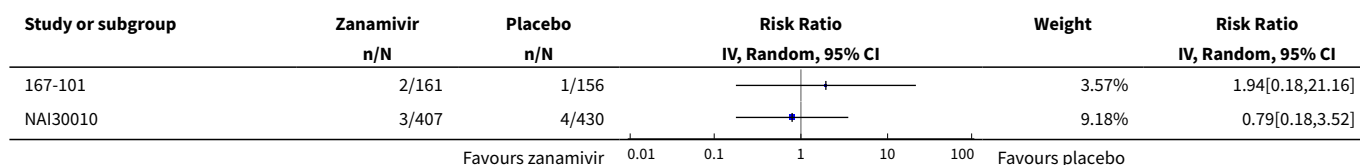
**Analysis 4.38. Comparison 4 Zanamivir versus placebo for prophylaxis,
Outcome 38 Adverse events: headache in prophylaxis (off-treatment).**

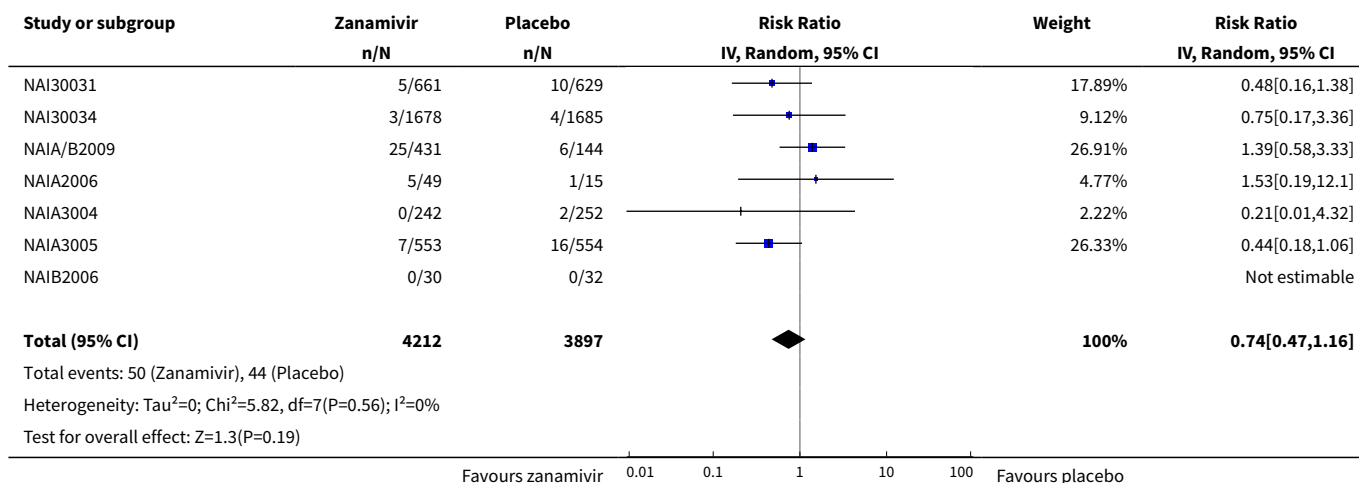


**Analysis 4.39. Comparison 4 Zanamivir versus placebo for prophylaxis,
Outcome 39 Adverse events: cough in prophylaxis (off-treatment).**

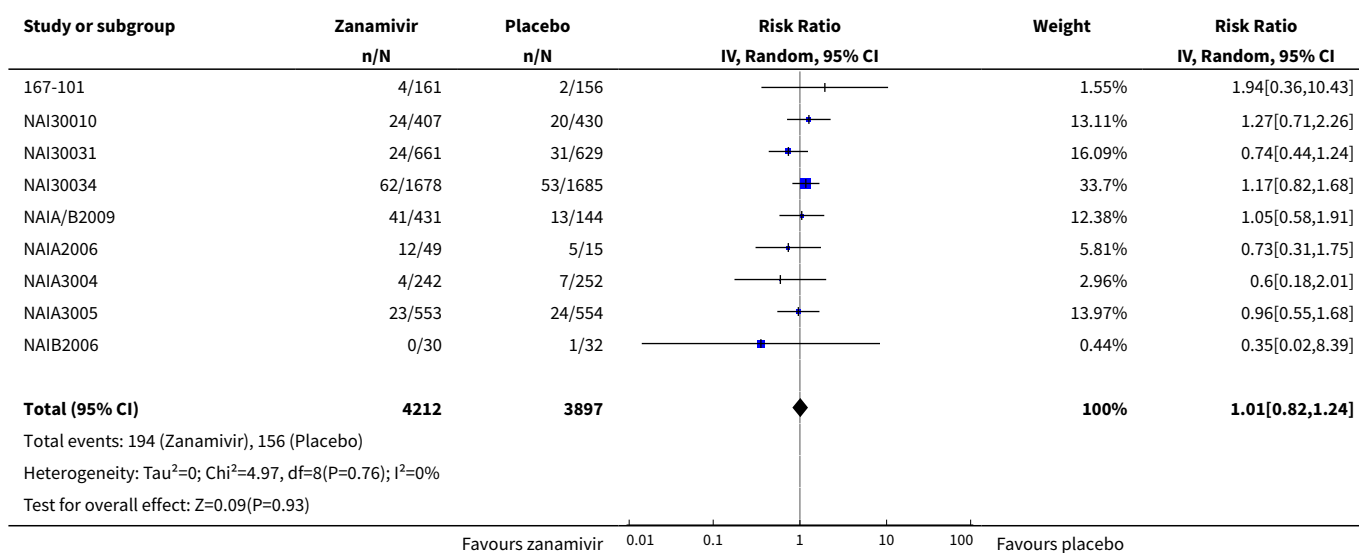


**Analysis 4.40. Comparison 4 Zanamivir versus placebo for prophylaxis,
Outcome 40 Adverse events: fatigue in prophylaxis (off-treatment).**

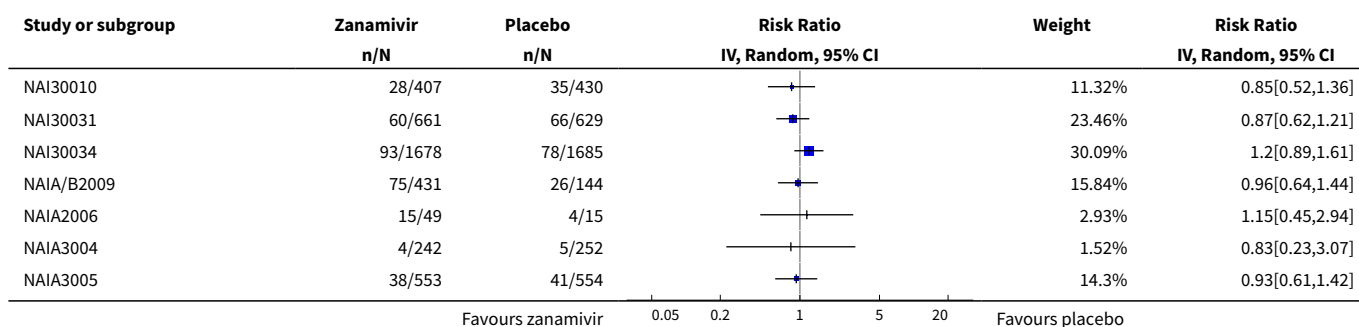


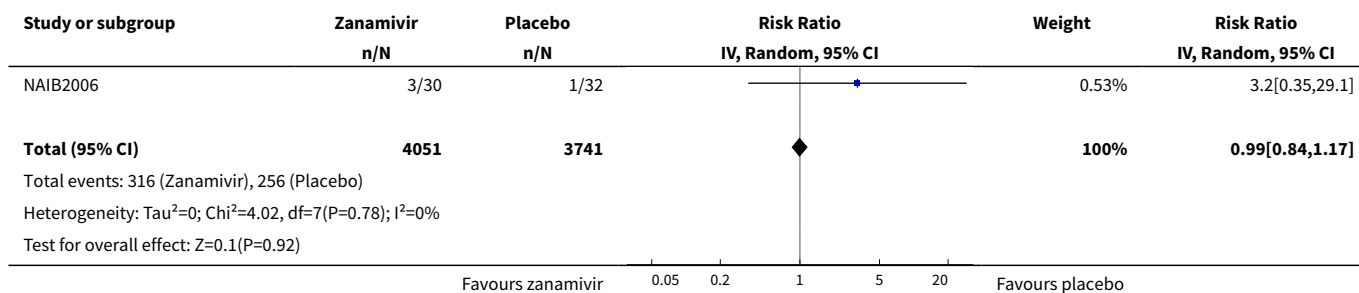


Analysis 4.41. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 41 Adverse events: neurological body system in prophylaxis (off-treatment).

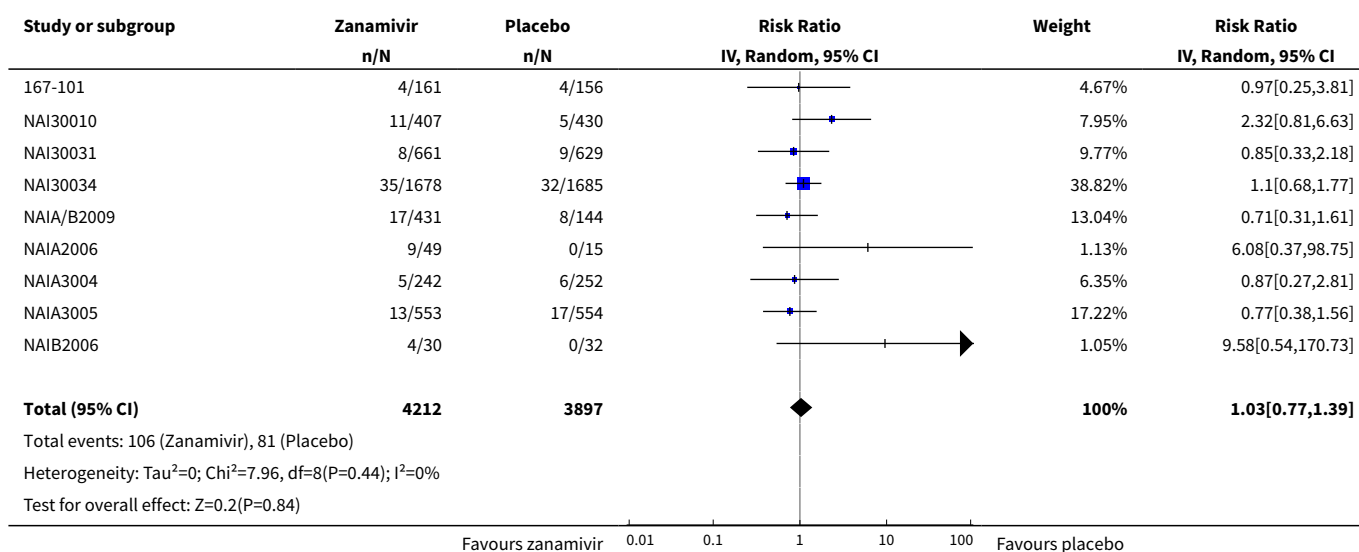


Analysis 4.42. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 42 Adverse events: ear, nose and throat in prophylaxis (off-treatment).

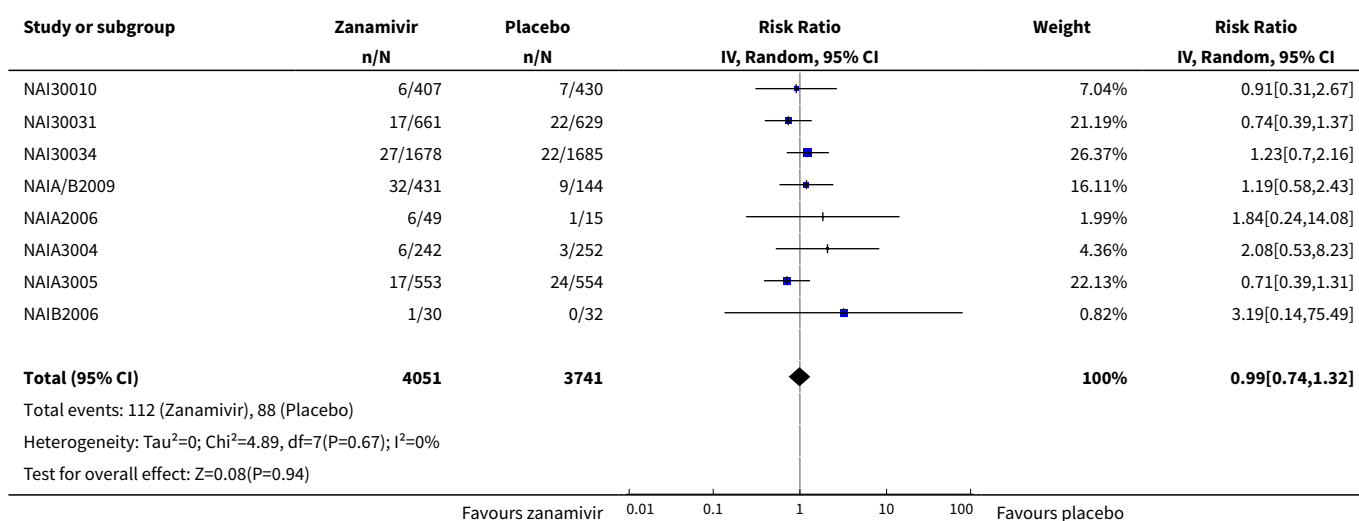




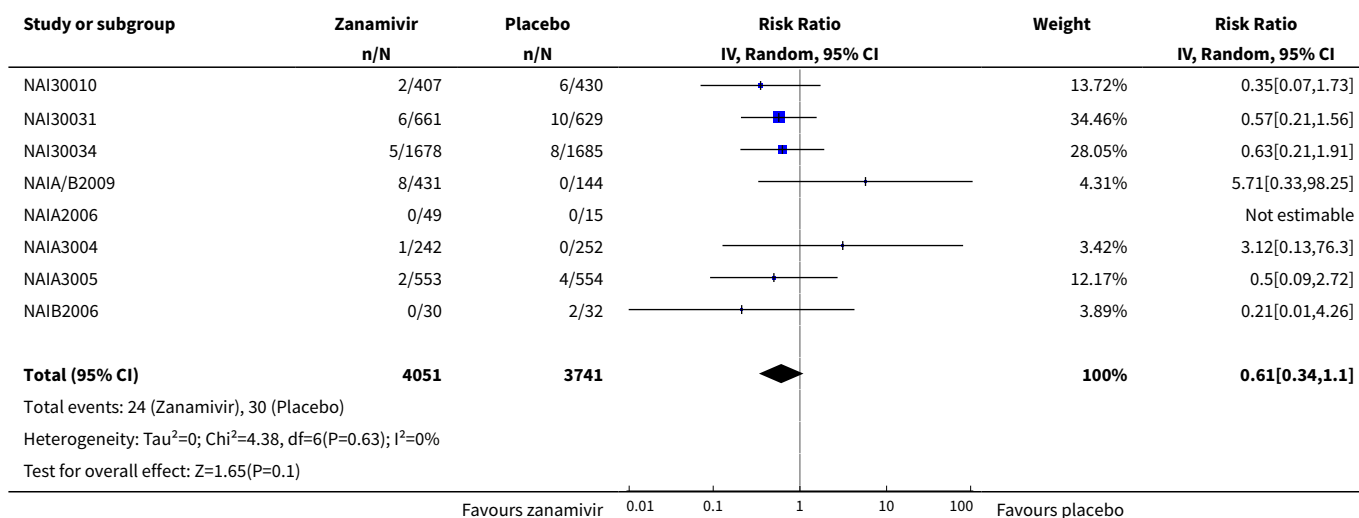
Analysis 4.43. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 43 Adverse events: musculoskeletal body system in prophylaxis (off-treatment).



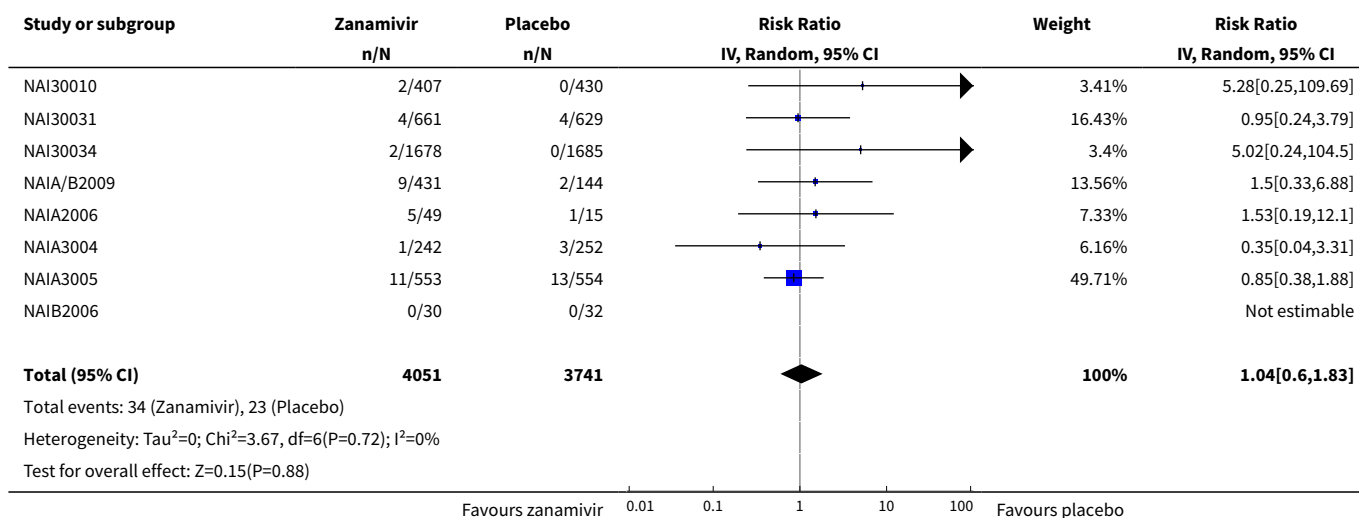
Analysis 4.44. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 44 Adverse events: non-site specific in prophylaxis (off-treatment).



Analysis 4.45. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 45 Adverse events: injury in prophylaxis (off-treatment).



Analysis 4.46. Comparison 4 Zanamivir versus placebo for prophylaxis, Outcome 46 Adverse events: endocrine and metabolic in prophylaxis (off-treatment).

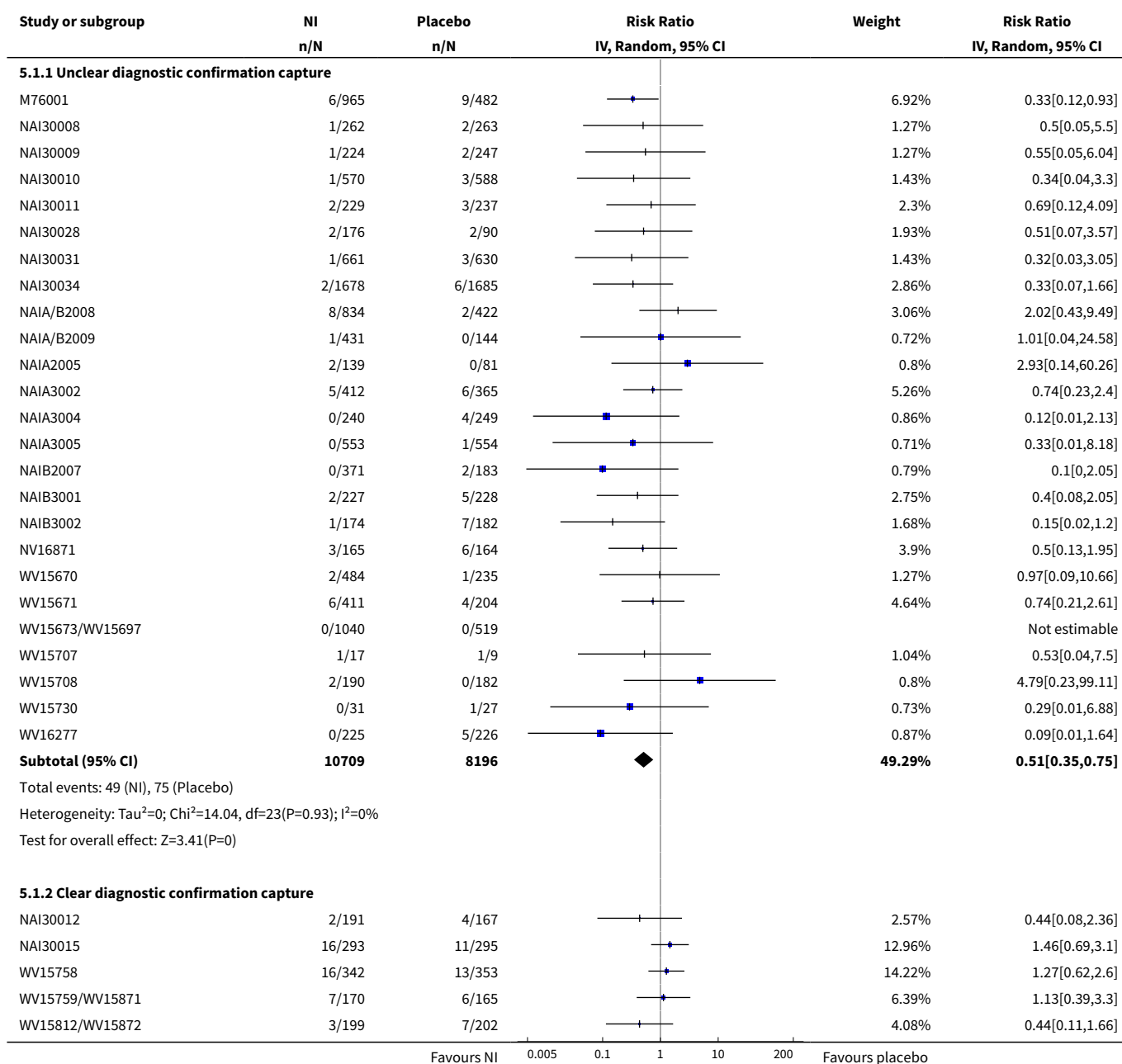


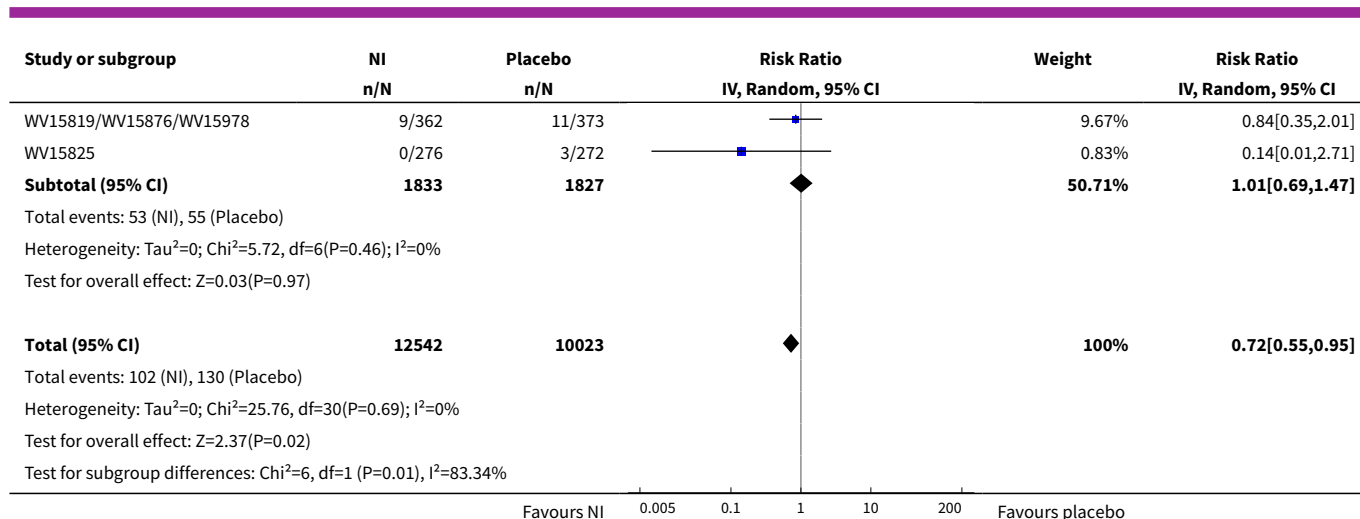
Comparison 5. Neuraminidase inhibitor versus placebo for treatment or prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications: pneumonia	32	22565	Risk Ratio (IV, Random, 95% CI)	0.72 [0.55, 0.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Unclear diagnostic confirmation capture	25	18905	Risk Ratio (IV, Random, 95% CI)	0.51 [0.35, 0.75]
1.2 Clear diagnostic confirmation capture	7	3660	Risk Ratio (IV, Random, 95% CI)	1.01 [0.69, 1.47]

Analysis 5.1. Comparison 5 Neuraminidase inhibitor versus placebo for treatment or prophylaxis, Outcome 1 Complications: pneumonia.





ADDITIONAL TABLES

Table 1. Blank case report forms' data capture for secondary illnesses in oseltamivir trials

Study	Where in CRF (PDF pg #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including px)
M76001	1167	Yes/no answer to question: "Is this event a secondary illness related to influenza?" Secondary illness is defined: sinusitis, otitis, bronchitis, pneumonia + other chest infections that are not diagnosed as bronchitis and/or pneumonia	Investigator	In form for "Adverse events or intercurrent illness"	No	Px
NV16871	361, 389	Form states: Have there been any changes in the patient's health including any new conditions or worsening of existing conditions since day 1 (please include secondary illnesses)? Yes/No. If "Yes", please record the details on the "Adverse events or secondary illness" form in the Additional Forms section of the CRF on pg 30.0. All serious adverse events must be reported within 1 working day of occurrence to Roche Pg 30.0 of CRF (PDF pg 389) defines secondary illnesses as sinusitis, otitis media, bronchitis and pneumonia, and asks additional questions such as relationship to test drug and outcome,	Investigator	Secondary illness not listed as efficacy outcomes Recording of secondary illnesses was to occur in a form titled "Adverse event or secondary illness"	No	Px

Table 1. Blank case report forms' data capture for secondary illnesses in oseltamivir trials (Continued)

and leaves space for investigator's comments on the adverse event						
WV15670	732, 754, 791, 832	CRF form (PDF pg 732) states: Secondary illness reminder Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? yes [] Complete secondary illness page (not the adverse event page) no [] Secondary illness page CRF (PDF pg 754) requests information on date of onset, date resolved, whether treatment was given and, if so, what treatment or medical procedures, total daily dose, and start/end date of treatment or medical procedure In addition, participants could fill in information related to a secondary illness in their diary card in the free-text box called "Notes" which prompts participants: "Please can you record below any extra information about your flu which may be of interest to us, (for example: did your flu symptoms re-occur, and if so when?), and have you taken any other treatments. If so please record the treatment name and the dates you took it." (PDF pg 791)	Participant mediated through Investigator	For investigators, on "Secondary illness" form For participants, on "Notes" section of diary card	No	
WV15671	740, 889, 1018	CRF form (PDF pg 740) states: Secondary illness reminder Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? yes [] Complete secondary illness page (not the adverse event page) no [] Secondary illness page CRF (PDF pg 889) requests information on date of onset, date resolved, whether treatment was given and, if so, what treatment or medical procedures, total daily dose and start/end date of treatment or medical procedure Secondary illnesses are listed as sinusitis, otitis, bronchitis, pneumonia and other chest infections that are not diagnosed as bronchitis and/or pneumonia	Participant mediated through investigator	Mentioned in M1 and RAP as tertiary outcomes not mentioned in protocol	No	Px

Table 1. Blank case report forms' data capture for secondary illnesses in oseltamivir trials (Continued)

In addition, participants could fill in information related to a secondary illness in their diary card in the free-text box called "Notes" which prompts participants: "Please can you record below any extra information about your flu which may be of interest to us, (for example: did your flu symptoms re-occur, and if so when?), and have you taken any other treatments. If so please record the treatment name and the dates you took it." (PDF pg 1018)

WV15673/ WV15697	From 483	No mention of pneumonia, secondary illness, complications in the CRFs	Unclear	Secondary illnesses not listed in protocol as end-points. They are listed as safety end-points in the RAP which states that "pre-defined" secondary illnesses were "sinusitis, otitis, bronchitis, pneumonia, and other chest infections that are not diagnosed as bronchitis and/or pneumonia, plus recurrence of symptoms from the diary card once alleviation had occurred." (PDF pg 479)		
WV15707	From 98	Pg 117 Secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? yes ☐ - Complete secondary illness page (not the adverse event page) no ☐ Pg 131: Diagnostic procedures 1) Were there any diagnostic procedures or tests carried out since day 1 as a result of influenza or secondary illness	Participant mediated through investigator	Mentioned in RAP as tertiary endpoints pg 57-8	Yes	Px

Table 1. Blank case report forms' data capture for secondary illnesses in oseltamivir trials (Continued)

		that were not scheduled as part of protocol? Yes Type of diagnostic procedure or test 1 Chest X-rays, 2 ECG, 3 Bacterial culture, 4 Bronchoscopy, 5 Pulmonary function test, 6 Viral culture (other than influenza), 7 Blood tests (other than antibody sample), 8 Other <i>specify</i> No Secondary illness page CRF (PDF pg 158) requests information on date of onset, date resolved, whether treatment was given and, if so, what treatment or medical procedures, total daily dose and start/end date of treatment or medical procedure				
WV15708	From 460	Secondary illness reminder at pg 474: Has the patient reported any new episodes of sinusitis, otitis, bronchitis, other chest infection or pneumonia since screening? yes ☐ ... <i>Complete adverse event page</i> no ☐ "Adverse events" CRF collected data on date of onset, initial intensity, test drug adjustment, whether treatment was given (if so, what), most extreme intensity, relationship to test drug, outcome, whether it led to hospitalisation and a free-text line for recording "Comments on AE" (e.g. PDF pg 479)	Participant mediated through investigator	Secondary illness not mentioned in protocol	No	Px
WV15730	From 340	Secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? yes ☐ ... <i>Complete secondary illness page (not the adverse event page)</i> no ☐ The secondary illness page is descriptive of dates and px	Participant mediated through investigator	Listed as tertiary endpoints in RAP at pg 297	No	Px
WV15758	From 637	Has the patient reported any new adverse events or symptoms (including intercurrent illnesses and secondary illnesses)? yes ☐ record in the adverse events/intercurrent illness section of the case	Participant mediated through investigator	Listed as secondary illnesses in core report Module 1-2 (pg 36)	Yes	Px

Table 1. Blank case report forms' data capture for secondary illnesses in oseltamivir trials (Continued)

no ☐ report form						
Diagnostic confirmation of otitis media from pg 648 onwards						
WV15759/871	From 665	Has the subject reported any adverse events including secondary and inter-current illnesses?	Participant mediated through investigator	Secondary illnesses not mentioned in protocol, but secondary outcome in core report	Yes	Px
				Note: worth looking at comparisons 1.49 to 1.51 in RM5. No effect but in bronchitis this study has a more conservative effect than NV 16871 which has no definitions and no diagnostics		
WV15799	From 642	Secondary illness defined as in M76001. There is a generic physical examination form at pg 704 including "lungs" normal/abnormal specify _____ At pg 709 has the patient reported any new AE including intercurrent or secondary illnesses yes/no. If y record the adverse events/intercurrent illness section of the CRF (noted at pf 746 on to be at the back of the CRF) with <u>FULL HISTORY, PHYSICAL EXAMINATION AND DIAGNOSTIC WORK UP QUESTIONS FOR BRON+PNUM+LRTI+SIN+OM</u> including questions about CXR, MRI, sputum etc.	Investigator	Proportion of contacts who are classified as having a secondary illness subsequent to a confirmed episode of influenza listed as tertiary endpoints	Yes	Px
WV15812/872	From 285	Has the patient reported any new adverse events or symptoms (including intercurrent illnesses and secondary illnesses)? yes ☐ record in the adverse events/intercurrent illness section of the case no ☐ report form At pg 450-74 is DIAGNOSIS OF SECONDARY ILLNESS page which is very similar to the one at serial 10 EXHAUSTIVE list of diagnostic procedures	Participant mediated through investigator	Listed as secondary tertiary in protocol at pg 252	Yes	Px

Table 1. Blank case report forms' data capture for secondary illnesses in oseltamivir trials (Continued)

WV15819/978/876m 412	Pg 437 (adverse event reminder): Has the patient reported any new adverse events or symptoms (including intercurrent illnesses)? yes ☐ record in the adverse events/intercurrent illness section of the case no ☐ report form In CRF pg 447 and 443 usual secondary illness reminder From pg 471 DIAGNOSTIC OF SECONDARY ILLNESS. This is a one page list of diagnostics similar to that at serial 10. The question is: "Were there any diagnostic procedures or tests carried out since day 1 as a result of influenza or secondary illness that were not scheduled as part of protocol?" If yes list per serial 10 From pg 486 is a list of diagnostic tests	Participant mediated through investigator	Secondary illness listed as secondary (required antibiotics) and tertiary outcomes in core report and as an addition in protocol amendment at pg 21	Yes	Px
WV15825	From 389 There is a usual note: please go to diagnosis of secondary illness at back of CRF. Pg 487: Is this event a secondary illness related to influenza? DIAGNOSTIC OF SECONDARY ILLNESS From pg 510-40 with exhaustive list of diagnostics as per serial 10	Participant mediated through investigator	Secondary illness listed as secondary outcomes in protocol pg 346 Secondary illnesses recorded on "Adverse events" CRF	Yes	Px
WV16277	From 415 Not found	Not found	Secondary illness not listed as efficacy outcomes		

#Events within the first 2 days of the study were excluded

*Note that some events are reported as secondary illness and adverse event (AE) but some events are reported as secondary illness only and some events are reported as adverse event only

BRON = bronchitis

CRF = case report form

CXR = chest x-ray

ECG = electrocardiogram

LRTI = lower respiratory tract infection

MRI = magnetic resonance imaging

OM = otitis media

PNUM = pneumonia

px = prescription

~RAP = reporting analysis plan

SIN = sinusitis

Table 2. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA)

Mentioned study	File name	Pages where study is mentioned (separated by commas)	Note
113502			
113625			
113678			
114045			
NAI108166			
105934			
NAI106784			
107485			
108127			
112311			
112312			
113268			
GCP/95/045			
NAI10901	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	15,15	
NAI10902			
NAI30008	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	15	7 documents with 14 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	13	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	19, 19, 20	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	1, 1, 3, 4, 4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/21036ltr.pdf	2	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_MEDR.pdf	33	

Table 2. Table of contents for studies of zanamivir described in regulatory documentation from the FDA

(USA) <i>(Continued)</i> NAI30009	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	1.2	7 documents with 110 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR- RES_P1.pdf	10, 10, 12, 13, 13, 14, 14, 17, 29, 42, 61, 62, 64, 64, 65, 65, 68	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR- RES_P2.pdf	33, 34, 36, 43, 43, 43, 43, 52, 52, 52, 53, 53, 56, 57	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 5, 6, 6, 8, 8	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_MEDR.pdf	3, 3, 3, 3, 3, 3, 4, 4, 5, 8, 9, 9, 10, 10, 11, 11, 11, 14, 14, 15, 16, 17, 19, 19, 19, 20, 20, 22, 23, 23, 23, 24, 24, 24, 25, 25, 25, 25, 25, 25, 26, 26, 26, 27, 27, 28, 28, 28, 29, 29, 31, 31, 31, 31	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_MICROBR.pdf	3, 3, 4, 4, 4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_STATR.pdf	2, 2, 2, 4, 7, 12, 18, 18, 18, 19	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR- RES_P1.pdf	31.56	1 document with 2 instances
NAI30010	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	1.2	6 documents with 65 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR- RES_P1.pdf	10, 12, 13, 14, 14, 15, 17, 62, 62, 62, 64	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR- RES_P2.pdf	34, 34, 36, 43, 53	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 6, 6	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_MEDR.pdf	3, 3, 3, 3, 3, 4, 5, 18, 19, 21, 21, 22, 23, 23, 23, 23, 24, 25, 25, 25, 26, 26, 26, 26, 27, 27, 27, 28, 28, 29, 29, 29, 30, 31, 31, 31, 32	

Table 2. Table of contents for studies of zanamivir described in regulatory documentation from the FDA
(USA) *(Continued)*

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_STATR.pdf	2, 2, 13, 13, 13, 19	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	6	1 document with 1 instance
NAI30012	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	1	1 document with 1 instance
NAI30015			
NAI30020			
NAI30028			
NAI30034			
NAI40012			
NAIA1009	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR-RES_P1.pdf	56	4 documents with 17 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR-RES_P2.pdf	1, 1, 1, 48, 49, 52	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 6	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_MEDR.pdf	3, 3, 6, 7, 20, 31, 31	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	18	5 documents with 5 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	9	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR-RES_P2.pdf	52	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	11	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_STATR.pdf	2	
NAIA3002	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	13 documents with 122 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	6, 6, 7, 7, 14, 15, 22, 22, 23	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	1, 4, 4, 12, 12, 12, 12, 17	

Table 2. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (Continued)

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	4, 14, 14, 14, 14, 14, 15, 15, 15, 15, 16	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview2.pdf	1, 2, 3, 4, 4, 5, 6, 6, 6, 8, 8, 9, 9, 9, 12, 12, 15, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview3.pdf	5, 5, 6, 6, 6, 7, 7, 7, 8, 8, 9, 9, 9, 10, 11, 12, 13, 13, 14, 15, 15, 17, 18, 18, 19, 20, 21	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	1, 1, 1, 1, 2, 6	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	4, 5, 10, 12	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	1, 1, 2, 2, 2, 2, 3, 3, 4, 4, 5, 5, 7, 8, 10, 11, 12, 14, 16, 16, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	2, 2, 6, 6, 8, 8, 9, 10	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	10	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-stats.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	15	1 document with 1 instance
NAIA3003	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	17, 17, 18	3 documents with 6 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	4.4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	22	
NAIA3004	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	14	4 documents with 8 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	18, 18, 19	

Table 2. Table of contents for studies of zanamivir described in regulatory documentation from the FDA
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	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	4, 4, 4	
NAIA3005	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	14	5 documents with 12 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	12, 12, 12, 13, 14, 15, 15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	14.15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_ADMINCOR- RES_P2.pdf	38	
NAIB1002			
NAIB3002	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	14 documents with 99 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	14, 15, 15, 15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	11.12	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	4, 14, 14, 14, 14, 14, 14, 14, 14	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview2.pdf	9, 9, 9, 9, 9, 9, 10, 11, 12, 12, 12, 12, 13, 13, 13, 14, 14, 14, 15, 15, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview3.pdf	4, 5, 6, 6, 6, 7, 7, 7, 8, 8, 8, 9, 9, 11, 12, 12, 13, 13, 14, 15, 17, 18, 18, 19, 20, 21	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	1, 1, 1, 1, 2	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	4, 5, 10, 12	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	2, 3, 3, 7, 8, 10, 11, 14, 15, 16, 16, 16	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	7, 8, 8, 8, 9, 9	

Table 2. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (Continued)

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	10.2	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-stats.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	5.5	
NAI30011			
NAIB2007	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	7 documents with 18 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	14, 15, 15, 16, 16, 17, 17, 17, 18	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	3	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	8, 10, 10, 15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	2	
NAIA2006			
NAIB2006			
NAIB1007			
C94-009	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	17	1 document with 1 instance
C94-085	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	17	2 documents with 2 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview9.pdf	22	
NAIB1001	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	17	1 document with 1 instance
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/20000426_001/21-036-S001_RELENZA_BIOPHARMR.pdf	6	1 document with 1 instance
NAIA2005	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	10 documents with 44 instances

Table 2. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) *(Continued)*

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	7, 17, 10	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin3.pdf	2.4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	4.5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	2, 2, 3, 3, 3, 3, 5, 6, 6, 6, 6, 8, 8, 8, 9, 11, 12, 12, 13, 14, 14, 14, 14, 14, 15, 18	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	3.4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	2, 5, 9, 15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	10	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-microbiology.pdf	21	
NAIB2005	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin1.pdf	15	9 documents with 43 instances
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-admin2.pdf	17, 20, 20, 22, 23	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview1.pdf	5.5	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview4.pdf	3, 3, 3, 7, 8, 8, 8, 9, 10, 11, 11, 11, 11, 11, 12, 12, 12, 13, 14, 14, 14, 14, 14, 14, 14, 15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	3.4	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview7.pdf	2, 9, 15	
	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview8.pdf	2	

Table 2. Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) *(Continued)*

	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-microbiology.pdf	21	
NAIA/B2008	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview6.pdf	4	1 document with 1 instance
NAIA2010	Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036-medreview5.pdf	16	1 document with 1 instance
NAIA/B2009			
167-02			
167-03			
167-05			
167-04			
JNAI-03			
JNAI-02			
JNAI-01			
JNAI-07			
JNAI-04			
PE-01			
167-101			
167T3-11			

Zanamivir trials citation by trial ID and source FDA file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which regulatory file. Blank spaces indicate no citation for known trials.

All the studies have been searched in the folder "Tamiflu and Relenza/Relenza/Relenza - NDA 021036/19990726_000/021036". File name is left blank when the study was not present in that folder.

Table 3. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA)

Referenced study	File name	Pages where study is mentioned (separated by commas)	Note
NP15717	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	46.46	6 documents with 13 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	14, 15, 15	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	

Table 3. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA
(USA) *(Continued)*

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	2	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_BioPharmr.pdf	5, 8, 10, 13, 31	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
NP15718	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	17	1 document with 1 instance
NP15728	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	16.35	3 documents with 6 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	11	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	45, 46, 47	
NP15757	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	92, 93, 104, 122, 126, 131, 144, 144, 145	1 document with 9 instances
NP15826	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	47	9 documents with 26 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	2	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_BioPharmr.pdf	4, 5, 5, 8, 8, 8, 10, 17, 29, 30, 30, 30, 30, 30, 31, 31	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	9.1	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	9.1	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	

Table 3. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA

(USA) <i>(Continued)</i> NP15827	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	10.12	2 documents with 7 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	16, 16, 17, 17, 17	
WP15525	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	21, 25, 26, 27, 27, 27, 27, 42, 42, 44	3 document with 13 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	2.2	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_BioPharmr.pdf	29	
WP15647	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	24, 27, 27	2 documents with 4 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	44	
WP15648	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	39	3 documents with 8 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	44.44	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	94, 128, 153, 153, 154	
WP15676	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	28.33	3 documents with 4 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	11	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	45	
WV15670	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	2, 44, 44	6 documents with 45 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6, 19, 37, 38, 39, 39, 39, 39, 40, 41, 41, 42, 43, 44, 48, 48, 49, 49	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1, 25, 25, 35, 35, 39, 39, 47	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	3, 3, 4, 4, 5, 5, 5, 8, 9, 10, 17, 17, 21, 22,	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	189	

Table 3. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA
(USA) *(Continued)*

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
WV15671	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	2, 44, 44	7 documents with 50 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6, 16, 19, 24, 24, 25, 25, 26, 27, 27, 28, 32, 34, 35, 36, 37, 38, 39, 39, 39, 40, 41, 46, 49, 49	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1, 25, 25, 35, 38, 47	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	3, 4, 4, 5, 5, 5, 5, 9, 10, 10, 15, 17, 21	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	189	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
WV15673	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	3 documents with 50 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	18, 18, 18, 20, 21, 21, 21, 22, 39	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	58, 59, 71, 71, 71, 71, 71, 72, 72, 73, 73, 76, 76, 76, 76, 76, 77, 77, 79, 82, 83, 83, 84, 122, 124, 125, 126, 128, 131, 131, 132, 133, 134, 134, 145, 145, 156, 169, 177, 189	
WV15697	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	39	2 documents with 40 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	58, 59, 71, 71, 71, 71, 71, 72, 72, 73, 73, 76, 76, 76, 76, 76, 77, 77, 79, 82, 83, 83, 84, 122, 126, 128, 131,	

Table 3. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (Continued)

		131, 131, 132, 133, 134, 145, 145, 152, 153, 156, 162, 189	
WV15708	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	3 documents with 39 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	23, 35, 39, 41	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	71, 71, 71, 71, 71, 72, 72, 72, 72, 75, 75, 75, 75, 77, 77, 78, 79, 79, 82, 82, 122, 125, 125, 126, 131, 134, 134, 135, 135, 149, 151, 152, 152, 153	
WV15708D	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3	2 documents with 3 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	23.35	
WV15730	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_bior.pdf	44.44	5 documents with 15 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6, 9, 19, 49, 50, 50	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	1, 1, 25, 25, 27	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	189	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	3	
WV15731	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	17	4 documents with 9 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5, 30, 37	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	5.6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5, 30, 37	
WV15758	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P1.pdf	12, 19, 19, 36	9 documents with 92 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	2, 8, 17, 39, 39, 57, 57	

Table 3. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (Continued)

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_BioPharmr.pdf	3, 4, 5, 5, 5, 8, 10, 17, 27, 30	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Corres.pdf	6.9	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5, 5, 9, 9, 10, 11, 12, 12, 16, 18, 18, 18, 19, 19, 31, 31, 31, 33, 33, 35, 36, 37, 37, 37, 37, 37, 37, 37, 40, 43	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	2, 4, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5, 5, 9, 9, 10, 11, 12, 12, 16, 18, 18, 18, 19, 19, 31, 31, 31, 33, 33, 35, 36, 37, 37, 37, 37, 37, 37, 37, 40, 43	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6, 6, 8	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	2.3	
WV15759	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P1.pdf	12.13	7 documents with 44 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	39	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5, 10, 30, 30, 30, 30, 31, 32, 32, 33, 34, 37, 37, 37, 40, 44	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	2, 4, 4, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5, 10, 30, 30, 30, 30, 31, 32, 32, 33, 34, 37, 37, 37, 40, 44	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6, 6, 9	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	2	
WV15799	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	28, 28, 28, 28, 28, 29, 29, 30, 30, 30, 30, 30, 31, 31, 31, 31, 32, 32, 32, 32, 32, 33, 33, 34,	4 documents with 89 instances

Table 3. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (Continued)

		34, 35, 35, 35, 36, 37, 37, 37, 37, 38, 38, 38, 39, 39, 40, 40, 40, 40, 40, 58, 60, 71, 71, 71, 71, 71, 72, 72, 73, 76, 76, 76, 77, 78, 79, 84, 85, 122, 125, 125, 126, 126, 128, 131, 140, 140, 140, 143, 147, 149, 156, 162, 169, 175, 187, 203, 208, 208	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	10.11	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	10.11	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6.7	
WV15812	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	3, 6, 10, 12	2 documents with 9 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	6, 8, 10, 25, 35	
WV15819	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P1.pdf	6, 10, 12, 15	2 documents with 8 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/19991027_000/21087_Tamiflu_medr_P2.pdf	2, 6, 6, 39	
WV15825	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20001117_002/21-087SE1-002_review.pdf	41, 41, 41, 41, 42, 42, 42, 42, 42, 43, 44, 58, 59, 71, 71, 71, 71, 71, 72, 72, 72, 72, 73, 73, 75, 75, 77, 77, 78, 79, 79, 79, 80, 80, 80, 81, 82, 85, 125, 125, 126, 126, 128, 131, 134, 134, 135, 135, 137, 137, 138, 145, 150, 151, 152, 152, 155, 156, 162, 169, 180, 204, 211	1 document with 64 instances
WV15871	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P1.pdf	12.13	7 documents with 42 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Admindocs_P2.pdf	39	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	5, 11, 30, 31, 31, 32, 32, 32, 33, 34, 37, 37, 37, 37, 37, 40	

Table 3. Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (Continued)

	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Microbr.pdf	2, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	5, 11, 30, 31, 31, 32, 32, 32, 33, 34, 37, 37, 37, 37, 37, 37, 40	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021087/20040624_016/021087_S016_TAMIFLU CAPSULES - DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20040624_010/021087_S016_TAMIFLU CAPSULES - DRY POWDER_BIOPHARMR.pdf	2	
WV15872	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Medr.pdf	11.33	2 documents with 4 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu - NDA 021246/20001214_000/21-246_Tamiflu_Statr.pdf	11.33	

Oseltamivir trials citation by trial ID and source FDA file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which regulatory file. Blank spaces indicate no citation for known trials.

Search strategy:

WV15758 OR WV 15758 OR Trial 15758 OR Trial15758 OR Trials 15758 OR Trials15758 OR 15758 OR study 15758 OR study15758

Table 4. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK)

Mentioned study	File name	Pages where study is mentioned (separated by commas)	Note
NAI106784			
107485			
108127			
112311			
112312			
113268			
GCP/95/045			
NAI10901			
NAI10902			
NAI30008	Relenza treatment submission executive summary.pdf	4	3 documents with 10 instances
	Relenza treatment submission full document.pdf	5, 26, 26, 26, 146	
	Relenza treatment submission main text.pdf	5, 26, 26, 26	

Table 4. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) *(Continued)*

NAI30009	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	7 documents with 461 instances
	NAI30009 study report pdf\CSR30009.pdf		
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf		
	NAI30009 study report pdf\suptables.pdf		
	NAI30009 study report pdf\tables.pdf		
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 18, 19, 27, 30, 31,	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 18, 19, 27, 30, 31, 76, 128, 130, 132, 134, 144	
NAI30010	NAI30010 study report\Final NAI30010 for sign-off.pdf		7 documents with 399 instances
	NAI30010 study report pdf\NAI30010 HO final FSR.pdf		
	NAI30010 study report pdf\suptables.pdf		
	NAI30010 study report pdf\tables.pdf		
	Relenza prophylaxis submission.pdf	2, 5, 8, 11, 12, 19, 20, 21, 23, 24	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 27, 30, 31, 76, 135, 137, 139, 141, 143, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 27, 30, 31	
NAI30012	Relenza treatment submission executive summary.pdf	4	3 documents with 8 instances
NAI30012	Relenza treatment submission full document.pdf	5, 26, 26, 146	
NAI30012	Relenza treatment submission main text.pdf	5, 26, 26	
NAI30015	Relenza treatment submission full document.pdf	146	1 document with 1 instance
NAI30020			
NAI30028			
NAI30031			
NAI30034			
NAI40012			

Table 4. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) *(Continued)*

NAIA1009	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	101	2 documents with 3 instances
	NAI30009 study report pdf\CSR30009.pdf	28.34	
NAIA3002	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	9 documents with 513 instances
	NAI30009 study report pdf\CSR30009.pdf	34.95	
	NAI30009 study report pdf\NAI30009 HO final FSR.pdf	22	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf		
	NAIA3002 study report pdf\NAIA3002 supporting tables 2.pdf		
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 47, 49	
	Relenza treatment submission full document.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31, 63, 63, 63, 76, 106, 106, 107, 107, 109, 109, 112, 112, 114, 114, 115, 115, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31	
NAIA3003	Relenza prophylaxis submission.pdf	10	1 document with 1 instance
NAIA3004	Relenza prophylaxis submission.pdf	10	1 document with 1 instance
NAIA3005	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	36, 94, 94, 94, 95, 96, 96, 101	5 documents with 310 instances
	NAI30010 study report pdf\NAI30010 HO FSR.pdf	6.18	
	NAIA3005 study report pdf\A3005cr01.pdf		
	NAIA3005 study report pdf\TABS.pdf		
	Relenza prophylaxis submission.pdf	2, 5, 6, 12, 13, 13, 15, 15, 16, 16, 17, 17, 18, 18	
NAIB1002			
NAIB3001	NAI30009 study report pdf\CSR30009.pdf	34, 50, 95	11 documents with 374 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10.22	
	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	

Table 4. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (Continued)

	NAI30010 study report pdf \NAI30010 HO FSR.pdf	17.17	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf		
	NAIB3001 study report pdf\NAIB3001 supporting tables 1.pdf		
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 18, 27, 30, 31, 32, 63, 63, 63, 76, 99, 99, 101, 101, 103, 103, 105, 105, 144, 162	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 18, 27, 30, 31, 32	
NAIB3002	NAI30009 study report pdf\CSR30009.pdf	34.95	10 documents with 579 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	22	
	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 48, 50	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf		
	NAIB3002 study report pdf\NAIB3002supporting tables 1.pdf		
	NAIB3002 study report pdf\NAIB3002supporting tables 2.pdf		
	Relenza treatment submission full document.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31, 63, 63, 63, 76, 117, 117, 117, 118, 118, 120, 120, 122, 122, 124, 124, 125, 125, 127, 127, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31	
NAI30011	Relenza treatment submission full document.pdf	146	1 document with 1 instance
NAIB2007	NAI30009 study report pdf\CSR30009.pdf	95	10 documents with 379 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 29	

Table 4. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) *(Continued)*

	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2007 study report pdf\b2007cr.pdf		
	NAIB2007 study report pdf\TABLES.pdf		
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25,26	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 29	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 19, 27, 30, 31, 76, 91, 91, 92, 92, 94, 94, 96, 96, 98, 98, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 19, 27, 30, 31	
NAIA2006	NAIA2005 study report pdf\A2005cr.pdf	38, 73, 74	4 documents with 6 instances
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
NAIB2006	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	3 documents with 3 instances
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
NAIB1007			
C94-009			
C94-085			
NAIB1001			
NAIB_1001			
NAIA2005	NAI30009 study report pdf\CSR30009.pdf	95	12 documents with 895 instances
	NAIA2005 study report pdf\A2005cr.pdf		
	NAIA2005 study report pdf\APPS_ALL.pdf		
	NAIA2005 study report pdf\TBS_ALL.pdf		
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 48, 48	
	NAIA3005 study report pdf\A3005cr01.pdf	25	

Table 4. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) *(Continued)*

	NAIB2005 study report pdf\b2005cr.pdf	7, 7, 22, 25, 26, 34, 34, 42, 71, 72, 72	
	NAIB2007 study report pdf\b2007cr.pdf	76	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 47, 47	
	Relenza treatment submission full document.pdf	16, 16, 16, 16, 17, 18, 27, 30, 76, 77, 77, 77, 79, 79, 79, 80, 80, 82, 82, 84, 84, 85, 144, 144	
	Relenza treatment submission main text.pdf	16, 16, 16, 16, 17, 18, 27, 30	
NAIB2005	NAI30009 study report pdf\CSR30009.pdf	95	12 documents with 838 instances
	NAIA2005 study report pdf\A2005cr.pdf	7, 8, 8, 24, 24, 25, 43, 70, 74, 74	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 48, 48	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2005 study report pdf\APPSNEW.pdf		
	NAIB2005 study report pdf\b2005cr.pdf		
	NAIB2005 study report pdf\TBS_ALL.pdf		
	NAIB2007 study report pdf\b2007cr.pdf	76	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 47, 47	
	Relenza treatment submission full document.pdf	16, 16, 16, 16, 17, 18, 27, 30, 76, 77, 79, 79, 85, 85, 85, 86, 86, 88, 88, 90, 90, 144, 144	
	Relenza treatment submission main text.pdf	16, 16, 16, 16, 17, 18, 27, 30	
NAIA/B2008	NAI30009 study report pdf\CSR30009.pdf	95	6 documents with 16 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 29, 29	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25, 26, 26, 26, 77	

Table 4. Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) *(Continued)*

	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 29, 29	
NAIA2010	NAIA3005 study report pdf\A3005cr01.pdf	25	1 document with 1 instance
NAIA/B2009	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	3 documents with 3 instances
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
167-02			
167-03			
167-05			
167-04			
JNAI-03			
JNAI-02			
JNAI-01			
JNAI-07			
JNAI-04			
PE-01			
167-101			
167T3-11			

Zanamivir trials citation by trial ID and source NICE file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which file. Blank spaces indicate no citation for known trials

Table 5. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK)

Referenced study	File name volume*	Pages where study is mentioned (separated by commas)	Note
133312			
GS97-802			
133312			
GS-97-801			
JP15734			
JP15735			

Table 5. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) *(Continued)*

JV15823			
JV15824			
JV16284			
M76001	1	33, 36, 37, 37, 38, 38, 39, 67, 68, 94, 95, 224	1 document with 12 instances
M76006			
ML20910			
ML22789			
ML22879			
MV21118			
MV22841			
NCT00298233			
NCT00555893			
NCT00707941			
NCT00799760			
NCT00830323			
ML25018			
NCT00867139			
NCT00873886			
NCT01002729			
NP15717	6	32, 75, 76, 77	2 documents with 5 instances
	8	68	
	6	73.98	1 document with 2 instances
NP15718			
NP15728			
NP15757	8	68	1 document with 1 instance
NP15826	6	32, 75, 75, 75, 76, 76, 77, 78, 79, 80, 98	1 document with 11 instances
NP15827	8	68	1 document with 1 instance
NP22770			

Table 5. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) *(Continued)*

NP25138			
NP25139			
NV16871			
NV20234			
NV20235			
NV20236			
NV20237			
NV22155			
NV25118			
NV25182			
PP16351			
WP15517	1	185.245	1 document with 2 instances
WP15525	1	185.245	1 document with 2 instances
WP15647			
WP15648			
WP15676			
WP15901			
WP22849			
WV144181			
WV15670	1	33, 36, 37, 37, 38, 38, 39, 47, 48, 48, 49, 49, 50, 53, 54, 54, 55, 163, 171, 188, 207, 209, 224, 245, 245, 252, 253, 253	7 documents with 1193 instances
	10	7, 36, 37, 37	
	2		
	3		
	4	90	
	6	35.98	
	8	65	
	2	20, 20, 20, 20, 20	1 document with 5 instances

Table 5. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) *(Continued)*

WV15671	1	33, 36, 37, 37, 38, 38, 39, 47, 48, 49, 49, 50, 53, 54, 54, 55, 163, 171, 188, 207, 209, 224, 245, 245	7 documents with 1222 instances
	10	7, 36, 37, 37	
	2	82	
	4		
	5		
	6	35.98	
	8	66	
WV15673	8	66	1 document with 1 instance
WV15673D	8	66	1 document with 1 instance
WV15697	8		1 document with 1 instance
WV15697D	8		1 document with 1 instance
WV15707	1	33, 36, 37, 37, 38, 67, 68, 224, 245, 245, 245, 246	1 document with 12 instances
WV15708			
WV15708D			
WV15730	1	33, 36, 37, 37, 38, 38, 39, 47, 53, 54, 55, 186, 207, 224, 245, 245, 246	4 documents with 22 instances
	10	7, 36, 37	
	2	82	
	4	90	
WV15731	6	98	1 document with 1 instance
WV15758	1	36, 37, 82, 83, 84, 85, 86, 92, 94, 95, 97, 106, 224, 246	4 documents with 424 instances
	6		
	7		
	8	68	
WV15759	1	36, 37, 94, 95, 95, 109, 113, 114, 121, 122, 224, 246	1 document with 12 instances
WV15799	1	137, 139, 139, 232, 233	3 documents with 499 instances

Table 5. Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) *(Continued)*

	8		
	9		
WV15812	1	36, 37, 37, 38, 38, 39, 67, 68, 68, 107, 107, 107, 108, 108, 121, 121, 122, 123, 224, 246	2 documents with 197 instances
	10		
WV15819	1	33, 36, 37, 37, 38, 58, 58, 59, 59, 60, 61, 62, 62, 65, 65, 67, 68, 224, 246	2 documents with 173 instances
	10		
WV15825	8	66, 66	1 document with 2 instances
WV15871	1	109, 246	1 document with 2 instances
WV15872	1	36, 37, 37, 38, 38, 39, 67, 68, 68, 107, 107, 108, 108, 121, 121, 122, 123, 224	1 document with 18 instances
WV15876	1	246, 246	1 document with 2 instances
WV15978	1	67, 70, 175, 246, 246	1 document with 5 instances
WV16193			
ML16369			

Oseltamivir trials citation by trial ID and source NICE file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which file. Blank spaces indicate no citation for known trials.

All the studies have been searched in the folder "Roche submission".

When there is the number of the volume but no pages are mentioned, it means that the code of the study is cited more than 100 times.

*Number of the volume of the Tamiflu NICE submission.

Table 6. Time to alleviation* of clinically significant symptoms of influenza-like illness (in all participants and participants with no use of relief medication)

Study	Sample size		Median days to alleviation for all participants		Difference in days (P value)	Median days to alleviation and no use of relief medication		Difference in days (P value)
	Zanamivir (n)	Placebo (n)	Zanamivir	Placebo		Zanamivir	Placebo	
NAI30008	262	263	6.0	7.0	1.0 (0.123)	8.0	10.0	2.0 (0.037)
NAI30009	224	247	4.5	5.0	0.5 (0.011)	5.0	6.0	1.0 (0.002)
NAI30010	76	81	4.5	5.5	1.0 (0.033)	5.5	6.75	1.25 (0.150)
NAI30011	237	229	4.50	5.00	0.50 (0.495)	7.0	7.0	0.0 (0.623)
NAI30012	191	167	6.5	7.5	1.0 (0.159)	9.0	10.0	1.0 (0.131)
NAI30015	293	295	2.17	2.67	0.5 (0.166)	3.17	3.83	0.66 (0.058)
NAIA3002	412	365	5.5	6.0	0.5 (0.228)	7.0	8.0	1.0 (0.054)
NAIB3002	174	182	5.0	7.5	2.5 (< 0.001)	5.5	8.25	2.75 (< 0.001)

*Alleviation defined as no fever (temperature $< 37.8^{\circ}\text{C}$), cough recorded as none or mild and muscle/joint aches and pains, sore throat, feverishness/chills and headache recorded as absent/minimal

Table 7. Oseltamivir versus placebo for treating influenza in healthy adults

Oseltamivir versus placebo for treating influenza in healthy adults						
Patient or population: healthy adults with influenza						
Settings: community, nursing homes						
Intervention: oseltamivir versus placebo for treatment						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Risk difference (95% CI)	NNTB or NNTH (95% CI)
	Assumed risk	Corresponding risk				
	Placebo	Oseltamivir versus placebo for treatment				
Time to first alleviation of symptoms in adult treatment (ITT population) (hours)		The mean time (hours) to first alleviation of symptoms adults in the intervention groups was 16.76 lower (25.1 to 8.42 lower)	16.8 hours (8.4 to 25.1)	3954 (8)	N/A	N/A
Adverse events: nausea in adult treatment (on-treatment)	Study population		RR 1.57 (1.14 to 2.15)	4452 (8)	-3.66% (-7.39 to -0.9)	NNTB = 28 (14 to 112)
	64 per 1000	101 per 1000 (73 to 138)				
Adverse events: vomiting in adult treatment (on-treatment)	Study population		RR 2.43 (1.75 to 3.38)	4452 (8)	-4.56% (-7.58 to -2.39)	NNTB = 22 (14 to 42)
	32 per 1000	77 per 1000 (56 to 108)				
Adverse events: diarrhoea in adult treatment (on-treatment)	Study population		RR 0.67 (0.46 to 0.98)	4452 (8)	2.33% (0.14 to 3.81)	NNTB = 43 (27 to 709)
	71 per 1000	47 per 1000 (32 to 69)				
Complications: self reported, investigator-mediated, un-verified pneumonia in adult treatment	Study population		RR 0.55 (0.33 to 0.90)	4452 (8)	1.00% (0.22 to 1.49)	NNTB = 100 (67 to 451)
	22 per 1000	12 per 1000 (7 to 20)				
Adverse events: cardiac body system in adult treatment (on-treatment)	Study population		RR 0.49 (0.25 to 0.97)	3943 (6)	0.68% (0.04 to 1.00)	NNTB = 148 (101 to 2509)
	13 per 1000	7 per 1000 (3 to 13)				
Adverse events: hospital admission in adult treatment	Study population		RR 0.92 (0.57 to 1.50)	4394 (7)	0.15% (-0.78 to 0.91)	NNTB = 687 (NNTB 110 to ∞ to NNTH 128)
	18 per 1000	17 per 1000 (11 to 28)				

Table 7. Oseltamivir versus placebo for treating influenza in healthy adults (Continued)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Negative risk differences indicate harms; positive risk differences indicate benefits.

CI: confidence interval; RR: risk ratio; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm

Table 8. Oseltamivir versus placebo for treating influenza in healthy children
Oseltamivir versus placebo for treating influenza in healthy children
Patient or population: healthy children with influenza

Settings: community

Intervention: oseltamivir versus placebo for treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Risk difference (95% CI)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Oseltamivir versus placebo for treatment				
Time to first alleviation of symptoms in child treatment (hours)		The mean time (hours) to first alleviation of symptoms in children in the intervention groups was 8.04 lower (33.34 lower to 17.26 higher)		1329 (3)		Not significant
Hospital admission in child treatment (safety population)	Study population		RR 1.92 (0.7 to 5.23)	1359 (3)	-0.81% (-3.72 to 0.26)	NNTH = 124 (NNTB 379 to ∞ to NNTH 27)
	9 per 1000	17 per 1000 (6 to 46)				
Complications: bronchitis in child treatment	Study population		RR 0.65 (0.27 to 1.55)	1359 (3)	1.08% (-1.69 to 2.25)	NNTB = 93 (NNTB 45 to ∞ to NNTH 59)
	31 per 1000	20 per 1000 (8 to 48)				
Complications: otitis media in child treatment	Study population		RR 0.8 (0.62 to 1.02)	1359 (3)	3.26% (-0.33 to 6.18)	NNTB = 31 (NNTB 17 to ∞ to NNTH 308)
	163 per 1000	130 per 1000 (101 to 166)				
Complications: pneumonia in child treatment	Study population		RR 1.06 (0.62 to 1.83)	1359 (3)	-0.22% (-3.07 to 1.41)	NNTH = 450 (NNTB 71 to ∞ to NNTH 33)
	37 per 1000	39 per 1000 (23 to 68)				
Adverse events: diarrhoea in child treatment (on-treatment)	Study population		RR 0.87 (0.58 to 1.28)	1358 (3)	0.93% (-2.01 to 3.02)	NNTB 108 (NNTB 34 to ∞ to NNTH 50)
	72 per 1000	63 per 1000 (42 to 92)				

Table 8. Oseltamivir versus placebo for treating influenza in healthy children (Continued)

Adverse events: vomiting in child treatment (on-treatment)	Study population		RR 1.7 (1.23 to 2.35)	1358 (3)	5.34% (1.75 to 10.29)	NNTH = 19 (10 to 57)
	76 per 1000	130 per 1000 (94 to 179)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Negative risk differences indicate harm; positive risk differences indicate benefits.

CI: confidence interval; RR: risk ratio; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm

Table 9. Zanamivir versus placebo for treating influenza in healthy adults
Zanamivir versus placebo for treating influenza in healthy adults
Patient or population: healthy adults with influenza

Settings: community, nursing homes

Intervention: zanamivir versus placebo for treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Risk difference (95% CI)	NNTB or NNTH (95% CI)
	Assumed risk	Corresponding risk				
	Placebo	Zanamivir versus placebo for treatment				
Time to first alleviation of symptoms in adult treatment (days)		The mean time (days) to first alleviation of symptoms in adults in the intervention groups was 0.60 lower (0.81 to 0.39 lower)	0.60 days (0.39 to 0.81)	5411 (13)	N/A	N/A
Complications: pneumonia confirmed with X-ray in adult treatment	Study population		RR 1.02 (0.35 to 3.02)	946 (2)	-0.06% (-6.56 to 2.11)	NNTH = 1540 (NNTB 48 to ∞ to NNTH 16)
	32 per 1000	33 per 1000 (11 to 98)				
Adverse events: nausea/vomiting in adult treatment (on-treatment)	Study population		RR 0.6 (0.39 to 0.94)	6553 (15)	1.63% (0.24 to 2.48)	NNTB = 62 (41 to 411)
	41 per 1000	24 per 1000 (16 to 38)				
Adverse events: psychiatric body system in adult treatment (on-treatment)	Study population		RR 1.16 (0.57 to 2.38)	4732 (10)	-0.09% (-0.76 to 0.24)	NNTH 1132 (NNTB 421 to ∞ to NNTH 132)
	6 per 1000	6 per 1000 (3 to 13)				
Complications: bronchitis in adult treatment	Study population		RR 0.75 (0.61 to 0.91)	6072 (12)	1.80% (0.65 to 2.80)	NNTB 56 (36 to 155)
	72 per 1000	54 per 1000 (44 to 65)				

Table 9. Zanamivir versus placebo for treating influenza in healthy adults (Continued)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Negative risk differences indicate harms; positive risk differences indicate benefits.
CI: confidence interval; RR: risk ratio; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm

Table 10. Zanamivir versus placebo for treating influenza in healthy children
Zanamivir versus placebo for treating influenza in healthy children
Patient or population: healthy children with influenza

Settings: community

Intervention: zanamivir versus placebo for treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Risk difference (95% CI)	NNTB or NNTH (95% CI)
	Assumed risk	Corresponding risk				
	Placebo	Zanamivir versus placebo for treatment				
Time to first alleviation of symptoms in children (days)		The mean time (days) to first alleviation of symptoms in children in the intervention groups was 1.08 lower (2.32 lower to 0.15 higher)		723 (2)	NA	NA
Complications: sinusitis in child treatment	Study population		RR 0.87 (0.12 to 6.45)	737 (2)	0.19% (-8.09 to 1.31)	NNTB = 519 (NNTB 13 to ∞ to NNTH 77)
	15 per 1000	13 per 1000 (2 to 96)				
Complications: otitis media in child treatment	Study population		RR 1.0 (0.59 to 1.72)	737 (2)	0.00% (-5.13 to 2.92)	NNTB = > 1000 (NNTB 35 to ∞ to NNTH 20)
	71 per 1000	71 per 1000 (42 to 122)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Negative risk differences indicate harms; positive risk differences indicate benefits.
CI: confidence interval; RR: risk ratio; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm

Table 11. Oseltamivir versus placebo for preventing influenza in healthy children
Oseltamivir versus placebo for preventing influenza in healthy children
Patient or population: healthy children without influenza

Settings: community

Intervention: oseltamivir versus placebo for prophylaxis

Table 11. Oseltamivir versus placebo for preventing influenza in healthy children (Continued)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Comments
	Assumed risk	Corresponding risk			
	Placebo	Oseltamivir versus placebo for treatment			
No data	—	—	—	—	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

Table 12. Zanamivir versus placebo for preventing influenza in healthy adults
Zanamivir versus placebo for preventing influenza in healthy adults

Patient or population: healthy adults without influenza

Settings: community, nursing homes

Intervention: zanamivir versus placebo for prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Risk difference (95% CI)	NNTB or NNTH (95% CI)
	Assumed risk	Corresponding risk				
	Placebo	Zanamivir versus placebo for prophylaxis				
Symptomatic influenza in prophylaxis of individuals	Study population		RR 0.39 (0.22 to 0.70)	5275 (4)	1.98% (0.98 to 2.54)	NNTB = 51 (40 to 103)
	33 per 1000	13 per 1000 (7 to 23)				
Asymptomatic influenza in prophylaxis of individuals	Study population		RR 0.97 (0.76 to 1.24)	5275 (4)	0.14% (-1.1 to 1.1)	NNTB = 729 (NNTB 91 to ∞ to NNTH 91)
	50 per 1000	48 per 1000 (38 to 60)				
Symptomatic influenza in household prophylaxis	Study population		RR 0.22 (0.13 to 0.36)	824 (2)	14.84% (12.18 to 16.55)	NNTB = 7 (6 to 9)
	190 per 1000	42 per 1000 (25 to 68)				
Asymptomatic influenza in household prophylaxis	Study population		RR 0.90 (0.6 to 1.35)	824 (2)	1.32% (-2.2 to 3.84)	NNTB = 76 (NNTB 26 to ∞ to NNTH 46)
	107 per 1000	97 per 1000 (64 to 145)				
Complications: pneumonia in adult prophylaxis	Study population		RR 0.30 (0.11 to 0.8)	7662 (6)	0.32% (0.09 to 0.41)	NNTB = 311 (244 to 1086)
	5 per 1000	1.5 per 1000				

Table 12. Zanamivir versus placebo for preventing influenza in healthy adults (Continued)
(1 to 4)

Complications: bronchitis in adult prophylaxis	Study population		RR 0.49 (0.02 to 1.19)	7662 (6)	0.79% (-0.29 to 1.24)	NNTB = 127 (to NNTB 81 to ∞ to NNTH 341)
	15 per 1000	8 per 1000 (3 to 18)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Negative risk differences indicate harms; positive risk differences indicate benefits.
CI: confidence interval; RR: risk ratio; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm

Table 13. Oseltamivir versus placebo for preventing influenza in healthy adults

Oseltamivir versus placebo for preventing influenza in healthy adults

Patient or population: healthy adults without influenza

Settings: community, nursing homes

Intervention: oseltamivir for prophylaxis

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Risk difference (95% CI)	NNTB or NNTH (95% CI)
	Assumed risk	Corresponding risk				
	Placebo	Oseltamivir versus placebo for prophylaxis				
Symptomatic influenza in adult prophylaxis of individuals	Study population		RR 0.45 (0.30 to 0.67)	2479 (3)	3.05% (1.83 to 3.88)	NNTB = 33 (26 to 55)
	55 per 1000	25 per 1000 (17 to 37)				
Symptomatic influenza in household prophylaxis	Study population		RR 0.2 (0.09 to 0.44)	405 (1)	13.6% (9.52 to 15.47)	NNTB = 7 (6 to 11)
	170 per 1000	34 per 1000 (15 to 75)				
Adverse events: psychiatric body systems in adult prophylaxis (all events on- and off-treatment)	Study population		RR 1.80 (1.05 to 3.08)	3434 (4 studies)	-1.06% (-2.76 to -0.07)	NNTH = 94 (36 to 1538)
	13 per 1000	23 per 1000 (14 to 40)				
Adverse events: headache in adult prophylaxis (on-treatment)	Study population		RR 1.18 (1.05 to 1.33)	3434 (4)	-3.15% (-5.78 to -0.88)	NNTH = 32 (18 to 115)
	175 per 1000	207 per 1000 (184 to 233)				
Adverse events: nausea in adult prophylaxis (on-treatment)	Study population		RR 1.96 (1.2 to 3.2)	3434 (4)		NNTH = 25 (11 to 116)

Table 13. Oseltamivir versus placebo for preventing influenza in healthy adults (Continued)

	43 per 1000	85 per 1000 (52 to 138)			-4.15% (-9.51 to -0.86)	
Adverse events: vomiting in adult prophylaxis (on-treatment)	Study population		RR 1.91 (0.7 to 5.22)	3434 (4)	-0.95% (-4.41 to 0.31)	NNTH = 106 (NNTB 319 to ∞ to NNTH 23)
	10 per 1000	20 per 1000 (7 to 55)				
Adverse events: headache in adult prophylaxis (off-treatment)	Study population		RR 0.88 (0.63 to 1.24)	3434 (4)	0.44% (-0.89 to 1.37)	NNTB = 226 (NNTB 74 to ∞ to NNTH 113)
	37 per 1000	33 per 1000 (23 to 46)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Negative risk differences indicate harms; positive risk differences indicate benefits.

CI: confidence interval; RR: risk ratio; NNTB: number needed to treat to benefit; NNTH: number needed to treat to harm

Table 14. Zanamivir versus placebo for preventing influenza in healthy children
Zanamivir versus placebo for preventing influenza in healthy children

Patient or population: healthy children without influenza

Settings: community

Intervention: zanamivir versus placebo for prophylaxis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Comments
	Assumed risk	Corresponding risk			
	Placebo	Zanamivir versus placebo for treatment			
No data	—	—	—	—	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

Table 15. Psychiatric adverse events in oseltamivir prophylaxis trials

	Oseltamivir		Placebo		Total	
Event type	# Events	%	# Events	%	# Events	%
Confusion	5	0.25	1	0.07	6	0.17
Depression	14	0.7	6	0.42	20	0.58

Table 15. Psychiatric adverse events in oseltamivir prophylaxis trials (Continued)

Hallucinations	2	0.1	0	0.00	2	0.06
Anxiety	7	0.35	8	0.56	15	0.44
Psychosis	2	0.1	1	0.07	3	0.09
Schizophrenia	1	0.05	0	0.00	1	0.03
Bipolar disorder	0	0	1	0.07	1	0.03
Sleeping disorder	2	0.1	0	0.00	2	0.06
Aggression	1	0.05	0	0.00	1	0.03
Stress symptoms	3	0.15	0	0.00	3	0.09
Restlessness	1	0.05	0	0.00	1	0.03
Nervousness	1	0.05	0	0.00	1	0.03
Suicide ideation	1	0.05	0	0.00	1	0.03
Paranoia	1	0.05	0	0.00	1	0.03
Alcohol related	6	0.3	2	0.14	8	0.23
Total	47	2.35	19	1.32	66	1.92

Of the 66 events, 12 were classified as severe intensity (10 oseltamivir, 2 placebo)

Table 16. Proportions of contacts with positive serology data (WV15799 ITTIINAB population)

Positive serology	Group		Total
	Placebo	Tamiflu	
	N %	N %	
No	166 83.0	192 93.7	358
Yes	34 17.0	13 6.3	47
Total	200	205	405

ITTIINAB population: ITT influenza-infected index cases who had negative virology at baseline
Chi² P = 0.001

Table 17. Oseltamivir and placebo intervention contents by trial

Trial ID	Description oseltamivir/batch no.	Description placebo/batch no.	Certified content	Certified content	Ref (PDF page number)

Table 17. Oseltamivir and placebo intervention contents by trial *(Continued)*

			(oseltamivir)	(placebo)	
M76001	Size 2 capsules containing 75 mg oseltamivir/V01-00 (GS 4104), batch number GMZ 0082	Size 2 placebo capsules for oseltamivir/V02-00 (GS 4104), batch number GMZ 0083	Unknown (certificate of analysis not provided)	Unknown (certificate of analysis not provided)	20
WP16263	Grey opaque body, light yellow opaque cap/PT2247C01	Grey opaque body, ivory opaque cap/GMZ 0163	Oseltamivir 97.5 mg	Dehydrocholic acid	19 and 422
WV15670	Size 2 capsules containing 75 mg Ro 64-0796/V01-00 (GS 4104), batch number GMZ 0067; caramel opaque body, caramel opaque cap	Size 2 placebo capsules for Ro 64-0796/V02-00 (GS 4104), batch number GMZ 0066; caramel opaque body, caramel opaque cap	Oseltamivir 94.3 mg	Dehydrocholic acid 6.13 mg	13, 834-5
WV15671	Capsules (size 2) containing 75 mg Ro 64-0796 (GS 4104)/V01; batch number GMZ 0067/GMZ 0065. Capsules are caramel opaque body, caramel opaque cap. Also used batch GMZ 0067 capsules caramel opaque body, caramel opaque cap (for oseltamivir 94.3 mg)	Matching placebo-capsules (size 2) for Ro 64-0796 (GS 4104)/V02; batch number GMZ 0066. Capsules are caramel opaque body, caramel opaque cap	Oseltamivir 93.1 mg and oseltamivir 94.3 mg	Dehydrocholic acid 6.13 mg	13, 764-7
WV15673/ WV15697	GS 4104 (Ro 64-0796) provided as size 2 caramel-coloured capsules containing 75 mg of active drug and packaging material consisting of dehydrocholic acid, dibasic calcium phosphate dihydrate, pregelatinised starch, povidone, talc and sodium stearyl fumarate." Ro 64-0796/V01-00 batch GMZ 0067; caramel opaque body, caramel opaque cap	Placebo provided as size 2 caramel-coloured capsules, containing dehydrocholic acid, dibasic calcium phosphate dihydrate, pregelatinised starch, povidone, talc and sodium stearyl fumarate Ro64-0796/V02-00 batch GMZ 0066; caramel opaque body, caramel opaque cap	94.3 mg	Dehydrocholic acid 6.13 mg	385, 540-2
WV15707	Ro 64-0796 was provided as a size 2 capsule containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Ro 64-0796 (GS4104)/V01-00 batch number GMZ 0082	Placebo was provided as a size 2 capsule containing dehydrocholic acid, dibasic calcium phosphate dihydrate and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Placebo Ro 64-0796/V02-00 batch number GMZ 0066	Ro 64-0796/002 100.5 mg	Dehydrocholic acid	3, 517-9
WV15708	Size 2 capsules of 75 mg; Ro 64-0796/V01-00 batch no. GMZ 0082; caramel opaque body, caramel opaque cap	Matching size 2 placebo capsules Ro 64-0796/V02-00 batch no. GMZ 0083; caramel opaque	Oseltamivir 100.5 mg	Dehydrocholic acid	21-2, 517-9

Table 17. Oseltamivir and placebo intervention contents by trial *(Continued)*

		body, caramel opaque cap			
WV15730	Ro 64-0796 was provided as a caramel, opaque, size 2 capsule containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Ro 64-0796 (GS4104)/V01-00 batch number GMZ 0082	Placebo was provided as a caramel, opaque, size 2 capsule containing dehydrocholic acid, dibasic (calcium phosphate dihydrate and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Placebo Ro 64-0796/V02-00 batch number GMZ 0083	Oseltamivir 100.5 mg	Dehydrocholic acid	24, 504-5
WV15758	2 batches of the paediatric formulation were used in the present study: 1. Ro 64-0796/V20-01 (0.6% syrup); batch no. G HK 0180/05 2. Ro 64-0796/V20-01 (0.6% syrup); batch no. G HK 0180/06	2 batches of the corresponding placebo formulation were used: 1. Ro 64-0796/V19-01; batch no. G HK 0179/04 2. Ro 64-0796/V19-01; batch no. G HK 0179/05	Oseltamivir 0.768 g (G HK 0180/05), 0.763 g (G HK 0180/06)	Dehydrocholic acid	27, 1043-5
WV15759/15871	Ro 64-0796 was to be provided as a dry powder for reconstitution with water. The powdered formulation contains the active ingredient, sorbitol and saccharin sodium (sweeteners), betacarotene (colouring agent), permageal 31 tutti frutti (flavour), cellulose, xanthan gum and methylhydroxy/propylhydroxybenzoate		Unknown (certificates of analysis not in our possession)	Unknown (certificates of analysis not in our possession)	36
WV15799	Ro 64-0796 was provided as ivory, opaque, size 2 capsule containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Ro 64-0796 (GS4104)/V14-00 batch numbers GMZ 0124/03 and GMZ 0129/03	Placebo was provided as an ivory, opaque, size 2 capsule containing dehydrocholic acid, dibasic calcium phosphate dihydrate and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. Placebo Ro 64-0796/V16-00 batch number GMZ 0136	Unknown (certificates of analysis not in our possession)	Unknown (certificates of analysis not in our possession)	24
WV15812/ WV15872	Ro 64-0796 was provided as size 2 capsules containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate	Matching placebo was provided as size 2 capsules containing dehydrocholic acid, dibasic calcium phosphate dihydrate, pregelatinised starch, povidone, talc, sodium stearyl fumarate	Unknown (certificate of analysis not provided)	Unknown (certificate of analysis not provided)	18

Table 17. Oseltamivir and placebo intervention contents by trial (Continued)

WV15876/ WV15819/ WV15978	Capsules (size 2) containing 95.8 mg oseltamivir phosphate, equivalent to 75 mg oseltamivir: formulation V14; batch numbers GMZ 0124/03, GMZ 0129/03. Both batches: grey opaque body, ivory opaque cap The following statement appears after the description of the placebo; whether it applies to oseltamivir capsules is unclear: "Excipients for each capsule consisted of dehydrocholic acid, dibasic calcium diphosphate dihydrate, pregelatinized starch, povidone, talc, sodium stearyl fumarate."	Matching placebo capsules (size 2) for oseltamivir: formulation V16; batch numbers GMZ 0136, GMZ 0163. Both batches: grey opaque body, ivory opaque cap The following statement appears after the description of the placebo; whether it applies to oseltamivir capsules is unclear: "Excipients for each capsule consisted of dehydrocholic acid, dibasic calcium diphosphate dihydrate, pregelatinized starch, povidone, talc, sodium stearyl fumarate."	Oseltamivir 95.7 mg (GMZ 0124/03); 97.9 mg (GMZ 0129/03)	Dehydrocholic acid	21, 944-9
WV16277	Oseltamivir was provided as size 2 capsules containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate.. Oseltamivir: 75 mg capsules, Ro 64-0796/V14, batch number PT2247C01 Capsules are caramel opaque body, caramel opaque cap	Matching placebo was provided as size 2 capsules, containing dehydrocholic acid, dibasic calcium phosphate dihydrate, pregelatinised starch, povidone, talc, sodium stearyl fumarate Matching placebo capsules: Ro 64-0796/V16, batch number GMZ 0163. Capsules are caramel opaque body, caramel opaque cap	Unknown (certificate of analysis not provided)	Unknown (certificate of analysis not provided)	20
NV16871	Capsules containing 75 mg of active drug and packaging material consisting of pregelatinised starch, povidone, talc and sodium stearyl fumarate. All participants over the age of 13 or who weighed > 40 kg received this dosage form. 2. A paediatric suspension containing 12 mg oseltamivir per ml of reconstituted solution and the following excipients: sorbitol, titanium dioxide, sodium benzoate, xanthan gum, monosodium citrate, saccharin sodium and Permaseal 11900-31 tutti frutti (flavour). All participants of 12 years and under or who weighed ≤ 40 kg received this dosage form or 10 doses Ro 64-0796/V14 (oseltamivir 75 mg capsules), batch PT2247C01	Matching placebo was to be provided as capsules and as suspension Ro 64-0796/V16 (placebo capsules), batch GMZ 0163 Ro 64-0796/VF01 (placebo powder for oral suspension), batch C0318A001	Unknown (certificate of analysis not provided)	Unknown (certificate of analysis not provided)	13-14, 24

Table 17. Oseltamivir and placebo intervention contents by trial *(Continued)*

Ro 64-0796/V37 (oseltamivir powder for oral suspension), batch B1023

NB Most content dosage unavailable at review time-lock.

APPENDICES

Appendix 1. Glossary of terms used in this review

Public health drugs: Drugs in which a considerable quantity of public money has been invested and/or are on the WHO essential drugs list.

Clinical study reports: Detailed reports of a clinical trial usually submitted to regulators following a prescribed ICH format. Roche's follow a modular structure (see Appendix 11). Reports can be several hundred pages long and contain details of the planned design, conduct (protocol), analysis (reporting analysis plan or RAP) and results of the trial.

Compliharm: Term describing events defined as either complications or harms according to ambiguous criteria that appeared to include time of analysis (with times either unspecified or inconsistent among trials) and whether participants were infected (by influenza) or not. In oseltamivir treatment trials some potential harms or complications could both be caused by medication or influenza infection (e.g. vomiting), hence our classification as a compliharms.

Time lock: Date (12 April 2011) after which no documentation would be reviewed in the January 2012 version of the review. A cutoff was made necessary by the sheer scale of our data holdings. We were initially funded to review the full clinical study reports of the 10 treatment trials included in the Kaiser et al paper. We were able to access the 10 Module 1s and regulatory comments (approximately 6000 pages in total). As the funder-stipulated deadline to producing our review progressively shortened and our understanding of the issues evolved we received notification that while the balance of the 10 study reports were unlikely to be accessible by our deadline, we would receive substantial quantities of regulatory documents from the EMA in four tranches. When we held our second face to face meeting in April 2011 we had just received our first tranche of clinical study reports consisting of just over 10 thousand pages, bringing our total holdings to 16,000 pages. We decided that we did not have the resources to review any further documentation within our current funding and imposed a data time lock. Any documentation received after this date would be reviewed if and when we had more resources. The balance of documents (a further 14,000 pages) are included in this review.

TOC: Table of content of regulatory reviews and comments on industry submissions. Our TOC indicates which trial is cited in which document on which page how many times.

TOCE: Annotated version of the TOC. Comments and annotation are preliminary and form the basis for the weaving of the important aspects into the review narrative. (See also [Table 2](#); [Table 3](#); [Table 4](#); [Table 5](#)).

Trial ID: Means of identifying a trial. Usually made up of letters and numbers (WV 15799). At times the ID bears a letter suffix indicating the last version of the protocol followed in the trial (e.g. WV 15799H, i.e. trial carried out following amendment H).

Regulatory information: Term comprising clinical study reports (data) and regulatory comments and reviews.

Modules: Basic structure of Roche's trial reports see ([Appendix 11](#)). Today, the term 'Modules' refers to the components of a regulatory submission, as set by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) ([ICH 2011](#)). Clinical study reports are just one 'Module' of a regulatory submission.

FOI: Freedom of Information. Enshrined by law in the US and EMA policy in Europe. FOI requests in this review have been a means of access to clinical study reports and regulatory comments (regulatory information).

CONSORT-based extraction: Extraction, synthesis and appraisal method used in this review for data from clinical study reports. Reconstructions were done by pairs of review authors and assessed in the authors' plenary session to decide whether included trials could proceed to stage 2 of the analysis. The structure of the reconstruction follows that of the CONSORT statement.

Protocol: Document reporting the trial's planned design and conduct, with amendments (when relevant). Confusingly also used in submissions and regulatory documents as synonymous with study.

IPD: Individual patient data. Anonymised individual data listings of characteristics and results, which form the basis for the synthetic analyses in clinical study reports.

Trial programme: Series of trials designed and carried out to achieve registration or to answer specific questions. Usually programmes of the same drug or intervention focus on the same indication or the same study population.

Reporting Analysis Plan (RAP): Plan of analysis usually linked to trial protocol explaining what and how the authors intend to analyse.

Japanese Summary Basis for Approval (of a drug) (JSBA): Summary of the application dossiers included as one of the documents prepared and attached by the sponsoring pharmaceutical company. These are submitted to the regulatory body for approval of a new drug.

Appendix 2. The story of A159

The 2009 review: from A047 to A159

In the midst of the A/H1N1 influenza outbreak in June 2009, the Australian and UK governments commissioned an update of our long-standing Cochrane review on neuraminidase inhibitors (NIs) for influenza in (otherwise) healthy adults (known as A047). Prior to the emergence of influenza A/H1N1 in 2009, governments worldwide stockpiled nearly CHF 7.6 billion worth of oseltamivir (Jack 2009). The World Health Organization (WHO) considered antivirals for influenza important (WHO has recently added oseltamivir to the list of essential medicines (WHO 2011; WHO 2013a; WHO 2013b)). Oseltamivir and zanamivir have been prescribed for the treatment of influenza worldwide since the outbreak of 2009 A/H1N1 influenza. The review (on healthy adults) had first been published in 1999 (as A047) and was updated in 2006 and 2008. At the same time a similar review on children (as Shun-Shin 2009 or A046) had also been published.

As the review had been updated the previous year, we initially anticipated that the commissioned 2009 update would not require substantial effort and likely reflect only updated pharmacovigilance data and not the incorporation of new trial evidence (Doshi 2009).

In the end, the 2009 update was inconclusive regarding whether or not oseltamivir reduced the risk of complications of influenza (Jefferson 2010a), as we were unable to verify the data underlying manufacturer and government claims to this effect. The claims were based on clinical trial evidence included in a published pooled analysis of 10 manufacturer-funded clinical trials of oseltamivir for the treatment of influenza in people of 13 years and older (Kaiser 2003). Eight of the 10 trials in the Kaiser et al pooled analysis have never been published (Jefferson 2009a), and their complete data sets were not available from either the authors or the manufacturers. Some of the published trials had been ghost written (Cohen 2009). The largest of the 10 Kaiser trials (M76001), involving over 1400 people, had been briefly reported in conference abstract format but the person whose name appeared on the abstract could not recall ever presenting its results or being involved with the study (Cohen 2009). Our early requests for data from the 10 Kaiser studies were met with an offer from Roche to sign a confidentiality agreement with an embedded secrecy clause preventing us from mentioning the existence of the agreement. The unsigned agreement can be seen at http://www.bmj.com/highwire/filestream/440792/field_highwire_adjunct_files/0.

At the time of publication of the 2009 update and its linked investigation by the *BMJ*, we were unaware of the size and depth of the oseltamivir evidence development programme. We thought it comprised around 36 trials and we expected that only a proportion of these would fit our inclusion criteria. We also did not realise the size and the level of detail that the clinical study reports contained.

On 31 December 2009, Roche released the core reports (or Module 1s) of the 10 Kaiser trials with no legal agreement signed (only a web-based agreement that we would not share the documents with other commercial companies). After requesting Roche to provide us with the full study reports, Roche said that the Module 1s were all that were needed for us to complete our job (Doshi 2012a). The missing Modules (or parts), numbered 3 to 4 according to the trial in question, contained protocols, amendments, individual listings and demographic information. It seemed to us that these documents would have contained some important additional material for understanding the trials, their design and interpretation but we were not sure.

In 2010 we started exploring the relationship between the available Module 1s for the only two Kaiser trials that had been published (trials WV15670 or Nicholson 2000 and WV15671 or Treanor 2000).

At about this time we started getting concerned that the oseltamivir trial programme was considerably larger than we first thought. Our interest was awakened by the casual discovery of a confidential 2009 Roche Tamiflu Investigator's Brochure, which was freely accessible on the web. This reported a clinical trial programme of over 60 studies. Searching for an unpublished and hitherto unseen data set requires constructing a reasonably accurate list of all studies of the drug in question. The Roche Investigator's Brochure did not mention some studies we were aware of, and reinforced an idea that we had become clear was essential: the need to develop our own list of trials, because a single, authoritative, up-to-date and complete list of all clinical trials conducted on humans using for both drugs did not seem to exist.

When thinking about our next update we decided not to use publications because the majority of treatment trial evidence for Tamiflu remained unpublished, because we had found some discrepancies between CSRs and published equivalents and, mostly, because clinical study reports were so much more detailed and comprehensive than short journal articles, enabling a more thorough critical analysis of the trials. We also decided to expand the scope of A047 by including evidence relating to people of all ages except for immune-suppressed individuals. This, de facto, amounted to the creation of one new review (A159) with a new protocol subsuming A047 and A046. The protocol for A159 was publicly posted in December 2010.

A new source of evidence for A159

Today the obvious source of information on clinical study reports would be trial registries and company websites, but most trials of both NIs were carried out before inception or wide acceptance of centralised registries and company websites. In 2009-11, company websites did not and still do not have extensive lists of trials with downloadable clinical study reports. Most people had never heard of clinical study reports before media coverage of our efforts.

We decided to construct our list by using multiple cross-referencing methods. We constructed a list beginning with clinical trials identified from previous review updates. To this end, we added additional trials in humans from multiple sources, including manufacturer submissions to regulators, drug product information sheets, previous published reviews, Health Technology Assessment (HTA) documents and public and manufacturers' registers (Burch 2009; Cooper 2003; Jefferson 2006; Tappenden 2009; Turner 2003), such as www.ClinicalTrials.gov and www.roche-trials.com. Regulatory documents also aided the identification of unknown trials. Finally, we also conducted traditional database and grey literature searches (Appendix 5) to identify previously unknown trials.

One of the first things we learned was that to ensure the list did not include duplicate entries, we had to assign to each trial a Unique Trial ID. 'Author' is not a good choice of Unique Trial ID, as different authors can be present across different versions of the same trial (that is, the authors of clinical study reports can be different from publications arising from the same clinical trial). Nor are any other details connected to publications a good option for Unique Trial ID because not all studies are published. Some trials will have company-specific codes and some will have public clinical trial registry numbers, or both, or neither. To simplify recognition and terminology we used the manufacturer protocol ID as our Unique Trial ID.

Our list was only going to be useful if it had sufficient details to enable us to decide whether it met our inclusion criteria. For each Unique Trial ID, we gathered the following details.

1. Unique Trial ID
2. Other IDs
3. Phase of study
4. Sponsor
5. Short description
6. Official trial title
7. First authors (name and email)
8. Type of trial
9. Comparator
10. Outcomes assessed
11. Date of trial
12. Study period (days)
13. Population
14. Number of participants planned
15. Number of participants enrolled
16. Number of participants completing
17. Trial status (for example, completed, ongoing or early termination)
18. Publication status (a citation or understanding of why it was not published)
19. How identified (to record how the trial was discovered)
20. Notes

Once we had as complete a list of trials as possible, we contacted manufacturers and sent them our draft list, asking them to check the accuracy and completeness of our list. Roche, GlaxoSmithKline (GSK) and BioCryst all did so, and in doing so we learned of hitherto unknown trials.

Occasionally, the existence of further unknown trials was detected weeks and months after we thought we had a 'complete' list. This may be inevitable given that trial identification often takes place in unpredictable ways, for example while reading through detailed regulatory reports.

We engaged in prolonged correspondence with Roche and GSK and requested a series of regulatory documents under freedom of information policies from both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). No substantial comments were made by Roche on the protocol of 159 which has been publicly available in one form or another since December 2010.

Specifically, we applied to EMA under their new release policy for 26 clinical study reports in their holdings relating to oseltamivir and GSK's zanamivir. The result was the delivery (starting in late March 2011) of 16 clinical study reports, all containing Modules 1 and 2 plus one complete report for oseltamivir (trial [WP16263](#)). (See table 1 in [Doshi 2012b](#)). None were available for zanamivir, as the EMA had not played a part in its market authorisation. These formed the basis for the 2012 version of A159.

At the date of completion of data searches for A159 (12 April 2011), Roche had only provided us with partial clinical study reports despite five requests for full clinical study reports. The material obtained from Roche included the first section (or so-called 'Module 1' or 'Core Report') of a full clinical study report, each of which contain four to five Modules ([Appendix 11](#)) for the 10 oseltamivir treatment trials included in the [Kaiser 2003](#) meta-analysis. Not contained in the provided Module 1s are trial protocols with the list of amendments and original reporting analysis plans. These Module 1s comprise 3195 pages. Roche had not made available any further material and indicated it did not intend to answer our requests for clarification on aspects of trials and for availability of the missing parts of complete clinical study reports. In addition we had a 53-page report in English of the treatment trial [ML16369](#), sponsored by Shanghai Roche Pharmaceutical Ltd. Regardless of success with our requests to obtain full clinical study reports, we decided to update our review with available material and subsequently update it as and when additional data became available.

Our searches of publication databases did not add any significant information.

Following a change of policy at the EMA prompted by similar efforts of the Nordic Cochrane Centre ([Gotzsche 2011](#)), we received an additional eight clinical study reports (10,737 pages) in response to a freedom of information request. An additional 14,700 pages of further clinical study reports and 33 pages of regulators' comments arrived after our search deadline. All of the materials received from the EMA are related to oseltamivir. The EMA has no access to information for zanamivir, as it is a nationally authorised product in Europe (correspondence with Xavier Luria, 23 March 2011 and David Mackay 20 July 2011). At present we hold all Module 1s and 2 of oseltamivir trials we have requested. From GSK we have received the promise of individual patient data. Many of the clinical study reports used in this review were obtained via freedom of information requests.

We still await an FDA decision regarding similar requests sent to FDA in January 2011.

We were able to download 2673 pages of Summary Basis for Approval (SBA) documents from the FDA website, 31 from EMA and 508 pages of Japanese SBA. We indexed the content and then constructed an extended table of contents, giving a summary of each file, thereby facilitating navigation of these complex documents. Once the table of contents had been constructed, we postulated that given the huge work involved in reviewing lots of regulatory files, including clinical study reports, we needed new instruments to indicate which parts were more important than others, thus focusing our efforts. We experimented with a variety of methods reported in the earlier version of the review. We have now devised and used what for us is a satisfactory instrument for critically assessing clinical study reports in their entirety. We intend publishing this separately.

The EMA releases, coupled with documents from the FDA SBA for both drugs, formed the basis for the version of A159 that we eventually published in January 2012. The review reported our efforts to get to the bottom of the issue of the effects of NIs by appraising evidence from unpublished clinical study reports (see Glossary ([Appendix 1](#)) and regulatory documents containing comments and reviews. We called the body of clinical studies and regulatory comments 'regulatory information' as all of these documents are either created for or by regulators. To our knowledge this was the first Cochrane review ever conducted on the basis of regulatory documents only.

Due to funding timelines and the sizeable amount of regulatory information already available to us we decided to review material available as at 12 April 2011. This meant reviewing FDA SBA material and core reports (Module 1s) in our possession from EMA data releases received by this time.

Study selection and extraction in 2011

In 2011 our methods were a mixture of established and novel, reflecting the size of the task, our lack of experience in dealing with large amounts of very detailed regulatory information and the lack of a complete set of clinical study reports. For example, scanning of titles and abstracts was done in double, but selection of studies for inclusion from the list constructed during our search was done in quadruple with disagreements resolved by discussion.

For many studies we only had titles and in some cases a very brief description of content, thus we assigned three categories to our trials:

1. definitely included;
2. definitely excluded; and
3. trials for which we needed further information.

We excluded studies definitely not meeting the inclusion criteria on the basis of the available information (e.g. the title described the trial as a pharmacokinetic study). Where appropriate we requested further information from the trials' sponsor, usually copies of the clinical study reports (minus participant identification) for each trial that was definitely included or for which we needed further information. We did not contact first/corresponding authors of published versions of the trials on the basis of our experience with the 2009 review.

Data extraction and management reflected the lack of established methods for reviewing regulatory material. We subdivided the extraction, appraisal and analysis of the data into a two-stage exercise, including studies in the analysis phase only if we judged their reports reliable and complete. To help structure the information we used CONSORT statement-based extraction forms aimed at assembling a concise version of the clinical study reports, which included all important methods as well as defined and extracted all relevant outcomes. We colour-coded the original text to flag up uncertainty or lack of clarity or need for more information from other (then inaccessible) parts of the clinical study report.

During this process we excluded all six peramivir trials as we were informed by the manufacturers that no clinical study reports would be available. The 2012 A159 review was based on 15 oseltamivir clinical study core reports and 10 very brief zanamivir study reports. The former came from EMA, while the latter had been part of a GSK submission to the UK's National Institute for Health and Care Excellence (NICE) which the *BMJ* had passed onto us together with the SBA material. Our 2010 protocol for A159 was not very detailed on how we would handle this mass of information for the simple reason that no one had ever done it before. We quite literally were learning as we were going along and our understanding of the structure and content of clinical study reports evolved. We created and tested five post-protocol hypotheses (see [Appendix 10](#)), which had originated from the findings in the reports. The best example was our finding of an unnaturally high (up to 80%) influenza positivity rate in treatment trials, which in some cases had been pooled because of lack of viral circulation. We hypothesised that screening for influenza positivity had been carried out prior to enrolment of people with influenza-like illness. This was not borne out by the evidence available to us. We know now that a far simpler explanation is more likely: careful selection of the time period for trial participant enrolment based on when surveillance data suggested high influenza activity led to the recruitment of small numbers of participants from each of many centres with a high likelihood of influenza positivity, but at the time we had limited information available. The 201

2 A159 review analyses were based on the ITT population, which we had found to be the only reliable analysis unit as oseltamivir appeared to have an effect on antibody production in people with influenza, leading to an imbalance in numbers of subjects in the influenza-infected (so-called ITTI) sub-population. This in effect introduced confounding in what otherwise should have been well-designed double-blind trials. The only effect that was clearly identifiable was a modest shortening of influenza-like illness symptoms by less than a day. This led us to believe that oseltamivir had an aspecific powerful effect on symptoms not mediated by any action on influenza viruses but possibly via an anti-inflammatory mechanism. The trials had been clearly designed with a commercial focus in mind and some of the claims made by the manufacturer (especially on the effect on interruption of transmission and on pneumonia) were not supported by the evidence in our possession.

2012 to the present day

Soon after the publication of the review, the *BMJ* agreed to publish our correspondence with Roche, GSK, EMA, Centers for Disease Control and Prevention (CDC) and WHO, recording our attempts at retrieving the full reports without any conditions attached and to understand the basis for promotion of the drugs (especially oseltamivir) by public health bodies. The correspondence (which is hundreds of pages long) formed the basis for what then became the *BMJ* Open Data campaign and a stimulus for the later AllTrials campaign. Public exposure of our efforts and copious media coverage had the direct effect of ensuring the unconditional release of 77 reports of oseltamivir of 82 studies sponsored by Roche and the equivalent of the 30 studies we had requested from GSK. For the full correspondence see <http://www.bmj.com/tamiflu> and <http://www.bmj.com/relenza>. The reports (amounting to over 100,000 pages) are made available with this review for the first time at [insert URL when available], marking a small but significant victory for open science.

Before receiving the full reports, we resumed reviewing the remainder of the material we had received in 2011. This mainly consisted of Module 2s (Roche terminology for pre-study documents). Module 2s contained the information originally denied to us by Roche: study protocols with their amendments, randomisation lists, blank case report forms (CRFs), certificates of analysis describing appearance and content of active and control capsules and, at times, statistical analysis plans (SAPs). CRFs are containers for the rawest form of recorded data at the individual participant level.

We had no tools for reviewing and synthesising this information, so again we had to create our own. The instrument is made up of three parts each with a separate function. In the first part there is a template for a brief summary description of the trial. The format fits into the RevMan Characteristics of Included Studies (CIST) table and is mainly descriptive. The second part is the appraisal of the trial following the Cochrane 'Risk of bias' format. The third part reconstructs the trial timeline and provides a checklist and position in the document of the various elements such as protocol, protocol amendments and study period with dates. The last part aims to check the internal consistency and coherence of each element (such as numbers screened, numbers randomised, interventions, comparators) across all the different documents, starting from the earliest available version of the protocol. The form also contains suggestions on where to look for the information. This is based on our experience gained in this review and in a descriptive review of 78 clinical study reports of 14 different drugs and biologicals ([Doshi 2013](#)).

While designing the tool we also asked ourselves whether access to Module 2 information (and later the full study reports) changed our perception of the trial and specifically our 'Risk of bias' assessment. We found that access to what are supposed to be full study reports should provide clarity and remove the rationale for 'unclear' risk of bias judgements and ideally remove the concept of risk leaving just 'bias', at least for certain study design elements such as attrition bias. Either a design element introduces bias or it does not. In the case of the 15 full oseltamivir clinical study reports we reviewed when constructing our tool, only one contained a protocol which predated the beginning of participant enrolment, only two had statistical analysis plans that clearly predated participants' enrolment and three had clearly dated protocol amendments. No clinical study report reported a clear date of unblinding.

During the latter part of 2013, we received from the manufacturers tens of thousands of pages of full clinical study reports for both programmes combined.

The history and conclusions form the backdrop to this version of A159.

Oseltamivir studies received from Hoffman La Roche SA in CSR format:

Neuraminidase inhibitors for preventing and treating influenza in adults and children (Review)

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1. [WV16277](#)
2. [WV15819/WV15876/WV15978](#)
3. [WV15707](#)
4. [WV15812/WV15872](#)
5. [WV15730](#)
6. [M76001](#)
7. [WV15670](#)
8. [WV15671](#)
9. [NV16871](#)
10. [WV15759/WV15871](#)
11. [WV16193](#)
12. [WV15825](#)
13. [WV15708](#)
14. [WV15799](#)
15. [WV15673/WV15697](#)
16. [WV15758](#)
17. [NV20235](#)
18. [M76006](#)
19. [NV20236](#)
20. [NP15717](#)
21. [PV15616](#) (= GS 97-801)
22. [PV15615](#) (= GS 97-802)
23. [JV16284](#)
24. [WV15731](#)
25. [NV22155](#)
26. [NP15719](#)
27. [WP16254](#)
28. [WP16094](#)
29. [WP18308](#)
30. [WP16225](#)
31. [WP16134](#)
32. [PP15974](#)
33. [NP16472](#)
34. [NP15718](#)
35. [WP16226](#)
36. [NP25139](#)
37. [NP25138](#)
38. [NP15901](#)
39. [WP15525](#)
40. [NP25140](#)
41. [NP15728](#)
42. [NP15810](#)
43. [NP15826](#)
44. [PP16351](#)
45. [WP22849](#)
46. [NP22770](#)
47. [WP20727](#)
48. [PP16361](#)
49. [WP15517](#)
50. [NP15729](#)
51. [BP21288](#)
52. [WP21272](#)

- 53. [JP15735](#)
- 54. [WP15647](#)
- 55. [WP15648](#)
- 56. [WP15676](#)
- 57. [WP16263](#)
- 58. [NP15757](#)
- 59. [NV25118](#)
- 60. [NP15743](#)
- 61. [NP15881](#)
- 62. [NP15912](#)
- 63. [WP15979](#)
- 64. [WP16137](#)
- 65. [WP16295](#)
- 66. [NP15827](#)
- 67. [NV25655](#)
- 68. [JV21490](#)
- 69. [JP15734](#)
- 70. [NV22158](#)
- 71. [ML17713](#)
- 72. [ML22789](#)
- 73. [NV25182](#)
- 74. [ML17279](#) – publication only
- 75. [ML19340](#) – publication only
- 76. [JV15823](#) – English translation of Gaiyo summary
- 77. [JV15824](#) – English translation of Gaiyo summary
- 78. [ML17279](#) (=WV17052)
- 79. [ML19340](#) (= COSMOS Study)

Zanamivir studies received from GSK in CSR format:

- 1. [167-101](#)
- 2. [JNAI-01](#)
- 3. [JNAI-04](#)
- 4. [JNAI-07](#)
- 5. [NAI30008](#)
- 6. [NAI30009](#)
- 7. [NAI30010](#)
- 8. [NAI30011](#)
- 9. [NAI30012](#)
- 10. [NAI30015](#)
- 11. [NAI30020](#)
- 12. [NAI30028](#)
- 13. [NAI30031](#)
- 14. [NAI30034](#)
- 15. [NAIA/B2008](#)
- 16. [NAIA/B2009](#)
- 17. [NAIA2005](#)
- 18. [NAIA2006](#)
- 19. [NAIA3002](#)
- 20. [NAIA3003](#)
- 21. [NAIA3004](#)
- 22. [NAIA3005](#)
- 23. [NAIB2005](#)

24. [NAIB2006](#)
25. [NAIB2007](#)
26. [NAIB3001](#)
27. [NAIB3002](#)
28. [PE-01](#)
29. [167T3-11](#)
30. [NAIA2010](#)

Appendix 3. Compliharms: events alternatively recorded as complications or harms

Roche clinical study report of oseltamivir treatment trial: "The following symptoms, signs and common sequelae associated with influenza were excluded from specific adverse event reporting if they occurred during the period of drug treatment provided their appearance was in conjunction with one or more other influenza-related symptoms. The recrudescence of single discrete signs/symptoms associated with influenza syndrome were recorded as adverse events."

[Event by body system]

Respiratory

Cough
Pneumonia
Bronchitis/tracheitis
Sinusitis
Dyspnoea/difficulty breathing

Cardiovascular

Tachycardia

Eyes, ears, nose and throat

Sore throat
Nasal obstruction
Earache
Otitis
Coryza
Conjunctivitis

Central nervous system

Headache
Fatigue

Musculoskeletal

Myalgia

Other

Fever
Rigor
Malaise/asthenia
Chills

Source: "Appendix 1. Events Associated with Influenza Syndrome". Roche Clinical Study Report No. W-144117, Protocol WV15707, Module I-43

A 1999 FDA medical review of oseltamivir: "As symptoms and common sequelae of influenza were collected as endpoint data, these symptoms, signs and common complications were specifically excluded from reporting as adverse events. The following table [above] lists events associated with influenza syndrome which were excluded from adverse event reporting. ... In addition, following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event; however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness). Comment: As the applicant [Hoffman-La Roche] stated in a written response dated 6/11/99, some sites incorrectly reported symptoms occurring prior to the cessation of the primary illness as secondary illness."

Emphasis in the original. Oseltamivir Medical Review. US FDA Center for Drug Evaluation and Research, Application No. 021087, 25 October 1999, page 15. www.accessdata.fda.gov/drugsatfda_docs/nda/99/21087_Tamiflu_medr_P1.pdf

Appendix 4. Searches for clinical study reports

Searching an unpublished and hitherto unseen data set requires constructing a reasonably accurate list of all studies of the drug in question. The obvious source of such information would be trial registries but most trials of both NIs were carried out before inception or wide acceptance of centralised registries. As single, authoritative, up-to-date and complete lists of all clinical trials conducted on humans using a given drug are rarely available in the public domain, there was no alternative to constructing our own. We decided to do so by using multiple, cross-referencing methods. We constructed a list beginning with clinical trials identified from previous review updates. To this end, we added additional trials in humans from multiple sources, including manufacturer submissions to regulators, drug product information sheets, previous published reviews, Health Technology Assessment (HTA) documents and public and manufacturers' registers (Burch 2009; Cooper 2003; Jefferson 2006; Tappenden 2009; Turner 2003), such as www.ClinicalTrials.gov and www.rocche-trials.com. Regulatory documents also aided the identification of unknown trials (see also [Searching other resources](#)). Finally, we also conducted traditional database searches ([Appendix 5](#)) and searches of grey literature to identify previously unknown trials.

To ensure the list did not include duplicate entries, we assigned each trial a Unique Trial ID. 'Author' is not a good choice of Unique Trial ID, as different authors can be present across different versions of the same trial (that is, the authors of clinical study reports can be different from publications arising from the same clinical trial). Nor are any other details connected to publications a good option for Unique Trial ID because not all studies are published. Some trials will have company-specific codes and some will have public clinical trial registry numbers, or both or neither.

The majority of trials cited in this review are manufacturer-funded (with corresponding manufacturer protocol IDs) and to simplify recognition and terminology we have used the manufacturer protocol ID as our Unique Trial ID.

A list is only helpful so long as it has sufficient details to enable us to decide whether it meets our inclusion criteria. For each Unique Trial ID, we gathered the following details.

1. Unique Trial ID
2. Other IDs
3. Phase of study
4. Sponsor
5. Short description
6. Official trial title
7. First authors (name and email)
8. Type of trial
9. Comparator
10. Outcomes assessed
11. Date of trial
12. Study period (days)
13. Population
14. Number of participants planned
15. Number of participants enrolled
16. Number of participants completing
17. Trial status (for example, completed, ongoing or early termination)
18. Publication status (a citation or understanding of why it was not published)
19. How identified (to record how the trial was discovered)
20. Notes

Once we had as complete a list of trials as possible, we contacted manufacturers and sent them our draft list, asking them to check accuracy and completeness of our list. Roche, GSK and BioCryst all did so, and in doing so we learned of hitherto unknown trials.

Occasionally, the existence of other hitherto unknown trials was detected weeks and months after we thought we had a 'complete' list. We feel this is inevitable given that trial identification often takes place in unpredictable ways, for example while reading through detailed regulatory reports. We engaged in prolonged correspondence with both manufacturers and requested a series of regulatory documents under FOI law from both the FDA and EMA.

Appendix 5. Searches of the electronic databases

Although this review focuses on the primary data sources of manufacturers, to check that there were no published randomised controlled trials (RCTs) from non-manufacturer sources, we ran electronic searches in the following databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 6) limited to year published 2010-2013 (20 search results);

- MEDLINE (January 2011 to July week 2, 2013) (56 search results) and MEDLINE (Ovid) from 1 January 2011 to July week 2, 2013 (56 search results);
- EMBASE (January 2011 to July 2013) (90 search results) and Embase.com from 1 January 2011 to July 2013 (90 search results);
- PubMed (NOT MEDLINE) no date limit (21 records). We searched PubMed to identify publisher submitted records that will never be indexed in MEDLINE and the most recently added records not yet indexed in MEDLINE.

To identify reviews that may possibly have referenced further trials we searched:

- the Database of Reviews of Effect (DARE) (2013 Issue 2 of 4 April) (four search results);
- the NHS Economic Evaluation Database (NHSEED) Issue 2 of 4 April 2013 (two search results) - both resources are part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 22 July 2013);
- the Health Economic Evaluations Database (HEED) (searched 22 July 2013) (three search results).

Previously we had searched the Cochrane Central Register of Controlled Trials (CENTRAL) (eight search results); MEDLINE (Ovid) from 1 May 2009 to 12 April 2011 (31 search results); EMBASE from 1 January 2010 to 12 April 2011 (54 search results); DARE (five search results) and NHSEED (five search results). CENTRAL, DARE and NHSEED are part of *The Cochrane Library*, www.thecochranelibrary.com (Issue 2, 2011, accessed 1 June 2011). All search results were loaded to an electronic library (EndNote).

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy for EMBASE. We imposed no publication or language restrictions.

MEDLINE (Ovid)

```

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 (influenza* or flu).tw.
5 or/1-4
6 Oseltamivir/
7 Zanamivir/
8 neuraminidase inhibitor*.tw.
9 (oseltamivir or zanamivir or tamiflu or relenza or peramivir or gs4071).tw,nm.
10 or/6-9
11 5 and 10

```

EMBASE.com

```

17 #13 AND #16
16 #14 OR #15 833616
15 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR
assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti
14 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
13 #4 AND #12
12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
11 oseltamivir:ab,ti OR zanamivir:ab,ti OR tamiflu:ab,ti OR relenza:ab,ti OR peramivir:ab,ti OR laninamivir:ab,ti OR gs4071:ab,ti
10 'sialidase inhibitor':ab,ti OR 'sialidase inhibitors':ab,ti
9 'neuraminidase inhibitor':ab,ti OR 'neuraminidase inhibitors':ab,ti
8 'sialidase inhibitor'/exp
7 'peramivir'/de
6 'zanamivir'/de
5 'oseltamivir'/de
4 #1 OR #2 OR #3
3 influenza*:ab,ti OR flu:ab,ti
2 'influenza virus a'/exp OR 'influenza virus b'/de
1 'influenza'/exp

```

Appendix 6. Searches for regulatory information

We searched the following sources:

1. the US Food and Drug Administration (FDA);
2. the European Medicines Agency (EMA) (formerly EMEA);
3. Roche;

4. the Japanese regulator (Pharmaceuticals and Medical Devices Agency (PMDA)) Summary Basis for Approval (SBA).

We conducted a search of the FDA regulatory documentation of the New Drug Applications (NDA) and supplementary New Drug Applications (sNDA) of both drugs (FDA 2011b). The FDA NDA documentation includes medical, statistical, microbiological and other reviews, product labels, reports of site inspections, meetings with manufacturers and records of the decision-making leading to registration and post-marketing requirements. We also searched 'Warning Letters' dispatched by the FDA (FDA 2011c).

To organise receipt of FDA materials, we created a Table of Contents (TOC) listing all the regulatory and pharmaceuticals documents accessible to us. The TOC's function was that of an index, searchable quick reference guide and research tool to enable us to carry out quantitative (e.g. citation density analysis) and qualitative analyses (e.g. theme summaries) of the content. We also needed a rapid aide memoir with brief summaries of the evidence contained in each regulatory document listed in the TOC. We called this aide memoir the TOCE (Table of Contents - Evidence). As the TOCE contains copious working personal notes aimed to understand the regulatory narrative, we have not reproduced it here but its content is woven into the narrative of this review.

Due to the length and format of regulatory documents, we realised in building the TOC that there was a need to formalise the search and identification methods of trials referenced in the FDA documentation. We concentrated on where each trial is mentioned in the documentation by its pharmaceutical code. So, for example, if trial WV15670 is mentioned 60 times by that code in a particular file, then the TOC will report the page numbers in which it is cited, which could be any number up to 60. The unit of search was the file, as a FDA PDF file can contain many different types of documents scanned into the same file. TOC and TOCE are among the tools we specifically constructed for the review (Appendix 1).

We wanted to validate our new methods, therefore we compared the yield of Optical Character Recognition (OCR) searching and handsearching of the PDF files of the FDA regulatory material using the same trial ID as a working example.

We also searched the material sent to us by Roche for our 2009 update.

We searched the website of the Japanese PMDA (http://www.info.pmda.go.jp/shinyaku/shinyaku_previous_index.html) for data relating to NIs approved in 1999 and 2000 and <http://www.info.pmda.go.jp/approvalSrch/PharmacySrchInit> for NIs approved since 2001. We identified 1575 pages of documents relating to the regulatory review by the PMDA and the Japanese Ministry of Health, Labor and Welfare (JMHLW) and the Japanese SBA of oseltamivir capsules for treatment (2000), and prophylaxis of oseltamivir dry syrup for children (2002) and oseltamivir capsules for prophylaxis of influenza (2004) and their re-examination results. The Japanese regulatory body introduced a system to disclose their examination results and SBA in 1999 instead of the prior system, 'full disclosure requirement system', which had been introduced in 1967. Although these documents included preclinical, methodological, clinical (pharmacological, toxicity and pharmacokinetics with metabolism) data and clinical (phase I to phase III) studies and contain more precise data than the published papers, no complete clinical study reports were publicly available. Therefore, one review author (RH) asked the JMHLW on 29 July 2010 to disclose all documents reporting the evidence base for the approval of oseltamivir for these indications. The JMHLW sent RH a letter of refusal dated 2 September 2010, with the explanation "because the disclosure of such documents might hurt the right, position or other fair benefit in the competition of the corporation concerned". We waited six months to take further action hoping that the required clinical study reports would be forthcoming from the manufacturers. When this did not happen, RH filed a suit to overturn the JMHLW decision with the Osaka (Japan) District Court on 28 February 2011. The District Court petition was rejected on 19 April 2013 and the Osaka High Court rejected it on 29 November 2013. No appeal to the Supreme Court was made because substantial clinical study reports had already disclosed from various sources.

Appendix 7. Modified CONSORT statement-based extraction template for clinical study reports

Title and drug name		
Include source documents used:		
Modified CONSORT extraction template http://www.consort-statement.org/		
Introduction CONSORT number		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses

(Continued)

Insert text:

Methods

Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons

Insert text:

Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected

Insert text:

Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered

Insert text:

Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons

Insert text:

Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines

Randomisation:

Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants and who assigned participants to interventions

Insert text:

(Continued)

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses

Insert text:

Results

Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped

Insert text:

Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

Insert text:

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Insert text:

Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory

Insert text:

Harms	19	All important harms or unintended effects in each group

(Continued)

(for specific guidance see CONSORT for harms)

Insert text:

Other information

Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

Insert text:

First author

Date of completion

Conflicts of interest

Second author check

Date of check

Conflicts of interest

Appendix 8. Stage 1 of the 2012 A159 review

Two review authors assessed each study (with studies allocated randomly to three pairs of review authors). The lists of included studies (33 for oseltamivir, 30 for zanamivir, six for peramivir) were randomly created by the program Edgar II ([Brown 2011](#)). Every study was openly allocated to each group according to its number.

We initially included six peramivir trials in the randomisation/allocation sequence but subsequently decided not to proceed further, as we were informed by the manufacturers that no clinical study reports would be available until after registration with the US Food and Drug Administration (FDA) (correspondence with Bill Sheridan, 20 August 2010). One review author (TJ) was assigned to the attempted reconstruction of clinical study reports from the FDA documents.

Two weeks before 'time lock' (see Glossary in [Appendix 1](#)) we received the first batch of clinical study reports from the EMA (formerly EMEA), containing an additional four clinical study reports (including one complete four-module clinical study report) of studies we wanted to include. This time random allocation was achieved by writing trial IDs on one set of tickets and asking an external researcher to allocate them to groups, the names of which had been written on another set of tickets.

Authors in pairs separately extracted data from the same clinical study reports of studies included in Stage 1 of the review. When we had more than one copy of the same clinical study reports from different sources (for example, clinical study reports submitted to a regulatory body and clinical study reports from a pharmaceutical company), we independently extracted data from each of the copies and then compared the results. We aimed to record and tabulate disagreements between data extracted from the same source and between different sources. We extracted data using a modified CONSORT statement-based extraction template ([Appendix 7](#)).

The modified CONSORT-based extraction template aimed to assemble a concise version of the clinical study reports, which would include all important methods as well as define and extract all relevant outcomes. The CONSORT-based extraction template includes the features that would be expected to be found in a published trial report but in far greater detail. Our reconstructions do not include introduction or discussion sections. We extracted the following for each trial.

1. Background and objectives.
2. Methods: including trial design, important changes to methods after trial commencement (such as eligibility criteria), with reasons.
3. Participants: including eligibility criteria for participants and settings and locations where the data were collected.
4. Interventions: the interventions for each group with sufficient details to allow replication, including how and when they were actually administered.
5. Outcomes: prespecified primary and secondary outcome measures, including how and when they were assessed and changes to trial outcomes after the trial commenced, with reasons.
6. Sample size: how it was determined and explanation of any interim analyses and stopping guidelines.
7. Randomisation: including sequence generation and method used to generate the random allocation sequence.
8. Blinding: who was blinded after assignment to treatment groups.
9. Statistical methods: methods used to compare groups for primary and secondary outcomes and methods for additional analyses, such as subgroup analyses and adjusted analyses.
10. Results: participant flow, numbers of participants randomly assigned, losses and exclusions after randomisation, together with reasons. Baseline demographic and clinical characteristics for each group.
11. Outcomes: primary and secondary outcome results for each group.
12. Ancillary analyses: results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.
13. Harms: all important harms or unintended effects in each group.

One review author completed the CONSORT-based extraction on the template in full ([Appendix 7](#)), with the name and date of completion and a statement of conflict of interests. A second review author checked the extraction. We extracted data, text, tables and figures directly from the relevant sections of the clinical study reports into the appropriate section of the template. We did not change the text in any way apart from clarifying abbreviations or spellings, but we highlighted some text. We used three types of text highlighting in the document.

Yellow: where text, figures or tables need to be checked with further information (for example, if an adverse event is referred to in appendices or a further clinical study reports Module).

Red: where text or comments were inserted by one or both review authors but required an additional opinion due to concerns that there is the potential for discrepancies in the clinical study reports.

Green: any text or tables added by us to the template (for example, a reconstructed table of adverse events).

Two review authors (CH, MT) independently piloted the reconstruction method on oseltamivir trial [WV15671](#) with data from Module 1 of the clinical study report from Roche and data submitted to the UK National Institute for Health and Care Excellence (NICE). We discussed the pilot reconstruction amongst the whole review team for clarification. At a face-to-face meeting we discussed the reliability and completeness of each reconstructed trial in the light of comments and other information from regulatory sources with a view to inclusion of the trial in Stage 2. We resolved all differences in opinion by consensus. We reached decisions on whether a trial moved to Stage 2 by consensus. We planned to record dissent when consensus was not possible.

Appendix 9. Applying inclusion criteria for the A159 2012 review

For the 2012 A159 review two review authors (CDM, MT) independently scanned the titles and abstracts identified from the searches of the published literature. None of the identified items were published versions of trials unknown to us. Four review authors (TJ, CH, MJ, RH) independently read all data relating to the studies on the list constructed during our search and selected studies that seemingly fulfilled our inclusion criteria. One review author (PD) compiled the assessments into a single sheet for another review author (CDM). One review author (CDM) resolved disagreements by discussion.

We assigned three categories to identified trials from our complete list:

1. definitely included;
2. definitely excluded; and
3. trials for which we needed further information.

We excluded studies definitely not meeting inclusion criteria on the basis of available information (e.g. the title described the trial as a pharmacokinetic study). Where appropriate we requested further information from the trials' sponsor, usually copies of the clinical study reports (minus participant identification) for each trial that was definitely included or for which we needed further information. We did not contact first/corresponding authors of published versions of the trials on the basis of our experience with the 2009 A047 review.

Appendix 10. Post-protocol hypotheses - methods and results

This text is carried over from the 2012 version of this review and is provided for record completeness

Methods

The hypotheses (expressed as null hypotheses) are listed below, in order of their generation (not necessarily of importance). Their rationale is explained further down the text.

Hypothesis 1. Incidence of certain harms is not associated with placebo content.

Hypothesis 2. Oseltamivir (or zanamivir) does not affect antibody production in treatment trials.

Hypothesis 3. Oseltamivir does not affect antibody production in post-exposure (or secondary prophylaxis) trials.

Hypothesis 4. The number of trial centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size).

Hypothesis 5. In oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection.

Hypothesis 1. Incidence of certain harms is not associated with placebo content.

Rationale. While reviewing the US Food and Drug Administration (FDA) critique of zanamivir, we noted the regulators' concern over the apparent drop in forced expiratory volume (FEV) following zanamivir inhalation ([FDA 1999a](#)), which appeared to be enhanced by the lactose powder excipient content of the active blister ([FDA 1999b](#)). The powder, which causes bronchospasm in susceptible individuals, was contained in both the active and the placebo blisters. This principle of using a matching placebo is of course correct but may have had the effect of increasing the incidence of bronchospasm (or asthma-related episodes) in both arms. This is clearly reported as a warning in the 1999 FDA label "Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation" ([FDA 2000b](#) p.10).

We reasoned by analogy and reviewed the medication content of the available clinical study reports of oseltamivir trials. The detailed information comparing content and physical characteristics and batch numbers is in [Table 17](#). Roche's use of the word 'matching' is not strictly correct as two principles present in the placebo capsules (dehydrocholic acid and dibasic calcium phosphate dihydrate) are not listed as being present in the active oseltamivir capsules. We could not locate the reason for such a choice in the clinical study reports but both substances may have gastrointestinal action if consumed in large enough quantities.

On this basis we formulated two **hypotheses**:

1a. There is no association between incidence of gastrointestinal harms and a placebo containing dehydrocholic acid in oseltamivir trials.

1b. There is no association between incidence of asthma-related events and a placebo containing lactose powder in zanamivir trials.

To test hypothesis 1a we assessed the oseltamivir trials for which we had clinical study reports Module 1 ([M76001](#); [WV15670](#); [WV15671](#); [WV15707](#); [WV15812](#)/[WV15872](#); [WV15730](#); [WV15819](#)/[WV15876](#)/[WV15978](#); [WV15758](#); [WV15799](#)) for gastrointestinal tract (GIT) harms including nausea, vomiting and diarrhoea as well as participants withdrawing from the studies due to adverse events. We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the χ^2 test and used τ^2 to estimate between-study variance. To investigate whether placebo containing dehydrocholic acid may be associated with gastrointestinal harms we compared adverse event rates in placebo groups from the oseltamivir trials (where placebo contained dehydrocholic acid) with adverse event rates in the placebo groups from the zanamivir trials (where placebo did not contain dehydrocholic acid). This comparison was done informally using 1) data obtained from the FDA labels of oseltamivir and zanamivir ([FDA 2000b](#); [FDA 2011a](#)) as well as 2) the trials for which we have clinical study reports. As a sensitivity analysis we assumed a similar gastrointestinal adverse event rate in the placebo groups of the oseltamivir trials as was observed in the placebo groups of the zanamivir trials and then repeated the meta-analysis (as described above). We also speculated that withdrawals in the placebo groups due to gastrointestinal adverse events were possibly related to dehydrocholic acid and removed these for the sensitivity analysis.

For hypothesis 1b we assessed asthma-related events in nine zanamivir trials for which we had clinical study reports ([NAIA3002](#); [NAIB3002](#); [NAIA2005](#); [NAIB2005](#); [NAIB2007](#); [NAIB3001](#); [NAIA3005](#); [NAI30010](#); [NAI30009](#)). We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the χ^2 test and used τ^2 to estimate between-study variance. To investigate whether placebo containing lactose powder may be associated with asthma-related events we informally compared event rates in placebo groups from the zanamivir trials (where placebo contained lactose powder) with event rates in the placebo groups from the oseltamivir trials (where placebo did not contain lactose powder). As a sensitivity analysis we assumed a similar asthma-related event rate in the placebo groups of the zanamivir trials as was observed in the placebo groups of the oseltamivir trials and then repeated the meta-analysis (as described above).

Hypothesis 2. Oseltamivir (or zanamivir) does not affect antibody production in treatment trials.

Rationale. All oseltamivir influenza treatment trials specify the primary efficacy analysis population as the influenza-infected population, not the randomised intention-to-treat (ITT) base population. The influenza-infected population (known as ITTI, or intention-to-treat-infected in clinical study reports) is determined post-randomisation based on the results of laboratory testing by culture and/or antibody rise (comparing paired sera from the same participant). The sample for culture and the first sample of sera are taken before commencement of trial product but the second or the third sera are taken after patients are treated with trial medication. It is vital that placebo and active groups of patients have the same odds of being classified as influenza-infected, otherwise any comparison between influenza-infected groups will be potentially affected by bias and will essentially be a non-randomised comparison. If trial medication affects the production of antibodies, the selection of the influenza-infected population (which is partly based on antibody production) is confounded by taking the trial medication.

Roche have stated on multiple occasions ([Smith 2006](#); [Ward 2005](#); section 3.2.4.2 Serology [WV15799](#)) that ingestion of oseltamivir does not affect antibody production and the FDA supports this, stating that "In studies of naturally acquired and experimental influenza, treatment with TAMIFLU did not impair normal humoral antibody response to infection" ([FDA 2011a](#)).

However, we noticed unequal numbers of individuals in the influenza-infected population subgroup in numerous trials. In addition, Takahashi et al reported that oseltamivir significantly suppressed respiratory mucosal secretory immunoglobulin (Ig) A responses to antigen (Ag)-specific antibody (Ab) production and also the induction of Ag-specific IgA Ab-forming cells in an animal experiment ([Takahashi 2010](#)). If taking oseltamivir affects the production of IgG antibody as well, it may affect the selection of the influenza-infected population.

We are also unsure of the implication for immunisation with influenza vaccine. According to the FDA, no influenza vaccine interaction study has been conducted with oseltamivir ([FDA 2011a](#)).

To test the hypothesis we compared: (1) the odds of participants in the ITT population subsequently classified as influenza-infected; and (2) the odds of participants in the ITT population with a four-fold or more rise of antibody between the placebo and active arms of the trials. If ingestion of oseltamivir does not affect antibody production then we expect the odds of being classified as influenza-infected to be the same for the placebo and active arms. Therefore, we tested a null hypothesis that the odds of having a four-fold or more rise of antibody was the same for the placebo and active arms. We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the Chi² test and used Tau² to estimate between-study variance. The trials included in this analysis were the 10 oseltamivir treatment trials analysed by [Kaiser 2003](#) plus [WV15758](#) for oseltamivir and [NAIA3002](#), [NAIB3002](#), [NAIA2005](#), [NAIB2005](#), [NAIB2007](#), [NAIB3001](#), [NAI30009](#) for zanamivir. These are all the treatment trials for which we have clinical study reports Module 1. In an additional analysis we also assessed the oseltamivir trial conducted in China by Shanghai Roche Pharmaceutical Ltd for which we have a partial clinical study report ([ML16369](#)).

Hypothesis 3. Oseltamivir does not affect antibody production in post-exposure (or secondary prophylaxis) trials.

Rationale. According to the clinical study report of [WV15799](#), the trial programme assessing the effects of oseltamivir in post-exposure prophylaxis (PEP) consisted of two trials: [WV15799](#) and [WV16139](#). The Module 1s of both trials together with copious FDA notes on trial [WV15799](#) were available to us at 'time lock'. However the PEP trial [WV16139](#) was not standard care or placebo-controlled and so we excluded it from the review.

[WV15799](#) was a double-blind, cluster-randomised trial in which contact clusters of index cases were randomised to oseltamivir 75 mg a day or placebo for seven days. The trial formed an integral part of the "pivotal" trials package for the supplementary application and review for prophylaxis use of oseltamivir 75 mg in people aged more than 13 years of age, submitted to the FDA on 22 May 2000, approved on 20 November 2000 ([FDA 2000c](#)). In the clinical study report Module 1 the manufacturer claimed that the trial provided evidence of the drug's capacity to prevent influenza in contacts by interrupting its transmission from index cases. Since all index cases were left untreated except for a paracetamol rescue pack, it is hard to see how such a claim can be made. The interruption of transmission claim has two components: reduction of viral spread from index cases (measured by nasal shedding of influenza viruses) and prevention of onset of influenza in contacts. This latter claim was based on the definition of (prevented) influenza cases: a mixture of symptoms signs and 'laboratory confirmation' (i.e. viral culture from the upper airways and/or at least a four-fold rise in antibody titres measured between baseline and two to three weeks later). The results of the trial later formed the basis for claims of the drug's effectiveness in interrupting transmission from person to person ([WHO 2007](#)) and allow time before the arrival of vaccines in the event of a pandemic. The interruption of transmission claim provided a powerful rationale for stockpiling oseltamivir (see for example vol 8, p.61-62 [NICE 2000](#): "Ro 64-0796 successfully interrupts the transmission of influenza within households ... and suggests that Ro 64-0796 [oseltamivir] would control the spread of influenza in other closed communities associated with high risk of transmission, such as nursing homes" ... "Ro 64-0796 also effectively interrupted virus transmission within households.")

The interruption of transmission indication was accepted by agencies such as the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC), but the US FDA refused to register and allow publicity based on any further indication beyond treatment and prophylactic effects on symptoms ([FDA 2000f](#)). Review of the evidence from the study protocol and Module 1 together with the FDA criticism explains the rationale for the FDA not supporting the manufacturers' claims. The design of the trial did not allow for comparison of the effects of treating index cases with oseltamivir versus placebo (as all index cases were not medicated) and a repeat viral culture was not performed for all participants. Viral culture was performed at baseline for all participants and thereafter only in participants with influenza-like illness symptoms (see Schedule of assessment for the contact case, [WV15799](#), and the FDA Medical Officer report ([FDA 1999c](#))). Any participants presenting at follow-up with symptoms of influenza had throat and nasal swabs taken in order to confirm the presence or absence of influenza infection ([FDA 2000c](#)), thereby missing out on potential asymptomatic infected people. However, a recent review of transmission studies has found no convincing evidence of spread from pre-symptomatic or asymptomatic subjects ([Patrozou 2009](#)), which might explain the FDA's caution in sanctioning any such claim for oseltamivir.

Our review of the clinical study report's Module 1 identified further problems with the conduct and reporting of the trial and discrepancies both within the clinical study reports and between the study and its protocol. In the protocol (version H) there is no mention of viral shedding measurement. This appears to be a post-protocol addition, which would explain the unsystematic nature of the viral excretion measurement remarked on by the FDA (i.e. taken from symptomatic contacts only). The primary population of analysis is the so called ITTIINAB population (contacts of ITT influenza-infected index cases who had negative virology at baseline). Although defined in the

protocol, the selection and presentation of results for the intention-to-treat contacts of the influenza-infected index case not infected at baseline (ITTIINAB) population has the effect of excluding 57% of the placebo (200/456) and 59% of the oseltamivir (205/497) participants. The effect of selection on the clustering was not formally tested in a sensitivity analysis. Nor is the potential weakness of such a choice discussed in the [WV15799](#) clinical study report. We carried out an analysis using Fisher's exact test, which showed that there was no statistical evidence that the placebo and oseltamivir groups' cluster sizes were distributed differently based on households with an infected index case ($P = 0.56$) (Table 2). By analysing the population by influenza status of the index case, instead of unit of randomisations (all index cases), the beneficial effects of the cluster-randomisations are potentially lost, introducing unknown biases into the analysis. In addition, the generalisability of the conclusions may not be easily applied to clinical practice where testing of suspected influenza cases is often not practical. Cross-checking the definition of ITTIINAB with that reported in the protocol of the other PEP trial, [WV16193](#) (excluded from this review) yields a different definition (PDF page 589) "The primary outcome in this study ([WV15799](#)) was the incidence of influenza occurring among contacts of influenza-infected index cases (the intent-to-treat-index-infected population)".

Throughout the clinical study report of trial [WV15799](#) there are many other apparently contradictory statements on important aspects of the trial, for example, on how many viral swabs and paired sera tests were carried out. The text at page 50 of the Module 1 reports that "For 21 of the 26 contacts with laboratory-confirmed clinical influenza in the ITTIINAB population the diagnosis was confirmed by culture" but Table 19 shows the 26 contacts as shedding virus at days two to eight. The same table reports that 178 placebo contacts and 201 oseltamivir contacts were negative for virology (which suggests that they were tested) at days two and eight. However, viral testing only took place at baseline and thereafter only in symptomatic participants. The number of contacts in which influenza was diagnosed only by serology is unclear but it appears to be five (26 minus 21). These inconsistencies highlight one of the fundamental conceptual problems in understanding the whole oseltamivir prophylaxis trial programme: the mode of action of the drug. Our interpretation of the text suggests that oseltamivir does not prevent infection and does not affect influenza antibody response. As stated above, the claim that oseltamivir does not affect antibody responses has been made by the manufacturers. However, an antibody response is part of the definition of influenza. We are unsure how it is possible that oseltamivir could prevent influenza by stopping symptoms appearing and antibodies rising while at the same time leaving antibody production unaffected.

It is for this reason that we decided to test whether administration of oseltamivir for PEP affected the production of antibodies to influenza viruses. The distribution of change in antibodies from baseline to follow-up was compared between the arms of the trials for contacts of the index cases. Analysis was performed using Wilcoxon two-sample test separately for each type of antibody in each trial. An additional analysis of proportion of contacts having a four-fold or greater rise in influenza-specific antibody titre in antibodies was compared between groups using the χ^2 test. Antibody data were not available for index cases, who were left untreated. In [WV15799](#), antibody testing may have been undertaken at day 1, day 8 and at day 21 ± 4 days for all contacts. Day 8 blood samples for influenza antibody analysis were stored to measure influenza antibody levels only in those contacts who did not attend the follow-up visit (day 17 to 25). Analysis was based on data from the ITTIINAB population at pages 59-60 and Appendix 60 of the clinical study report's Module 1.

Hypothesis 4. The number of trial centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size) and **Hypothesis 5.** In oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size).

Rationale. The proportion of ITT population in the treatment trials of NIs that are subsequently diagnosed as infected with influenza is higher (~ 50% to 80%) than is usually seen in the course of the winter season in routine clinical care, although high peaks can occur for a very limited period. We know that in some treatment trials, such as [WV15670](#) and [WV15671](#), centres were activated to "recruit subjects during an influenza outbreak in the locality, detected using standardised surveillance techniques." We postulated that unreported procedures may also have been used in the trials to obtain these high proportions of influenza to ILI cases. Two procedures that may have been used are: 1) use of rapid influenza tests to screen out patients based on negative results; 2) dropping of centres that recruited low proportions of infected patients. The use of rapid testing of patients prior to randomisation has been reported in at least one of the zanamivir treatment trials ([NAIB3001](#)), in oseltamivir trial [WV15670](#) as a means of excluding infection with H5N1 in the Hong Kong Centre, as a pilot surveillance in suburban London during the 1998 to 1999 winter ([NICE 2000](#) vol.1) and in most oseltamivir paediatric trials to exclude respiratory syncytial virus (RSV) infection. In addition, the schedule of testing varies by trial for the oseltamivir trials with swabbing performed either before randomisation or after randomisation. In at least one oseltamivir treatment trial ([WV15730](#)) it was reported that no viral culture was performed at centres from South America ([FDA 1999c](#)). As a result of these observations we reformulated **Hypothesis 4** as follows: the number of centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was primary outcome effect size) in oseltamivir treatment trials and **Hypothesis 5** as in oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection.

To test **hypothesis 4**, we used Spearman's rank method to estimate the correlation between average number of patients recruited per centre and the proportion of placebo patients subsequently diagnosed with influenza infection. The placebo patients were used for the proportion of patients subsequently diagnosed with influenza infection because, as we show later in the review, there is evidence that oseltamivir interferes with antibody production and antibody response was used to diagnose influenza infection. We did not analyse the

number of centres dropped from studies because information on this variable was not available in Module 1s of the clinical study reports for the included trials (information on patients recruited to each centre is reported in Module 2 which we do not currently have access to).

Hypothesis 5 was generated to attempt to explain the seemingly high proportion of influenza-infected influenza-like illness cases in treatment trials. However, we did not formally test this hypothesis as there was only one clinical study report reporting randomisation first then swabbing second ([WV15819/WV15876/WV15978](#)) (see also [Appendix 10](#)).

Results

The results of our post-protocol analyses are also reported in Figure and/or Table format.

Hypothesis 1a tested in a sensitivity analysis whether the incidence of gastrointestinal harms may be associated with exposure of participants to a placebo containing dehydrocholic acid. The data obtained from the oseltamivir trials clinical study reports is shown in Table 15.

Overall, the crude adverse event incidence in the placebo groups of the oseltamivir trials was 5.5% for nausea, 3.6% for vomiting and 7.0% for diarrhoea. This compares with crude incidence in the nine zanamivir treatment trials' placebo groups of 4.1% for nausea and vomiting (reported as a combined outcome in the clinical study reports) and 2.8% for diarrhoea. Two studies ([WV15670](#); [WV15671](#)) compared three treatment groups: oseltamivir 150 mg bid, oseltamivir 75 mg bid and placebo. To maintain the blinding in these trials, each participant took two pills twice daily. Therefore the participants in the oseltamivir 75 mg bid group took one placebo tablet twice daily. We note that in trial [WV15671](#) there was evidence of a dose-response effect of placebo on incidence of diarrhoea: oseltamivir 150 mg bid (5.9%), oseltamivir 75 mg bid (8.7%) and placebo (11.8%) ($P = 0.036$). However, there was no evidence found of a similar trend in trial [WV15670](#) ($P = 0.88$). We were unable to carry out a similar analysis for paediatric treatment trial [WV15758](#) because a detailed content of the placebo preparations is not available (see [Table 17](#)).

Random-effects meta-analysis of the data in Table 15 provided the following results.

Nausea: increased odds of adverse events due to oseltamivir (OR 1.62, 95% CI 1.17 to 2.26, $P = 0.004$).

Vomiting: increased odds of adverse events due to oseltamivir (OR 2.32, 95% CI 1.62 to 3.31, $P < 0.001$).

Diarrhoea: decreased odds of adverse events due to oseltamivir (OR 0.72, 95% CI 0.53 to 0.97, $P = 0.03$).

Withdrawal from treatment due to adverse events: no evidence of a difference between treatment groups (OR 1.08, 95% CI 0.66 to 1.76, $P = 0.75$).

We carried out a sensitivity analysis by assuming placebo rates of gastrointestinal adverse events in oseltamivir trials based on those observed in placebo groups of similar zanamivir trials. Overall rates of nausea, vomiting and diarrhoea in placebo groups of zanamivir treatment trials for adults and adolescents were 3%, 2% and 4% compared to oseltamivir treatment trials for adults and adolescents where rates were 6%, 3% and 10% respectively based on FDA-reported data ([FDA 2000b](#); [FDA 2011a](#)). Conversely, other common adverse events such as headaches, cough and dizziness had similar incidences of 2% to 3% in the placebo groups of zanamivir and oseltamivir treatment trials ([FDA 2000b](#); [FDA 2011a](#)). In the treatment trials of children the rates of nausea, vomiting and diarrhoea in placebo groups of zanamivir treatment trials were 2%, 3% and 2% compared to oseltamivir treatment trials of children where rates were 4%, 9% and 11% respectively. Our conservative estimate is that the oseltamivir placebo increased rates of nausea two-fold (risk ratio (RR) = 2), vomiting (RR 1.5) and diarrhoea (RR 2.5) compared to the placebo arms in zanamivir trials. Based on the adult and adolescent trials we could conservatively speculate that the substances in the oseltamivir trials placebo increase nausea, vomiting and diarrhoea by 100% (6%/3%), 50% (3%/2%) and 150% (10%/4%) respectively. This could also be considered a conservative assumption because it is plausible that the lactose powder used as the placebo in the zanamivir trials also induced gastrointestinal symptoms, especially in patients that were lactose intolerant. Adjusting the actual rates of these events in the oseltamivir trials placebo groups to be consistent with the zanamivir trials placebo group rates (as reported by the FDA ([FDA 2000b](#); [FDA 2011a](#))) and re-running the random-effects meta-analysis we obtained the following results.

Nausea: increased odds of adverse events due to oseltamivir (OR 3.33, 95% CI 2.44 to 4.54, $P < 0.001$; test for heterogeneity $P = 0.33$).

Vomiting: increased odds of adverse events due to oseltamivir (OR 3.46, 95% CI 2.51 to 4.78, $P < 0.001$; test for heterogeneity $P = 0.37$).

Diarrhoea: increased odds of adverse events due to oseltamivir (OR 1.86, 95% CI 1.39 to 2.50, $P < 0.001$; test for heterogeneity $P = 0.50$).

The estimated effect sizes for nausea and vomiting have increased based on the sensitivity analysis. The effect on diarrhoea has reversed, indicating oseltamivir is possibly associated with increased odds of this adverse event. The results of our analysis support an alternative interpretation to that of the FDA.

Finally, we carried out a sensitivity analysis of withdrawal from treatment due to adverse events by assuming no withdrawals due to gastrointestinal events in the placebo group. In total there were nine patients in the oseltamivir trials' placebo groups that withdrew due to gastrointestinal events. When these withdrawals are not included the following result is obtained based on random-effects meta-analysis:

Withdrawal from treatment due to adverse events: no evidence of a difference between treatment groups (OR 1.48, 95% CI 0.87 to 2.51, $P = 0.15$; test for heterogeneity $P = 0.40$).

We conclude that participants in placebo arms of oseltamivir treatment trials experience a higher rate of gastrointestinal adverse events compared to their zanamivir counterparts. As the zanamivir trials' inclusion criteria were similar to the oseltamivir trials (fever and two additional symptoms of influenza-like illness (ILI)) this observation cannot plausibly be explained by an incremental role of influenza infection in the genesis of such heterogeneity. It is possible that the difference in reported gastrointestinal adverse events in the placebo groups of zanamivir and oseltamivir trials is due to differences in the collection of these events. However, other common adverse events such as headaches, cough and dizziness had very similar rates in the placebo groups of zanamivir and oseltamivir trials. Despite the results of this sensitivity analysis it is impossible without a clear statement of dosage and rationale of use to assess the role of dehydrocholic acid and possibly calcium phosphate in the causation of such a high incidence of gastrointestinal adverse events.

For **hypothesis 1b** the data obtained from the zanamivir treatment trials clinical study reports are shown in Table 16.

Over all the nine zanamivir trials the incidence of asthma (including asthma exacerbation) in the placebo groups was 2.1% compared to 0.9% in the placebo groups of the oseltamivir trials. Random-effects meta-analysis of the data in Table 16 provided the following results for the combined outcome of any asthma event:

Asthma: decreased odds of adverse events due to zanamivir (OR 0.54, 95% CI 0.34 to 0.86, $P = 0.01$).

We carried out a sensitivity analysis by assuming placebo rates of asthma-related adverse events in zanamivir trials based on those observed in similar oseltamivir trials. If we assume a rate of asthma events in the placebo groups of the nine zanamivir trials similar to that observed in the oseltamivir trials we obtain the following result based on random-effects meta-analysis:

Asthma: no evidence of a difference between treatment groups (OR 1.27, 95% CI 0.71 to 2.26, $P = 0.42$; test for heterogeneity $P = 0.68$).

We conclude that zanamivir trial placebo recipients appear to have a higher incidence of asthma-related events than their oseltamivir counterparts. Again, as the inclusion criteria were similar for both trial programmes this finding is not likely to be due to severity of influenza infections but associated with exposure to lactose powder and possibly to the active principle. This is a point remarked on by the FDA.

For **hypothesis 2** (oseltamivir (or zanamivir) does not affect antibody production in treatment trials) the relevant trials showed strong and consistent evidence that patients randomised to active treatment had reduced odds of being classified as influenza-infected (OR 0.83, 95% CI 0.73 to 0.94, $P = 0.003$) with no evidence of heterogeneity (heterogeneity Chi^2 test = 2.80 (df = 7) $P = 0.90$; estimate of between-study variance $\text{Tau}^2 = 0.00$) (see Table 17). There was also strong evidence that patients randomised to active treatment had reduced odds of having four-fold or higher rise in antibody titres (OR 0.79, 95% CI 0.70 to 0.90, $P < 0.001$) with no evidence of heterogeneity (heterogeneity Chi^2 test = 4.61 (df = 7) $P = 0.71$; estimate of between-study variance $\text{Tau}^2 = 0.00$) (see Table 17).

In contrast, the zanamivir trials showed no evidence that patients randomised to active treatment had reduced odds of being classified as influenza-infected (OR 1.05, 95% CI 0.90 to 1.24, $P = 0.52$) with no evidence of heterogeneity (heterogeneity Chi^2 test = 3.03 (df = 6) $P = 0.81$; estimate of between-study variance $\text{Tau}^2 = 0.00$) (see Table 18).

These results have important implications for the oseltamivir treatment trials programme and for all ongoing trials. All influenza-infected populations are selected post-randomisation and post-trial termination on the basis of laboratory findings (all ITT participants being symptomatic at entry, with aetiology unknown). However, as oseltamivir appears to affect antibody production (or perhaps testing, or both), there may be some participants in the oseltamivir group who were infected with influenza but not diagnosed by the antibody rise and were therefore not counted in the influenza-infected population. These may have subsequently been excluded from the efficacy analysis. It is also possible that the strength of the antibody production limit to qualify for an influenza infection-induced antibody rise (four-fold and above from baseline) had the effect of selecting the 'stronger' responders into the influenza-infected subgroup of the oseltamivir arm. This would mean that the best antibody producers were selected and this may have led to inflated treatment estimates of efficacy in influenza-infected populations.

To investigate this possibility we calculated the correlation between the odds of being classified as infected in the oseltamivir group compared to the placebo group and the size of the primary treatment effect (time to alleviation of symptoms in the ITTI population). In treatment trials all participants are recruited on the basis of symptoms of influenza-like illness. According to the mechanism of action proposed by the manufacturer, infected participants given oseltamivir up to 48 hours from symptom onset should have an antibody response which, given the effects of randomisation, should be similar to that of placebo recipients. Non-responders or weak responders should be spread evenly across the trial arms. All treatment trials of oseltamivir showing evidence of a treatment effect on the primary outcome of the study were included in the analysis. This included two trials for which we did not have clinical full study reports ([ML16369](#); [JV15823](#)). We included these trials to increase variation in the two variables used for the analysis. In addition, two trials were excluded: [WV15707](#) which had a total ITTI sample size of 12 participants; and [WV15812](#)/[WV15872](#), which was a treatment trial in chronically ill adults that showed no evidence of a treatment effect. Results showed strong evidence of a correlation (Spearman rank correlation = -0.83, $P = 0.01$) (Table 19). The correlation was highly negative, indicating that lower odds of being classified as ITTI in the oseltamivir group compared to the placebo group is associated with larger treatment effects for the primary outcome of the studies. In contrast, there was no evidence of a correlation between the odds of being classified as infected in the oseltamivir group compared to the placebo group (Table 19) and the size of the treatment effect in the ITT population (Spearman rank correlation = -0.23, $P = 0.66$). A limitation of this analysis is that data for the ITT population for two trials were not available ([WV15730](#); [JV15823](#)) (Table 19).

Thus, all influenza-infected comparisons are potentially confounded by the action of the drug (oseltamivir but probably not zanamivir) and are essentially non-randomised comparisons. Any analyses should be based on ITT populations in oseltamivir treatment trials. Analyses and data considered for inclusion in systematic reviews should be based on the ITT (or safety) populations only.

Our analysis of **Hypothesis 3** shows that the odds of having a four-fold rise in antibodies is 0.33 (95% CI 0.16 to 0.67) for the oseltamivir group compared to placebo (hence a much bigger effect compared to the treatment trials). Due to insufficient information provided in the clinical study report we were unable to take account of the clustering in this analysis, hence the confidence intervals are possibly underestimated; however an analysis that takes into account clustering is unlikely to change the conclusions. These results show that oseltamivir prophylaxis is associated with lower odds of a four-fold rise in antibodies and this appears to be due to a difference in the distribution of antibody rise in H1A1H3 antibodies but not H1A1H1 or H1B antibodies (see [Table 16](#), [Table 21](#), [Table 22](#) and [Table 23](#)). In summary no conclusions can be drawn from the available evidence on the effects of the drug on viral transmission. The mode of action in prophylaxis appears mainly to be ascribed to symptom suppression or control. There is uncertainty around other possible effects of the drug especially given its interaction with the production of antibodies.

We rejected **Hypothesis 4** and are currently unable to test **Hypothesis 5**

We rejected **Hypothesis 4** as there was no evidence of correlation between average recruited subjects per centre and the proportion of placebo patients subsequently diagnosed with influenza infection (Spearman correlation = 0.26; $P = 0.53$). [Table 24](#) shows that the average recruited participants per centre ranged from 2 to 11 which appears very low for international, multicentre trials. Two studies failed to reach their recruitment target ([WV15707](#) and [WV15730](#)) and two clinical study reports were made up of multiple trials due to the original trial's poor recruitment ([WV15819/WV15876/WV15978](#) and [WV15812/WV15872](#)) ([Table 24](#)). In addition the proportion of placebo patients subsequently diagnosed with influenza infection ranged from 63% to 75%, implying little between-trial variation.

We are currently unable to test **Hypothesis 5** as only one oseltamivir clinical study report (of three trials) reported randomisation first then swabbing second ([WV15819/WV15876/WV15978](#)). In this study the proportion of placebo patients that were confirmed as influenza-infected was 68.1%. This compares with the other seven clinical study reports where swabbing was carried out first and randomisation second and the proportion of placebo patients that were confirmed as influenza-infected ranged from 63.2% to 74.9% with mean 68.1%. Hence it seems that swabbing after randomisation made no difference in the treatment trial programme where this practice is reported. However, with only one clinical treatment study report randomising prior to swabbing available to us, the power to detect a difference in the proportion of placebo patients subsequently diagnosed with influenza infection is low. We hope to be able to retest this hypothesis as more data become available.

Appendix 11. Example of contents of a Clinical Study Report (from page 1 of WV15670 report)

Final study report modules

This report consists of five modules. Those not supplied in this submission were obtainable from the sponsor on request.

MODULE I: CORE REPORT AND STUDY PUBLICATIONS

Introduction
Rationale
Objectives
Methodology
Efficacy results
Safety results
Discussion/conclusions
Appendices

MODULE II: PRESTUDY DOCUMENTS AND STUDY METHODOLOGY

Protocol and amendment history
Blank CRF
Subject information sheet
Glossary of original and preferred terms
Randomisation list
Reporting analysis plan (RAP)
Certificates of analysis
List of investigators
List of responsible ethics committees

MODULE III: INDIVIDUAL SUBJECT LISTINGS OF DEMOGRAPHIC AND EFFICACY DATA

Demographic data listings
Previous and concomitant diseases
Previous and concomitant medications

Efficacy listings

MODULE IV: INDIVIDUAL SUBJECT LISTINGS OF SAFETY DATA

Laboratory parameters

Vital signs data

MODULE V: STATISTICAL REPORT

FEEDBACK

From Michael Power, Sowerby Centre for Health Informatics at Newcastle, 15 December 2010

Summary

From: Michael Power <michael.power@schin.co.uk>

Date: 15 December 2010 18:51

Subject: Neuraminidase inhibitors for influenza - HTA project

To: "cdelmar@bond.edu.au" <cdelmar@bond.edu.au>, "jefferson.tom@gmail.com" <jefferson.tom@gmail.com>, Carl Heneghan <carl.heneghan@dphpc.ox.ac.uk>

Hi

I picked up Carl's Twitter request for comments on your draft protocol "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data". So, here are my two comments on the content.

The title confused me: I expected it to be a review of unpublished trials to complement your review of published trials. It would be longer but clearer if you could call it "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports for published and unpublished trials".

The section "How the intervention might work" could be reorganized along the lines of:

0) Metabolism: oseltamivir phosphate (OP), Tamiflu, is the pro-drug of oseltamivir carboxylate (OC), the effective form. OP dissociates in the gastrointestinal tract to form oseltamivir (OT) which is absorbed and metabolised into OC by hepatic carboxylesterase (h-CE).

1) Reducing the ability of the virus to penetrate the mucus in the very early stage of infection (Bhatia 2007; Matrosovich 2004; Moscona 2005; Ohuchi 2006).

2) Inhibiting neuraminidase, which enables influenza viruses to exit host cells (Liu 1995; Moscona 2005).

3) Central depression by OT (Hama 2008) may cause hypothermia (Ono 2008).

4) Inhibition by NIs of human sialidase may cause abnormal behaviour (Li 2007).

You have obviously put a huge amount of work and expertise into developing the protocol, and have an even bigger task ahead to complete the review. Congratulations for taking this on.

Best wishes

Michael

Reply

Thanks for the constructive comments.

1. We have re-titled the Protocol to address this concern (and that of feedback from GSK, see below);
2. We have re-examined the "How the intervention might work" section but made only small adjustments in the interest of keeping this section short;
3. We are not sure what problems you might have had printing the pdf file, and hope they are resolved with this new version.

Contributors

Chris Del Mar

From Juan C. Vergara, Intensive Care, Hospital Cruces, 48901 Barakaldo, Spain, 24 February 2011

Summary

From: JUAN CARLOS VERGARA SERRANO <JUANCARLOS.VERGARASERRANO@osakidetza.net>

Date: 24 February 2011 12:48

Subject: oseltamivir

To: jefferson.tom@gmail.com

I've read your Intervention Protocol: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data. And may be you can be interested in this letter I wrote to de BMJ: <http://www.bmj.com/content/340/bmj.c789.extract/reply>

1. Early use of oseltamivir does not reduce swine flu mortality, Juan C. Vergara, MD. Intensive Care Unit, Hospital Cruces. 48901 Barakaldo. Spain

As you say, in July the National Pandemic Flu Service started providing oseltamivir to anybody who telephoned with a plausible set of symptoms. From 23rd July to 1st December, the National Pandemic Flu Service (NPFS) in the UK, has provided more than one million courses of antiviral medication. By that time the Spanish Health Secretary General, José Martínez Olmos, at the Congress of Deputies, announced that only 6.000 patients (most of them hospitalised) had received oseltamivir in Spain. At the end of January there have been 411 deaths reported due to pandemic (H1N1) 2009 in the UK, and about 300 in Spain. That means 6.7 and 6.5 deaths per million, respectively. These data create serious doubts about the real utility of early use of oseltamivir in preventing deaths from Influenza A H1N1. <http://www.nhsdirect.nhs.uk/article.aspx?name=SbSwineflu>
http://www.congreso.es/public_oficiales/L9/CONG/DS/CO/CO_411.PDF

Competing interests: None declared

Yours sincerely;
J. C. Vergara

Reply

Thank you for your interest.

Contributors

Chris Del Mar

From Dr Helen Steel, GSK, UK, 30 March 2011

Summary

GSK comments on Cochrane Collaboration protocol: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data

General:

- The term '**unpublished data**' is used extensively in the protocol. However, it does not appear to be clearly defined either in the protocol or in Jefferson's comment in the 15 Jan 2011 edition of the BMJ. Additionally, the term '**unpublished data**' is misleading. It appears the Cochrane Group use this term interchangeably with Clinical Study Reports, regardless of whether a primary manuscript is available for a given study. We suggest this is clarified or preferably replaced, especially since the term appears extensively in the protocol including the title. Readers are likely to use the terms 'unpublished data' and 'unpublished trials' (trials for which no primary publication appears in the scientific press) interchangeably. A suggested replacement is 'Clinical Study Reports' since this term is not easily misinterpreted and is clearly defined in Jefferson's BMJ comment.
- The 'scope of clinical trial data' are defined in Jefferson's BMJ 15 Jan 2011 comment, as mentioned above (i.e. definitions for clinical study reports, raw data, unpublished trial, published trial, regulatory data). It would seem important that these and any other definitions introduced in the protocol are included in the protocol.

Description of Intervention

- This section incorrectly describes Relenza as 'nebulized zanamivir'. Relenza is formulated in Rotadisks containing foil blisters with a powder mixture of zanamivir and lactose. Relenza is administered by oral inhalation using a breath-activated device called the Diskhaler. Earlier clinical studies explored several methods of administration, including nebulized and intranasal routes but marketing approval in nearly all countries is currently available only for oral inhalation via Rotadisk/Diskhaler.

Types of Studies

- To meet the objective of providing a comprehensive review of neuraminidase inhibitors in preventing and treating influenza, it would seem appropriate that clinical trials from all sources (including sponsors other than industry) be included in this meta-analysis. Please clarify if this is your intent.

Outcome Measures

More details should be provided on the outcome measures section in the final protocol.

- For example, broad outcome measures are stated in the protocol but specific endpoints are not provided. The primary and secondary endpoints of the meta-analysis should be clearly defined in the final protocol.
 - e.g.1. A stated primary outcome in the treatment studies is 'symptom relief'. Does this refer to 'the time to alleviation of symptoms' or 'reduction in symptom score' or another endpoint? Time to alleviation of clinically significant symptoms was the primary endpoint used in the majority of GSK treatment studies.
 - e.g.2. Another stated primary outcome is 'Harms'. Please provide the specific endpoints. Will this refer to 'incidence of most common AEs' or 'incidence of common SAEs', 'incidence of complications' or another endpoint? It is not clear if 'harms' are the same as 'compliharms'. It is not clear what specific events will comprise compliharms.
- Prophylaxis studies: Several types of prophylaxis studies were conducted by GSK: household prophylaxis (post-exposure prophylaxis), community prophylaxis and outbreak control in nursing homes, and as such the designs and/or endpoints are different. It is possible to measure 'prevention of onset of influenza in contacts' in these studies but not 'reduction in viral spread from index cases' in the majority of prophylaxis studies.
- Hospitalisations: As studies were generally conducted in the setting of acute uncomplicated influenza, limited hospitalisation data were collected, and are available only for some studies.
- Extracting compliharms: There is a statement that 'AEs are reported for all participants while complications are only reported for infected subjects'. This statement is not accurate for GSK trials. AEs are reported for all study participants. However, AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness. Without knowing the specific safety endpoints, it is unclear whether this will affect the outcome of some of the harms analyses.

Data collection and analysis:

- The protocol indicates that clinical study reports will be requested (minus participant identification). In fact many documents for each study will need to be redacted not just to remove participant identification but any personally identifiable information including author and investigator identification.
- Missing Data. The protocol states "*At the participant level (i.e. within a trial) we will not make any assumptions about missing data.*" This is not possible, because an analysis of data that is collected in a trial can only be done in the context of assumptions about potential mechanisms that led to data being missing (e.g., missing completely at random, or missing at random).
- Meta-analysis Method. Little detail is given in the protocol. The protocol states that "*Whether or not heterogeneity is detected, we will perform a random effects meta-analysis. Random-effects methods will be used to compare the dichotomised outcomes (RR and absolute risk reduction (ARR) for efficacy and safety).*" There are several different Random Effects methods available (Bayesian or frequentist, DerSimonian & Laird or Maximum-likelihood or REML), and different approaches to handling rare events (various "corrections" to include trials with zero counts). Furthermore, would random-effects methods also used to compare the continuous outcomes?
- Fixed-effects Model. The protocol also states that fixed-effects models will be used in a sensitivity analysis. No details are given with regard to which fixed-effects models will be used. There are several fixed-effects models available including Inverse Variance, Mantel-Haenszel, and Peto's method. The appropriate method used should also depend on the outcome measures (dichotomous vs. continuous; relative vs. absolute). The approach and choice of models for sparse data and rare events should be provided. Furthermore, various methods in the framework of fixed-effects model may be explored to evaluate the robustness of the results.
- Hazard Ratio. The protocol states "*We will convert medians of treatment groups into (log) hazard ratios (estimating the variance of these) to enable meta-analysis of time to event outcomes.*" Although hazard ratio (HR) is a standard analysis and widely recommended approach for time-to-event data in clinical trials, the HR analysis may not be suitable for the Relenza studies with relatively short follow-up time because the assumption of proportional hazards required for the proportional hazards model may not hold. GSK did not follow this approach for the original analysis due to the concern stated above. Further the clinical and regulatory interest centred on differences in the time to alleviation not in the relative hazard between treatments. The above issues would be best addressed by using subject level rather than summary data, which GSK have offered to provide to the Cochrane Group.
- Analysis Populations. The protocol does not specify which populations will be used for the various analyses, for example, intent-to-treat or influenza-positive or other. We believe that influenza positive population is appropriate, especially for the efficacy analysis using time to alleviation of influenza symptom as a primary endpoint consistent with the prescribing information for Relenza.
- Study Duration. No details are given in the protocol with regard to how studies with different follow-up times will be handled.
- Trials with no Events. No details are given in the protocol with regard to how to deal with trials in which there are no events (such as death). By excluding studies with no events will make the event appear more common than it actually is. There are various techniques: Bayesian approach, continuity correction, combining similar trials to avoid having any components of the analysis that have no events.
- Sensitivity Analyses. Sensitivity analyses using different outcome measures, statistical models and/or continuity correction factors to assess the robustness of the results are strongly encouraged.

Reply

General:

- 'unpublished data'. We agree that this term is confusing, and are attracted to the proposal of using 'clinical study reports' instead.
- We have attempted to ensure all terms are clear.

Description of intervention

- Description of zanamivir (Relenza): we have corrected 'nebulized zanamivir' to 'powder inhalation'.

Types of studies

- Yes, we intend to comprehensively review clinical trials from all sources (including sponsors other than industry). This intent is clear from the subsection '**Electronic searching**' under the '**Search methods for identification of studies**' section.

Outcome measures

- Our specified outcomes are those of interest to patients, and their clinicians and policy-makers. They are therefore likely to be broader than the more specific endpoints selected by trialists. The purpose of Cochrane Reviews are usually to set clinically relevant review questions, and search the literature (or other sources) for answers to them. Sometimes answers to some questions are not available, and this is also documented. Where possible we report outcomes as pre-specified in the trial protocols, or as pre-specified in the review protocol, or otherwise reported as a post-hoc analysis.
 - e.g. 1. 'symptom relief' may refer to 'the time to alleviation of symptoms' or 'reduction in symptom score', or any other endpoint (including 'area under the curve of symptom score and time').
 - e.g. 2. 'Harms' include common adverse events (AEs) as well as serious AEs. We agree about the confusion of harms and complications, and have tried to capture the totality of these with the neologism 'compliharms' to avoid classification errors between their different labellings.
- Prophylaxis studies: We understand that it is possible to measure 'prevention of onset of influenza in contacts' in some GSK studies but not 'reduction in viral spread from index cases' in others.
- Hospitalisations: We understand that hospitalisation data may only be available for some studies. However patient hospitalisation is usually classified as a serious adverse event therefore we expect to identify hospitalisations (not reported separately) in that way.
- Extracting compliharms: Your statement that "AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness" underlies the complexity of analysing AEs and complications (our 'compliharms'). We have noted in the protocol that the limitation of complications only reported for the infected patients is relevant to the Roche trials only.

Data collection and analysis:

- We are interested that not only subject identification would be required to be removed from any documents of clinical study reports but also information personally identifying authors and investigators. We wonder why.
- Missing data. We have removed this statement.
- Meta-analysis method. DerSimonian & Laird method will be used. Note that in the case of zero cells (e.g. no events in one group) the RevMan software (which we will use for the analysis) automatically adds 0.5 to each cell of the 2x2 table for any such study. There are no continuous outcomes specified in this review.
- Fixed-effects model. Mantel-Haenszel method will be used except in the case of sparse data, in which case Peto's method will be used (as recommended in the Cochrane Handbook).
- Hazard ratio. We note the concerns with this outcome hence we will also consider analysis of this outcome as a continuous outcome noting that the data are likely to be skewed. We will use the inverse-variance random-effects method for this analysis.
- Analysis populations. All analysis will be using the intent-to-treat population as this is the most methodologically rigorous and clinically relevant.
- Study duration. We have specified in the protocol, where appropriate, that we will report outcomes for the on-treatment and off treatment time periods. If data are not available in the clinical study reports for any time period of the study then we will write to the relevant manufacturer to request the missing data.
- Trials with no events. As stated above the RevMan software automatically adds 0.5 to each cell of the 2x2 table for any such study.
- Sensitivity analyses. We note this point and agree. Where appropriate, a realistic sensitivity analyses will be conducted.

Contributors

Chris Del Mar

Feedback from Wolfgang Becker-Brueser, 30 January 2012

Summary

Dear Tom Jefferson,

I read your review about NI for prevention and treating influenza with interest. It's an important work. In the chapter "Why it is important to do this review" I found a small mistake concerning the worldwide stockpiling of oseltamivir which is mentioned to be "CHF 7.6 billion worth of oseltamivir (JACK 2009)". This would be an enormous amount "prior (!) to the emergence of influenza A/H1N1 in 2009". But Andrew

JACK wrote in the cited Financial Times (May 13, 2009): "Governments around the world had stockpiled 220m treatments to date, swelling sales since the start of 2003 to SFr7.6bn, largely on the basis of preparation for a pandemic virus that has yet to appear." So 7.6 billion SFr represent sales and not stockpiling.

Wolfgang Becker-Brueser (physician and pharmacist)

Reply

Thank you. The extent of stockpiling is a closely guarded secret this is why these are estimates. We will probably never know.

Contributors

Tom Jefferson MD

From Frederick G. Hayden, M.D., 2 February 2012

Summary

I am writing to comment on the recently updated meta-analysis by Jefferson and colleagues published through the Cochrane Collaboration and to request clarifications on several points, as well as to suggest some additional analyses that would be helpful in terms of taking greater advantage of this useful database. While I fully support access of Jefferson and other interested investigators to all of the published and unpublished data from the RCTs of oseltamivir and zanamivir for further analyses, this analysis only focuses on RCTs in ambulatory patients with uncomplicated influenza (the vast majority of whom were previously healthy) and on the period before the 2009 H1N1 pandemic. Consequently, I would urge these investigators to extend their efforts to other populations and datasets examining the risks and benefits of using neuraminidase inhibitors (NAIs) for treatment and prophylaxis. Furthermore, the authors should acknowledge the limitations of their analyses more explicitly and avoid inappropriate extrapolation to populations and influenza events that the RCTs did not adequately address. Differences in disease pathogenesis related to virus and host factors, as well as time to treatment, have important effects on the utility of antiviral agent interventions. My specific comments and recommendations for additional analyses follow:

1. Use of Intention to Treat (ITT) and ITTI-Infected Groups. The exclusive focus in the current treatment analysis on the ITT population is a readily rectified shortcoming. Outcomes in all three groups of relevance (ITT, ITT-infected, and ITT-noninfected) should be presented, so that readers can examine both clinical effectiveness and efficacy for the key endpoints, as well as events in those without documented influenza. Because NAI treatment would not be expected to provide any benefit in non-influenza illness, not presenting the ITT-infected outcomes in the analysis underestimates possible beneficial drug effects. Assessment of the non-infected group provides a valuable control and also enables a determination of whether there was a potential drug-disease adverse interaction of NAI treatment in non-influenza patients. Of note, our earlier pooled analysis of physician-diagnosed lower respiratory tract complications leading to antibiotic use found a significant benefit of oseltamivir in the influenza-infected patients but not in those enrolled in whom influenza infection was not detected by culture or serology [Kaiser 2003].

2. Sample size considerations. Severe outcomes of influenza infection are sufficiently uncommon in previously healthy people that even large RCTs or combining multiple RCTs would be very unlikely to detect them with confidence. The same point applies to very uncommon endpoints like microbiologically documented bacterial complications and rare adverse effects of treatment. Consequently, conclusions that there is no evidence (from trials) that NAIs reduce the risk of pneumonia, hospitalisations, deaths are overstated, as the evidence considered in this analysis is insufficient to properly address these questions.

The US CDC has estimated age-related influenza-related hospitalisation and mortality rates for both seasonal epidemics and the 2009 pandemic [Shrestha 2011]. Jefferson and colleagues should use such event estimates and others to make calculations of the necessary sample sizes to detect reductions in these severe outcomes with NAI therapy in a controlled RCT across a range of clinically relevant effect sizes (e.g., 20%, 35%, 50% reductions). In a related fashion, they should also provide more quantitative estimates for their ability to detect such outcomes with their existing database and comment more precisely on their power to capture particular endpoints.

3. Complications in ambulatory patients. Other clinically relevant endpoints in these previously healthy and at-risk persons warrant investigation. With regard to influenza-related complications, the most frequent in previously healthy children and adults are respiratory tract infections (otitis media, bronchitis) leading to antimicrobial use. These are usually not severe and typically not microbiologically documented with respect to etiologies but physician-diagnosed complications leading to antibiotic use is an outcome that has important clinical and public health implications (i.e., cost, antibiotic resistance, side effects) and also is sufficiently frequent to demonstrate effects of antivirals. We showed such a benefit in adults in our earlier pooled analyses of the then available RCT data on inhaled zanamivir [Kaiser 2000] and oral oseltamivir [Kaiser 2003]. The oseltamivir effect was confirmed in a recent meta-analysis [Hernan 2011], and another recent Cochrane report confirms an effect on otitis media in children [Wang 2011].

Given the large amount of data available to the investigators, it would be a valuable contribution to also explore the clinical outcomes in greater detail and to clarify the use of terms like severe outcomes. Although uncommon in the populations enrolled in these RCTs, endpoints such as radiographically documented pneumonia, microbiologically documented infections, and hospitalisation or death are clear and should be listed separately in those with or without proven influenza infection. Because of the importance of hospitalisations as an endpoint, it would be helpful to examine not only all-cause hospitalisations but also relevant subgroups based on likely causation (e.g.,

events in which influenza was documented or likely implicated including exacerbations of co-morbidities vs others like accidents, elective surgeries, conditions unlikely to be influenza-related). In addition to these events, exacerbations of underlying conditions (e.g., asthma, COPD, diabetes, CHF) are of medical importance in influenza outpatients with co-morbidities and should be examined.

4. Data from observational studies. Typically the patients who are most at risk of severe outcomes (older people, infants and young children, those with underlying chronic conditions) are not included in RCTs. In this regard, the current analysis is limited to placebo- or active-controlled RCTs largely done in previously healthy persons and does not consider the multiple observational studies from different countries that have consistently showed protective effects against severe outcomes like pneumonia and hospitalisation, particularly in those with co-morbidities, as well as reduced mortality if patients have been hospitalised. A considerable amount of new treatment data was generated in many countries during the 2009 H1N1 pandemic that found timely NAI treatment to be associated with a lower risk for intensive care admission and death (reference list available upon request).

While such data and analyses are weaker than RCT data and subject to bias, these observational studies address key endpoints in at-risk and seriously ill populations, including patients admitted to a hospital at the time of initiating therapy, that the available RCTs cannot and do not address. Furthermore, the standard of care has evolved such that placebo-controlled RCT in such patient groups would not be acceptable to investigators or ethics committees. The decision by Jefferson and colleagues not to consider and critically analyse the large amount of observational data with modern techniques means that they are not incorporating key information and many important patient groups in which the available data suggests medically important benefits from early NAI therapy. Such findings from observational data can inform antiviral treatment in more severely ill patients when no other data are available. As discussed above, not to include observational data means that conclusions of no effect on uncommon events or no severe adverse events being detected are almost inevitable. This should be made explicit in the design and the conclusion of the current report.

4. Influenza diagnosis and serologic results. The Jefferson report raises questions about the possible inhibitory effects of oseltamivir therapy on influenza-specific serologic rises and introduction of bias into the outcomes analysis. Further analyses might help to assess these possibilities. They should compare the primary endpoint of illness alleviation between the oseltamivir and placebo subgroups that were culture-positive (irrespective of serologic findings) at enrolment, and separately those that were culture-negative but had serologic evidence of infection.

Of note, one prior study of oseltamivir treatment in pandemic 2009 H1N1 patients, although not in seasonal influenza patients, suggested that early treatment could reduce antibody responses [Cowling 2010]. Jefferson and colleagues should examine the age-related frequencies of HAI seroconversions and the GMT titre rises in those with influenza-culture positive illness and separately in those with such HAI rises in absence of culture positivity. Of course, if still available, it would be interesting to test the culture-negative enrolment samples by RT-PCR.

The RCT data were generated over multiple seasons in which different influenza A and B viruses were circulating. Influenza B neuraminidases are generally less susceptible to oseltamivir carboxylate and several observational studies indicate that oseltamivir is less effective in influenza B- than influenza A-infected children [Sugaya 2007; Sato 2008]. It would be useful to examine the primary outcome in relation to virus type (A vs. B) and if possible A subtype (H3 vs. H1) in those with documented infections to expand on this point.

5. Other treatment endpoints of interest. Since those enrolled in the RCTs were outpatients, it would be useful to explore other endpoints that reflect patient recovery and impacts on the healthcare system (e.g., nonscheduled return visits for complications or adverse events). Perhaps more important than the time to alleviation endpoint used in the registrational trials might be the times to resumption of usual activities and return to pre-morbid status.

The authors raise the possibility that oseltamivir might have non-specific antipyretic effects, and one animal model study has also suggested possible adverse immunomodulatory effects of oseltamivir in RSV infection [Moore 2007]. Consequently, it would be interesting to examine the course of fever resolution (a much earlier event than cough resolution) and of symptoms in oseltamivir- and placebo-treated patients with and without documented influenza infections. In addition, it would be valuable to examine the correspondence (or lack thereof) between influenza virologic measures (e.g., enrolment virus titre, time to culture negativity, change in viral titres over time) and symptom resolution measures in both oseltamivir and placebo groups.

Various cost-effectiveness analyses on NAI therapy in low-risk populations have been published with widely divergent outcomes, largely depending on the input assumptions. Using this large database, a more refined analysis that incorporates both the direct and indirect (productivity losses) costs of influenza would be informative.

6. Adverse events with treatment. With regard to drug tolerability, it is important to examine not only the frequencies of reported adverse events but also assess indicators of their severity and interference with compliance (e.g., symptom days, patient reported severity, premature cessation of study drug).

Comparisons of AEs in the placebo groups across zanamivir and oseltamivir studies need to be interpreted with caution, since these studies were performed in different influenza seasons viruses and locations, with different protocols and case record forms, and by different investigators. Only one head-head RCT of treatment comparing these drugs has been published to date to my knowledge but the design did not include placebo only groups [Duval 2010]. In particular, comparisons in children (page 24) need to be age-adjusted as there were

major differences in those enrolled into the zanamivir (5 years and older) and oseltamivir trials (1 year and older), and the frequencies of gastrointestinal manifestations are much higher in younger children with influenza and other acute illnesses.

7. Prophylaxis endpoints of interest. The analysis of prophylaxis outcomes and the associated discussion requires clarification. The statement on page 5 says: "The FDA has also not allowed an indication for interference of viral transmission within households (the key concept behind post-exposure prophylaxis)." The key concept behind post-exposure prophylaxis is prevention of illness in exposed persons, and the primary endpoint in most prophylaxis studies has been symptomatic, laboratory-confirmed influenza illness. FDA and other regulatory agencies have approved both NAIs for post-exposure prophylaxis in households and also for longer duration pre-exposure chemoprophylaxis [reviewed in Khazemi 2009].

The Jefferson analysis seems to focus exclusively on the effect of chemoprophylaxis in "preventing the spread" of influenza, with endpoints presumably determined by evidence of culture or serologically confirmed infection irrespective of illness. While this is one endpoint of interest in such studies, the primary outcome of medical interest is prevention of influenza illness in those exposed. There is abundant RCT data, as well as observational data from the 2009 pandemic, that both inhaled zanamivir and oral oseltamivir have both statistically significant and medically important effects on preventing influenza-specific illness. Of note, the development of serologic evidence of infection without illness is advantageous in those receiving chemoprophylaxis, as it likely is an immunizing event that protects against future infection and illness by that strain. In addition several oseltamivir RCTs have shown significant but lesser effects on influenza infection in prophylaxis recipients [Welliver 2001; Hayden 1999]. The authors should present all of the relevant endpoints in their analysis of the prophylaxis trials.

8. Adverse effects with prophylaxis. The prophylaxis studies are particularly useful in assessing drug tolerability as symptoms of acute illness present in treatment studies are not confounders and there is a more prolonged duration of drug exposure. However, it is essential to examine not only the frequencies of reported adverse events but also indicators of their severity and possible interference with compliance (e.g., symptom days, patient reported severity, premature cessation of study drug).

For example, the Jefferson posting states that "Similarly, a published prophylaxis trial (Hayden 1999a, known by its trial ID WV15673/WV15697) describes headache as having "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)." but indicates that Japanese regulatory documents reached a different conclusion. My own review of the adverse event tabulations from our 6-week prophylaxis study (tables provided by the sponsor) indicates that the proportions of subjects reporting headache (not otherwise specified) that might have been related to study drug (unrelated reports excluded) during the treatment phase were similar across the placebo (N=116, 22.4%), oseltamivir 75 mg once (N=124, 23.8%), and oseltamivir 75 mg twice (N=132, 25.4%) daily dose groups [Hayden 1999]. Most of these reports indicated mild or moderate intensity and were self-limited. As indicated in the published paper [Hayden 1999], study withdrawals for AEs or illness occurred infrequently across these same groups (N=10, 1.9%; N= 8, 1.5%; N= 7, 1.3%). Of note, the specified causes for AE-related withdrawals included three reports of headache associated with other symptoms in the placebo group. In contrast, there were no reports of headache as reason for the withdrawals receiving oseltamivir; gastrointestinal complaints accounted for withdrawals in 4 of 8 oseltamivir 75 mg and 3 of 7 oseltamivir 75 mg twice daily recipients. The total numbers of patients with premature study withdrawal for any reason was 21 (4.0%), 17 (3.3%), and 16 (3.1%) across the three groups, respectively. Overall, severe AEs were reported in 82 (15.8%) of placebo, 75 (14.4%) of oseltamivir 75 mg, and 77 (14.8%) of oseltamivir 75 mg twice daily recipients. We were unable to include these details in the paper because of space limitations but my interpretation remains that no excess of clinically relevant oseltamivir-related headache occurred during this study. This type of detailed AE analysis incorporating severity measures provides necessary context in interpreting the possible importance of AEs.

9. Peer review. The questions raised and opinions expressed in this and earlier Cochrane reports on NAIs by Jefferson and colleagues have resulted in debate and sometimes confusion among practitioners and policy makers regarding the appropriate use of NAIs in seasonal and pandemic influenza responses. Given the importance of these issues, it would be helpful for any future updates to have proper independent review before posting or publication by the Collaboration, as the Cochrane methodology of publication and then independent peer review is not well understood by many people.

Thank you for the opportunity to provide comments. I look forward to seeing the responses from Dr. Jefferson and his colleagues on these points.

Sincerely,

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Submitter has modified conflict of interest statement: Disclosures to BMJ (Updated 4 June 2012)

Dr. Hayden received lecture and/or consulting honoraria from GSK until 2002 and from Roche until 2005. Gilead Sciences from 1996-1999 and Roche from 1999-2005 provided grant support to the University of Virginia for oseltamivir studies on which he was PI. Similarly GSK provided grant support to the University of Virginia for zanamivir studies from 1994-2001. Dr. Hayden served as medical officer in the Global Influenza Programme from 2006-2008 with funding provided to the University of Virginia through the National Institute of Allergy and Infectious Diseases (NIAID). Since 2008 to present the University of Virginia has received funding from the Wellcome Trust for his part-time work as influenza research coordinator at the Trust and through NIAID for his work as consultant the Southeast Asia Infectious Diseases Clinical Research Network. From 2008-11 the University also received honoraria for his participation in the Neuraminidase Inhibitor Susceptibility Network which received funding from Roche and GSK. Since 2008 to present, Dr. Hayden has been an unpaid consultant to multiple companies engaged in the development or marketing of influenza antivirals including Roche and GSK.

Dr. John Treanor reports receiving compensation as a member of the scientific advisory boards of Novartis and Immune Targeting Systems, and has performed consulting work for Pfizer. Within the last 3 years, his group has been funded to perform laboratory assays or conduct clinical trials for Sanofi, GlaxoSmithKline, Protein Sciences Corp, Wyeth, PaxVax, Ligocyte, and Vaxinnate.

Dr. Kaiser reports no financial disclosures.

Frederick G. Hayden

Reply

Response to Dr. Hayden's comments of 2 February 2012.

We thank Dr. Hayden for his detailed feedback. However nothing he writes allays our basic concerns that:

- (1) despite the 16,000 pages we analysed, we currently only have access to a very limited dataset hence cannot carry out many of the analyses Dr. Hayden suggests;
- (2) analysing the "influenza infected" population in Roche oseltamivir trials, as Dr. Hayden proposes, will lead to misleading results because the treatment groups are not comparable for this population;
- (3) the observational studies Dr. Hayden urges us to consider are generally of poor quality and only represent the small proportion of patients who are hospitalised with influenza;
- (4) the Kaiser et al (2003) analysis is seriously flawed;
- (5) data have been selectively reported.

Below, we provide point-by-point responses to Dr. Hayden's concerns. (Please note that point 4 appears twice, to follow the numbering in Dr. Hayden's letter.)

1. Use of intention to treat (ITT) and ITTI-infected [sic] groups

We agree, in principle, to conduct analysis using the ITT-infected (ITTI) sub-population provided that it is appropriately selected by the results of testing completed before the start of the trial (for example by using only the results of viral culture or rapid testing before randomisation).

However we argue that this is not possible in Roche oseltamivir trials. In these trials, the selection of "infected" or "non-infected" was dependent on the results of serology that is affected by "use" and "non-use" of oseltamivir. And the selection of those with "serology-positive results" appears to have given advantage to the oseltamivir group. Hence the method of selecting the ITT-Infected population in the trials has fundamental flaws and therefore the results are less reliable than those obtained using the ITT population.

2. Sample size considerations

The Kaiser et al analysis has a number of fundamental problems. First, analyses were performed on the ITT-infected sub-population which we have shown to be non-comparable between treatment groups. Second, the authors analysed an outcome that was different to that pre-specified in the trials. In the trials, complications included otitis media and sinusitis but in the Kaiser et al paper these were not included. This is an example of selective reporting or "cherry picking". Third, complications were not objectively or consistently measured in the trials. Fourth, outcomes such as pneumonia and bronchitis could be either reported as a complication or as an adverse event according to a classification criteria we do not understand and is not discussed in the Kaiser et al paper. And finally the data from the 10 trials was not meta-analysed, rather, it was combined as if generated from one single trial.

We could potentially address most of these limitations (except for the third) but we have not been given access to the data despite repeated requests to the manufacturer. However we were able to compare hospitalisations as those data were available to us for the ITT population.

We found no evidence of effect on hospitalisations based on seven studies with a median placebo group event rate of 0.84% (range 0% to 11%): odds ratio (OR) 0.95; 95% CI 0.57 to 1.61, $P = 0.86$). This result is quite different to that reported by Kaiser et al based on the (non-comparable) ITT Infected population.

In terms of power analysis, to detect a significant difference at this level of difference of 0.84% (placebo) vs 0.80% (oseltamivir), with alpha of 0.05 and power of 0.8, a RCT with approximately 800,000 participants is required.

3. Complications in ambulatory patients

As we have illustrated above the Kaiser et al (2003) analysis has fundamental flaws that we cannot address because the manufacturer refuses to provide us with the data necessary to conduct a proper analysis.

Analysis of the "population with proven influenza infection" (ITT-infected population) is not appropriate (see above). Data for the analysis of "population without proven influenza infection" are not available to us.

As we have shown above, the power to detect a difference in all-cause hospitalisation is very small hence to do a subgroup analysis on this outcome seems unwarranted.

The pharmacological/toxicological adverse effects of oseltamivir can be classified into two major types [3]. One is sudden type occurring during the hypercytokinemic state in the early phase of infection including sudden death [3,4], accidental death after abnormal behaviours and vomiting induced by the central depressing action of unchanged oseltamivir [4]. The second are delayed type of reactions including recurrence or exacerbation of influenza and/or other infection, diabetes, bleeding, renal impairment and delayed type neuropsychiatric reactions related to inhibition of the host's neuraminidase [3]. Sudden type adverse effects should be collected and analysed only during the early phase of influenza (for example, vomiting was only significantly increased within one day of treatment in the paediatric RCTs). However, delayed type adverse effects should be collected and analysed for a longer period to detect those reactions after a full course of treatment (for example the increase of pneumonia in the off-treatment period in the paediatric RCTs).

A recently published proportional mortality study has indicated that oseltamivir increases sudden type of death (odds ratio: 5.9) compared with zanamivir users by analysing all death cases among approximately 20 million 2009A/H1N1 influenza patients in Japan. This effect was also true for the comparison of oseltamivir users with non-users of antivirals [4].

4. Data from observational studies

Observational studies during the 2009 H1N1 influenza outbreak have assessed the effects of oseltamivir on a selected population of hospitalised patients. These represent a very small proportion of the total population who get influenza. While subgroup analyses are important, it is important to not lose sight of the fact that the use and governmental stockpiling of oseltamivir is for its routine use in asymptomatic and symptomatic members of the community. Our review thus considers the evidence base that applies to the vast majority of people.

In addition, the studies Dr. Hayden appears to be referring to are retrospective observational studies in which apparent treatment effects may be the result of an effective treatment but could also be due to confounding effects. Unfortunately there is no way to determine which of these possibilities is true. That is why drug regulators require evidence from RCTs to determine whether or not a drug is approved for use. According to the analysis by Jones and Hama [5], apparent protective effects against severe outcomes like pneumonia, hospitalisation and mortality are possibly derived from survivor treatment selection bias (or immortal time-bias). This is not an issue for randomised controlled trials because follow up begins at the time of randomisation which is the same for patients allocated to active drug and patients allocated to placebo. However in the case of observational studies treatment can begin at varying times (up to several days) after the onset of symptoms. Therefore a naive comparison that compares a binary outcome, such as death (or other adverse event), or time to an event (survival time) is at high risk of survivor treatment selection bias (also referred to as immortal time bias or simply time dependent bias). This bias can occur, for example, because patients who die early are not given the opportunity to receive treatment. In addition patients who are extremely sick may not be given the opportunity to receive antivirals because other treatments and procedures take priority. This bias can be addressed with an appropriate analysis however this has not been done in any of the observational studies of antiviral use for influenza that we have seen.

4. Influenza diagnosis and serologic results

We do not have access to the data required to conduct all these analyses.

5. Other treatment endpoints of interest

We do not have access to the data required to conduct these analyses (time to resumption of usual activities and return to pre-morbid status) using the ITT population.

By mentioning the evidence and possible mechanism of action for oseltamivir, we are arguing that fever alleviation and symptom reduction may not be caused by the reduction of viral load but may be the result of inhibition of host's immune functions including induction of cytokines and antibody production by inhibition of the host's neuraminidase in addition to central depression by oseltamivir.

Analysis of the population with documented influenza infection (ITT-Infected population) is not valid (see above). Hence we are unable to conduct a valid analysis in the influenza positive population and data for the influenza negative population has not been provided.

Antibody titre is one of the ways of selecting only subjects infected with influenza. However we have shown that the production of antibodies was consistently lower in the oseltamivir group compared to the placebo group in the treatment trials. Therefore the use of antibody production to confirm influenza in prophylaxis trials is not valid. Moreover comparison of the proportion with confirmed infection between the oseltamivir group(s) and the placebo group will provide misleading results.

Nor are "virus titre", "time to culture negativity" or "change in viral titres over time" a true measure of viral load, because oseltamivir as a neuraminidase inhibitor may conceal positivity by inhibiting the influenza virus from leaving the surface of host respiratory cells (which are covered by a mucous layer on the surface of the cells).

6. Adverse events with treatment

In principle we agree. However, there are many data that show the classification of severity is questionable: for example, we believe that *psychosis* or *hallucinations* should be classified as "severe" but this has not always been followed. Therefore, we are planning to propose using new classification methods for the analysis of adverse events in the next update of our review.

We agree that comparisons of adverse events in the placebo groups across zanamivir and oseltamivir studies need to be interpreted with caution.

We agree that the spectrum and severity of adverse events/reactions are different among age groups. Therefore, we propose analysing adverse events/reactions stratified by age, if possible, according to the data in the Clinical Study Reports or individual patients' data in the next step of our systematic review.

7. Prophylaxis endpoints of interest

As described on page 7 of our systematic review, the primary outcome measures for prophylaxis studies are:

1. influenza (both symptomatic and asymptomatic and laboratory-confirmed) and influenza-like illness (ILI);
2. hospitalisation and complications;
3. interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts);
4. harms.

We did not meta-analyse data from the prophylaxis trials in this systematic review because the substantial documents for prophylaxis trials were obtained after the time lock of 12 April 2011.

Due to the problems we have illustrated above on using virus titre to confirm influenza infection we plan to amend the primary endpoint for prophylaxis trials to influenza-like illness (ILI).

There is some fear that those with serologic negative infection without symptoms may be more easily infected with influenza virus in the future, because evidence from animal experiments shows that IgA antibody in the respiratory mucosa is reduced (to about 20% of the control group), while reduction of those of systemic IgG antibody (HI antibody) was slight and not statistically significant [6].

8. Adverse effects with prophylaxis

We agree that the prophylaxis studies are particularly useful in assessing drug tolerability.

As we discussed above ("7. Adverse events with treatment"), there are many data that show the classification of severity is questionable. For example, we believe that psychosis or hallucinations should be classified as "severe" but this has not always been followed. Therefore, we are planning to propose using new classification methods for the analysis of adverse events in the next step of the review.

We mentioned the statement "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)" as an example of reporting bias present in the paper (Dr. Hayden's reference no. 3; known by its trial ID WV15673/WV15697).

The numbers for headache are 47% (242/520) in high-dose oseltamivir group, 43% (335/520) in low-dose oseltamivir group and 39% (202/519) in placebo group. These proportions are not similar and show a significant linear trend of increase with oseltamivir dose ($P = 0.013$).

In addition, we would be grateful if Dr. Hayden were to supply the definition of "drug related headache among headaches reported as adverse events"? In particular, how was it decided whether a headache was drug-related or not? We cannot suggest signs or symptoms to distinguish oseltamivir-induced headache from placebo-induced headache.

We propose analysing adverse events in clinical study reports, including those for prophylaxis trials.

9. Peer review

We agree that there is confusion among policy-makers and practitioners but believe this to be justified: the data published and accessible to them appear to have some flaws that need to be resolved. We are encouraged by Dr Hayden's support for our obtaining all the data necessary to clear the confusion.

Cochrane systematic reviews are stringently peer-reviewed. Not only are they peer-reviewed by independent experts prior to publication but the protocols are also peer-reviewed before being undertaken, to reduce a priori biases. In addition, protocols are available for comment from outside the internal review process – Dr Hayden himself, or employees of Roche the manufacturer of oseltamivir, could have provided input about suggested alterations to the protocol which we would have been glad to receive. To this extent the peer-review process is more stringent than that employed by most other scientific journals.

RH, MJ, TJ, CDM, PD

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Additional feedback from Frederick G. Hayden, 10 August 2012

Summary

I am writing to respond to the comments and questions raised by Jefferson and his colleagues to my letter of 2 February 2012 about their report published through the Cochrane Collaboration. While the authors have provided helpful clarifications to many points, I remain concerned about their selective approach to data analysis and presentation. Resolution of these issues is important in anticipation of future analyses by Jefferson and colleagues or by others. Many of their responses indicate that analysis of the cohorts with proven influenza infection (ITT-infected) are not appropriate but further analyses of patient level data should be able to address their concerns (see below). Also they identify biases that could make oseltamivir look better but not those that could make it look worse than its effectiveness and tolerability likely are in reality. An impartial analysis would identify biases in both directions and attempt to deal with them in a balanced appraisal.

My specific comments and recommendations for additional analyses follow:

1. Use of intention to treat (ITT) and ITTI-infected groups. One obvious means of addressing the concern about selection bias in defining the ITT-infected (ITTI) population for analysis is to focus on those who were influenza virus-positive (irrespective of serologic results) at enrolment. These individuals (ITTI-virus) represented approximately 70-85% of those enrolled into the ITTI cohorts across the various RCTs.

In addition, those who were included in the ITTI group solely on the basis of seroconversion could be analysed separately to assess overall comparability in terms of symptom resolution and complications to those who were both virus-positive (ITTI-virus) and showed serologic rises. This might also help determine whether inclusion of data from virus-negative seroconverters would affect overall findings.

In contrast to the Cochrane statement that "And selection of those with "serology-positive results" appears to have given the advantage to the oseltamivir group", it might alternatively be disadvantageous (bias toward the null) or neutral in effect. If oseltamivir is most beneficial in preventing lower respiratory tract (LRT) complications leading to antibiotic use in those in whom it also prevents seroconversion, as one might expect if its overall treatment effect varies between patients based on timing of administration, individual pharmacokinetics or other factors, then its protective effect on complications will be underestimated because the benefits in those for whom it prevents seroconversion will not be counted. If, on the other hand, treatment works effectively only in those infected who seroconvert and has little or no effect in those in whom it prevents seroconversion, this would increase the apparent benefit. However, the only way in which this sequence seems possible would be if late treatment does not interfere with seroconversion but early treatment does AND late treatment is more effective than early. This is biologically implausible and inconsistent with the observed effects on time to treatment for other outcomes, in which early treatment is associated with greater effects. Alternatively, if oseltamivir treatment has a similar effect on LRT complications in infected who seroconvert and those who do not, this would reduce the numbers in the treated group with and without outcomes in a non-differential way.

In addition to a possible non-specific immunomodulatory effect of oseltamivir on serologic responses or possible confounding effect of prior inactivated influenza vaccine which might blunt antibody responses in those with proven influenza (1), one explanation for the apparently lower seroconversion rate in oseltamivir recipients would be that some oseltamivir recipients had low viral replication levels at enrolment that were quickly reduced by treatment and did not stimulate antibody rises, so that in these persons treatment prevented seroconversion. If one assumes that clinical outcomes are linked to viral replication levels as other reports suggest, such individuals would probably have shorter illness duration and also be less likely to develop LRT complications. Consequently, not counting them in the oseltamivir group would bias towards the null and under-estimate the effect of treatment on both illness resolution and complications.

In this regard, comparing outcomes in the ITTI-virus seroconverters vs non-seroconverters would be of interest if sufficient numbers are available. Also, as stated previously, analysis of the serologic responses based on time from symptom onset to enrolment, including both frequency of seroconversion and observed titres rises in the ITTI-virus group compared to placebo, might help address this possibility.

If I have interpreted their report correctly, the post-hoc analyses by Jefferson and colleagues found an absolute difference of 3.4% in overall infection rates between placebo (68.9%) and oseltamivir (65.5%) groups across the studies they analysed (Figure 5, Table 17).

This difference presumably approximates the fraction of virus-negative, non-seroconverting but possibly influenza-infected subjects in oseltamivir group. To what extent this difference might bias outcomes is uncertain but its relatively modest size suggests that

misclassification would not be a major confounder in either the ITTI or ITT-non-infected groups. Optimally in future studies more sensitive nucleic acid amplification testing will be used to detect infection by influenza and other respiratory viruses and facilitate more clear delineation of the groups of interest.

In summary, further analyses of the RTCs on oseltamivir and zanamivir, the outcomes in all groups of relevance (ITT, ITTI, ITTI-virus, and ITT-non-infected) are important and should be presented as fully as possible. As stated previously, separate assessment of the ITT-non-infected group provides a valuable control and also enables a determination of whether there was a potential drug-disease interaction of NAI treatment in non-influenza patients. As specific antiviral treatment would not be expected to provide benefit on illness resolution or complications in non-influenza illness, examining the ITT-non-infected groups allows this point to be tested directly. An analysis of 11 oseltamivir RCTs (2) confirmed lack of treatment effect on LRT complications in non-influenza-infected subjects compared to placebo. The failure to present outcomes in the ITT-infected or ITT-virus cohort underestimates possible beneficial drug effects, whereas full data presentation would enable readers to examine the event rates and magnitude of treatment effect sizes for key outcomes across all relevant groups for themselves.

2. Sample size considerations. The endpoint used in our pooled analysis of oseltamivir RCTs (3) was prospectively defined before the analysis was undertaken and was based on findings in our earlier study of zanamivir treatment effects (4) that indicated inhaled zanamivir reduced LRT illnesses leading to antibiotic prescriptions (RR, 0.60; 95% CI 0.42-0.85) but not upper respiratory tract ones (RR 0.90; 95% CI 0.63-1.27). The oseltamivir analysis used all studies available to us at the time, including unpublished clinical study reports, in order to avoid selection bias. The other endpoints of upper respiratory tract complications leading to antibiotic use (6.8% oseltamivir vs 5.9% placebo) and overall antibiotic use (14.0% oseltamivir vs 19.1% placebo; $P < .001$) were described in our 2003 paper (page 1760). Of note, the reductions in overall antibiotic use in influenza outpatients were similar for zanamivir (28%) and oseltamivir (27%) treatment. The limitations of the clinical diagnoses and retrospective approach used in these studies were described more fully in the earlier zanamivir paper (4). However, the simple pooled analysis we undertook in the oseltamivir paper did not correct for the higher proportion of influenza-infected, at-risk individuals in the placebo group, and this was a shortcoming. In any case, we pointed out this difference in the paper (page 1669) and presented the data by each group of interest (previously healthy or at risk) in Tables 3 and 4.

More importantly, our finding that early oseltamivir treatment reduced the likelihood of physician-diagnosed LRT complications leading to antibiotic use has been confirmed and extended (37% reduction in oseltamivir group; risk ratio 0.63 [95% CI 0.48, 0.82]) in a subsequent meta-analysis (that controlled for pre-enrolment risk status and included events from the time of enrolment) of the same 10 RCTs included in our paper and one additional one (2). Furthermore, this analysis found that the unpublished trials for which Jefferson and colleagues apparently do not have data were found to be no more favourable to oseltamivir than the published ones. When only the two published trials in previously healthy persons were considered, the reduction in the 24-day risk of LRT complications treated with antibiotics was 65% (risk ratio, 0.35; 95% CI 0.15, 0.82) in the oseltamivir arms.

3. Complications in ambulatory patients. Their comments on possible oseltamivir adverse events, including sudden death and neuropsychiatric adverse events (NPAEs), raises important points about the effects of influenza infection itself and possible drug-disease interactions. A well-documented relationship exists between NPAEs and influenza infection itself. Differing age-related patterns of influenza-associated encephalopathy/encephalitis and NPAEs have been reported in Japanese children and adolescents, and also age-related differences exist in NAI prescribing patterns in Japan. Consequently, careful analysis is required to assess possible associations. It is important to point out that causal relationships between oseltamivir use and such events remain to be proven. Some analyses have indicated comparable or lower NPAEs rates in oseltamivir-treated compared to non-treated influenza patients (reviewed in (5)) and no higher rates of NPAEs have been found in hospitalised infants in the USA (6). Oseltamivir administration to those with influenza-associated NPAEs does not appear to worsen manifestations (7;8). Of note, the crude reporting rates for possible oseltamivir-associated NPAEs in Japan and USA were significantly lower during the 2009 pandemic than during preceding influenza seasons (9).

As pointed out by Jefferson and colleagues, the possibility of late-onset adverse events requires that sufficient follow-up be incorporated into study design to examine both possible adverse and beneficial effects. However, the low frequencies of such events would likely require much larger numbers of subjects than enrolled in most RCTs. One approach is retrospective examination of large databases that link healthcare visits, clinical diagnoses, and drug administration registries. For example, one cohort study involving over 150,000 subjects (49,238 oseltamivir recipients, 102,692 control patients) reported that oseltamivir treatment of presumed influenza was associated with lower risk of TIA or stroke in the subsequent six months (10). This kind of observational study approach has been undertaken for investigation of outcomes and possible adverse events following influenza immunisation and should also be extended to antivirals.

4. Data from observational studies. Jefferson and colleagues indicate that possible survivor treatment selection bias in observational studies can occur because patients who die early are not given the opportunity to receive treatment. However, there is also the opposite concern that sicker patients, especially in a rapidly evolving illness like influenza, are more likely to initiate therapy at any given time after symptom onset than less ill ones. This would be a conservative bias and reduce the likelihood of observing a treatment effect. Clinical experience during the 2009 H1N1 pandemic indicated that late NAI treatment in critically ill or non-surviving influenza patients was frequently due to delayed consideration of the diagnosis or failure to appreciate the potential value of starting treatment beyond two days after symptom onset in those with progressive illness or high-risk conditions. This occurred often despite some of these patients having had prior outpatient contact for their acute illness. Although the published reports indicate that most critically ill patients ultimately received antiviral therapy, delayed treatment commonly led to initiation of NAI administration as part of a salvage effort in a deteriorating patient. In part because of critical care support, even those patients who died in hospital usually survived into the second week of illness.

or later. Those analysing the large amount of observational data that has been generated in recent years, particularly in the context of the 2009 H1N1 pandemic, need to keep these clinical observations in mind. Of note, a recent analysis of critically ill pandemic H1N1 patients in California compared mortality in untreated patients who survived at least to the day after symptom onset when NAIs were first given to the NAI-treated ones and found that cases who received NAI up to 4 days after symptom onset were more likely to survive ($P < 0.05$ for each day 0-4) (11).

An independent report on the observational studies of influenza antivirals published up to November 2010 (12) conducted a meta-analysis of the few studies providing effects adjusted for confounders and, while acknowledging the low quality of the evidence based on the GRADE assessment approach, concluded that in high-risk populations, oral oseltamivir may reduce mortality (odds ratio, 0.23 [95% CI 0.13 to 0.43]) and hospitalisation (odds ratio, 0.75 [95% CI 0.66 to 0.89]). In addition, as reported in multiple studies of hospitalised pandemic 2009 A(H1N1) patients, including high-risk ones like pregnant women and those admitted with pneumonia, treatment with oseltamivir up to 4 days and in some studies later after illness onset has been associated consistently with better outcomes (11;13-21). Such observations have served to reinforce US CDC recommendations for using influenza antivirals as early as possible in those with severe or progressive illness, those hospitalised with suspected or proven influenza, and outpatients at higher risk for influenza complications (22). Furthermore, given that the circulating influenza viruses have continued to change, with the pre-2009 A(H1N1) seasonal viruses being entirely replaced by A(H1N1)pdm09 and now antigenically drifted A(H3N2) and B viruses, ignoring observational data means that only information concerning NAI treatment for influenza viruses that are now no longer circulating is being considered.

5. Other treatment endpoints of interest. The possibility that oseltamivir might have non-specific antipyretic or immunomodulatory actions unrelated to its antiviral effects has been raised in part on the basis of murine studies (23;24). These possibilities or other symptom-modifying effects could be addressed by comparison of the course of fever and individual symptom resolution between oseltamivir and placebo recipients for those enrolled in the RTCs who did not have laboratory evidence for influenza (ITT-non-infected). Of note, antipyretics were provided to participants in these trials, so that use of paracetamol (acetaminophen) needs to be included as a confounder in such analyses.

In the published pivotal RCTs of oseltamivir treatment in adults, the fever and symptom reductions observed in oseltamivir recipients were in addition to the effects of paracetamol (acetaminophen). One previous RCT in adults with uncomplicated influenza compared amantadine to aspirin and found faster fever resolution in aspirin recipients but slower resolution of other symptoms and higher rates of adverse effects leading to drug cessation (25). While fever resolution is an objective endpoint of interest, it is generally short-lived and of limited clinical importance relative to other endpoints like time to symptom alleviation, time to return to usual activities/premorbidity status, and complications reductions.

The comment by Jefferson and colleagues on measuring viral loads is confusing. Virologic endpoints like quantitative virus titres (infectious and in recent studies viral RNA), time to culture negativity, and changes in titres over time are essential to determining whether a putative influenza antiviral treatment is exerting an antiviral effect and the magnitude of that effect. Failure to detect an antiviral effect raises questions about issues like compliance, drug absorption and disposition, lack of potency, and resistance emergence. Examining such virologic measures also serves to confirm the likely mechanism of antiviral action of NAIs, inhibiting release from infected cells and spread in respiratory tract secretions to initiate subsequent rounds of replication. Several observational studies during the 2009 pandemic found that early antiviral treatment (<2-3 days from symptom onset) was associated with reduced duration of viral RNA detection (26-28). Consequently, in the context of the oseltamivir RCTs, it would be valuable to examine the correspondence between upper respiratory tract influenza virologic measures and symptom resolution and LRT complications in both oseltamivir and placebo groups.

7. Prophylaxis endpoints of interest. As indicated in my initial letter, the key efficacy endpoint for an influenza antiviral used for prophylaxis should be symptomatic, laboratory-confirmed influenza illness. Given the potential for other respiratory viruses to cause febrile respiratory illness, a focus on ILI as the primary endpoint will inevitably underestimate the protective effects of an influenza-specific chemoprophylactic agent. Of note, various definitions of symptomatic illness and ILI have been used in the influenza prophylaxis RCTs to date, so that further analyses using standardised definitions would be a helpful contribution. Other secondary endpoints of interest include laboratory documented infection (irrespective of symptoms), ILI, virus-positive ILI, and laboratory-confirmed illnesses not meeting the ILI definition. Laboratory confirmation based on both viral culture and in future studies viral RNA detection would take advantage of the greater sensitivity of RNA detection.

8. Adverse effects with prophylaxis. As detailed in the oseltamivir seasonal prophylaxis study protocols and report, the relationship between drug receipt and adverse events, including headache, in these trials (29) was determined by the study staff and investigators during the trial under blinded conditions before data lock. The assessment of causality in adverse events (unrelated, remote, possible, probable) as related to drug administration was made using pre-specified criteria in the protocol (see Appendix 2) on an individual basis by both interviewing the affected participant and considering various factors including past patterns of headaches, associated symptoms, duration and severity, timing in relation to study drug, and whether the symptom persisted during drug administration. Because of its background frequency in the population, headache is a very common event in longer term studies. When it is mild or transient despite continued drug administration, or when it occurs in context of other events (URI, trauma, stress), headache is unlikely to be drug-related. Using these criteria and the analysis report provided by the sponsor Roche, we observed headache (not otherwise specified, NOS) that was probably, possibly, or remotely related to study drug administration in 22.4% of placebo, 23.8% of once daily oseltamivir, and 25.4% of twice daily oseltamivir recipients during the 6 weeks of prophylaxis (29). The proportions were 10.2%, 8.7%, and 10.8%, respectively, for headache (NOS) that was possibly or probably related to study drug administration.

Headache is a good example of where it is essential to examine not only the frequencies of reported adverse events but also their severity and functional impact, including premature cessation of study drug. In our 6-week prophylaxis trial (29), severe headache (NOS) irrespective of relationship to study drug administration was reported in 5.0% of placebo, 3.3% of once daily oseltamivir, and 6.9% of twice daily oseltamivir, respectively. Overall premature study withdrawals were found in 21 (4.4%) of placebo, 17 (3.3%) of once daily oseltamivir, and 16 (3.1%) of twice daily oseltamivir recipients. In three placebo but no oseltamivir recipients, headache was listed as a contributory factor. However, headache was reported to be a factor leading to cessation of oseltamivir prophylaxis in one subject in another prophylaxis study (30) and was also reported at a higher frequency during 6-weeks prophylaxis in a nursing home-based RCT (5.5% placebo vs 8.3% oseltamivir)(31), so that further analyses are warranted.

9. Peer review. I thank Jefferson and his colleagues for their clarifications on the Cochrane peer review process, and as indicated above, I have provided my own suggestions on the design of future analyses by them and others. In addition, I have provided a list to the Cochrane Editorial Unit of several dozen potential expert reviewers for future protocols and reports on influenza antivirals.

Thank you for the opportunity to provide these responses and comments.

Sincerely,

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Appendix 2 Definition of Adverse Event Relationship to Treatment

Probable

This category applies to those adverse events which are considered, with a high degree of certainty, to be related to the test drug. An adverse event may be considered **probable** if:

1. It follows a reasonable temporal sequence from administration of the study drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It disappears or decreases on cessation or reduction of dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias).
4. It follows a known pattern of response to the study drug.
5. It reappears upon re-challenge.

Possible

This category applies to those adverse events in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered **possible** if or when:

1. It follows a reasonable temporal sequence from the administration of study drug.
2. It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It follows a known pattern of response to the study drug.

Remote

In general, this category is applicable to an adverse event which meets the following criteria:

1. It does **not** follow a reasonable temporal sequence from administration of the study drug.
2. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It does not follow a known pattern of response to the study drug.
4. It does not reappear or worsen when the drug is re-administered.

Unrelated

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under **remote**, **possible**, or **probable**.

	Probable	Possible	Remote	Unrelated
Clearly due to extraneous causes	-	-	-	+

Reasonable temporal association with drug administration	+	+	-	-
May be produced by subjects clinical state	-	+	+	+
Known response pattern to suspected drug	+	+	-	-
Disappears or decreases on cessation or reduction in dose	+	-	-	-
Reappears on re-challenge	+	-	-	-

Reply

Reply to Hayden Letter 10 August 2012

Thank you for taking the trouble to provide further feedback to our responses to your first set of feedback comments.

You remain concerned about 1) "...selective approach to data analysis and presentation...", especially with respect to our concern that ITT-infected (ITTI) criteria are inappropriate; and 2) our identification of biases that may exaggerate the effectiveness of oseltamivir. You detail these concerns in more detail:

1. ITT and ITTI

You propose an analysis of ITTI in which patients are categorised not by an immune response (which we regard as potentially flawed because our interpretation of the data suggests the drug may interfere with the immune response) but instead by determining whether patients were seroconverting excreting influenza virus at enrolment.

This sounds sensible, and were the data of symptoms and baseline infectivity (by serology or even virus shedding) available to us in suitable format, we would include this analysis. By this, we would expect the randomisation of patients into the two groups to be independent of the initiation of the drug (that is the "influenza-positive" or "-negative") before the drug was administered, in case (as may be with the immune response) the drug interferes with virus excretion (as the manufacturer claims in some of its literature).

You also propose an analysis of those grouped by ITTI from serological conversion with those grouped by virus excretion. This also would be useful, to determine whether or not a bias exists in the current data (in either direction, as you point out – the possible mechanisms you outline are plausible).

However, your hypothesis "If oseltamivir is most beneficial in preventing lower respiratory tract (LRT) complications" IS one of the main issues to be confirmed.

As already described in our review, you reported a reduction of cytokine production in response to influenza infection by oseltamivir in humans:

- Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *New England Journal of Medicine* 1999;341(18):1336-43

These findings suggest that reduction of antibody production cannot simply be assumed to be the result of reduced viral load.

2. Sample sizes

You describe in more detail the Kaiser 2003 pooled analysis of complications:

- Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalisations. *Arch Intern Med* 2003;163:1667-72

This was central to the start of our unease, after it was pointed out to us (in this Feedback section!) by Hayashi that over half of the data in it were of unpublished trials. You state that the end-points were established a priori and not post hoc. You admit to shortcomings of the paper but point out that they were declared in the paper itself. You suggest that because the two published trials meta-analysed had no more favourable drug results than the unpublished, bias is less likely.

We think this is to misunderstand our central concern: we are unable to critically appraise the trials in the usual way because they are not available to us, nor, apparently, any other group unselected by the manufacturer. Incidentally we note that you yourself, even as an author, admit you were unable to locate the data for this paper on request, referring us instead to the sponsoring manufacturer, Roche:

- Cohen D. Complications: tracking down the data on oseltamivir. *BMJ* 2009;339:b5387.

This inability by you (authors) or sponsoring manufacturer to provide data for independent scrutiny is disgraceful, a view shared by others, <http://bmj.com/tamiflu>.

3. Adverse effects of NIs

We find it interesting that you call these adverse events 'complications'. You point to our concerns about neuropsychiatric adverse events (NPAEs), and (correctly) state that any association recorded in the literature "...remains to be proven..." with some references (all were retrospective studies and mostly sponsored by the manufacturer) that suggest that there is no increase over control groups. We have other references suggesting the opposite:

- Hama R. Fatal neuropsychiatric adverse reactions to oseltamivir: case series and overview of causal relationship. *Int J Risk Safety Med*: 20 (2008): 5-36: <http://npojip.org/english/no11.html>
- Nakamura K, Schwartz BS, Lindegårdh N, Keh C, Guglielmo BJ. Possible neuropsychiatric reaction to high-dose oseltamivir during acute 2009 H1N1 influenza A infection. *Clin Infect Dis*. 2010 Apr 1;50:e47-9.
- Kruker AT, Krause M. ["Oseltamivir-induced delirium"]. *Ther Umsch*. 2010 Dec;67(12):613-5. German.
- Chung S, Joung YS. Oseltamivir (Tamiflu) induced depressive episode in a female adolescent. *Psychiatry Investig*. 2010 Dec;7(4):302-4. Epub 2010 Nov 11.

The following are prospective cohort studies that aimed to analyse the association of NPAEs and administration of NIs, in particular oseltamivir.

- Fujiwara F, Ikushima S, Hibi N et al. An analysis of risk factors of abnormal behavior in two seasons (07, 08) of influenza infection. Presentation at the 40th annual meeting of the Japanese Society for Paediatric Infectious Diseases held on 15 and 16 (2008)
- Fujita T, Fujii Y, Watanabe Y, Mori M, Yokota S. A pharmacoepidemiological study on the relationship between neuropsychiatric symptoms and therapeutic drugs after influenza infection. *Jap J Pharmacoepidemiol* 2010; 15: 73-92.

This preliminary report on the analysis of randomised controlled trials of oseltamivir for prophylaxis contains our response to Roche's report discussing NPAEs and oseltamivir:

- Jones M, Hama R, Jefferson T, Doshi P. Neuropsychiatric adverse events and oseltamivir for prophylaxis (letter). *Drug Safety*, 2012, 35 (12): 1187-90.

A proportional mortality study indicates that oseltamivir increases sudden death (odds ratio: 5.9) compared with zanamivir users in an analysis of all deaths among ~ 20 million 2009A/H1N1 influenza patients in Japan. This effect is also observed for the comparison of oseltamivir users with non-users.

- Hama R, Jones M, Okushima H, Kitao M, Noda N, Hayashi K, Sakaguchi K. [Oseltamivir and early deterioration leading to death: a proportional mortality study for 2009A/H1N1 influenza](http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf). *Int J Risk Saf Med*. 2011;23(4):201-15. <http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf>

We have presented many of these studies in our previous reply to you, without response.

Of course the uncertainty about causation is true for many drug adverse events: our duty is to ensure that any such uncertainty is clearly articulated.

Nevertheless we entirely agree that "...observational studies ... undertaken for investigation of outcomes and possible adverse events following influenza immunisation ... should also be extended to antivirals." However, because this Cochrane review is limited to randomised data, such observational studies would be conducted outside this particular review.

4. Observational data

You point to our concerns about observational data in general for answering intervention questions. We acknowledge the plethora of observational data available, and even the meta-analysis of some of them. This does not detract from our continued concern that the best data for answering these questions are randomised, and to leave most of these data unavailable for independent scrutiny is unforgivable.

Moreover, the observational studies are regarded as poor in quality. A recent systematic review and meta-analysis of observational data for antivirals for the treatment of influenza concluded, "...therapy with oral oseltamivir and inhaled zanamivir may provide a net benefit over no treatment of influenza. However the confidence in the estimates of the effects for decision making is low to very low."

- Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al. *Ann Intern Med*. 2012 Apr 3;156(7):512-24. doi: 10.1059/0003-4819-156-7-201204030-00411. Epub 2012 Feb 27. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies

Incidentally, we are interested in rigorously meta-analysing these data ourselves, and have put in a protocol to do just that. (Jones M, Hama R. Effect of oseltamivir on mortality in treatment of 2009A/H1N1 influenza patients. PROSPERO 2012:CRD42012002245. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002245)

The proportional mortality study (above), analysing all influenza deaths in Japan and estimating populations who took antivirals and did not take them as the denominators, provides far more reliable estimates of risk from drug exposures than retrospective analysis of surveillance cases without exposed populations (denominators). Contrary to your suggestion "...there is also the opposite concern that sicker patients, especially in a rapidly evolving illness like influenza, are more likely to initiate therapy at any given time after symptom onset than less ill ones...", no such tendency was detected in this study. Proportions of patients treated with antivirals within 12 hours from the onset of fever were significantly lower in the "not mild" cases (26.5%) than "mild" cases (35.4%) at the time when antiviral was prescribed [Table 2b]. However, no patients who deteriorated before the first presentation at medical facilities were treated with antivirals before deterioration [Table 2a], while 78% of "mild" cases and 55% of "not mild" cases were prescribed antivirals within 48 hours from onset of fever [Tables 2a and 2b]. These may be related to the lower positive results (45%) of rapid testing for influenza virus in the "not mild" cases than that in the "mild" cases (60%) at the first consultation:

- Hama R, Jones M, Okushima H, Kitao M, Noda N, Hayashi K, Sakaguchi K. [Oseltamivir and early deterioration leading to death: a proportional mortality study for 2009A/H1N1 influenza](http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf). Int J Risk Saf Med. 2011;23(4):201-15. <http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf>

5. Other treatment endpoints of interest

Does oseltamivir have non-specific antipyretic or immune-modulatory actions unrelated to its antiviral effect?

We have already noted the hypothermic and immune-suppression effect of oseltamivir in humans, some from your own writing.

- Hama R. Fatal neuropsychiatric adverse reactions to oseltamivir: case series and overview of causal relationship. Int J Risk Safety Med 2008;20:5-36
- Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomised controlled trials for prevention and treatment. JAMA 1999;282:1240-6.

Your suggestion that antipyretic actions of oseltamivir be tested by comparing those randomised to oseltamivir against those not in the non-ITTI group is worth consideration (although the results might be difficult to interpret). Again, as mentioned above, it would be good to have access to sufficient data to allow this analysis and others we have outlined in the protocol.

We note your criticism about over-focusing on fever as a proxy for symptom resolution. We are of course interested in any good measure of the latter that is not only objective but also common to all trials. Nevertheless, despite your criticism, fever is a reasonable marker of 'illness' from infections such as influenza, and probably correlates reasonably well with symptom resolution (especially in the prophylaxis trials) and in the treatment trials (if fever is measured until complete resolution) – it is, after all, a cardinal symptom – and has the great advantage of being clearly measured.

You suggest that we test whether viral excretion correlates with symptoms of influenza. We agree that this would be an interesting analysis, were the data available to us (see above).

7. (Note there was no Point 6) Should we be focusing so much on influenza-like illness (ILI)?

Of course, if oseltamivir neither reduces antibody production to influenza virus nor conceals testing positivity, selecting only laboratory-confirmed influenza might be a reasonable end point for prophylaxis trials. However the facts suggest these cannot be assumed.

In any case, the Cochrane Collaboration is dedicated to finding the best available evidence to enable patients and their clinicians to make best-informed decisions. To that end, ILI is what the vast majority of clinicians and their patients will be facing. Therefore this is an end-point of direct relevance to them, and we make no apology for including it.

8. Adverse events in prophylactic trials

Thanks for this detailed information. Further analyses are indeed what we would like to undertake according to our protocol.

9. Peer review

Thanks for offering a list of your own colleagues to act as peer reviewers. We adhere to the principle of ensuring there is methodological expertise as well as content expertise. Your list will be useful to consider when finding peer reviewers.

As you may be aware, because this particular Review Group (Acute Respiratory Infections) has its Co-ordinating Editor as an Author on this review, the handling of the manuscript is managed by the Central Editorial Unit to minimise any potential conflict of interest.

Contributors

Chris Del Mar, Tom Jefferson, Rokuro Hama, Mark Jones, Peter Doshi, Carl Heneghan, Matthew Thomson.

Feedback from Adam Jacobs, 13 February 2013**Summary**

Comment: The selection criteria in the review seem highly unusual. The authors describe a 2-stage process for including trials.

In the first stage, they require that the trial reports they analyse have "external consistency". As far as I can tell, this means that they must be able to verify the contents of the report from an external source.

This seems an extraordinarily high bar to set. I am not aware that it is part of standard Cochrane methodology. If it were applied across Cochrane reviews more generally, I imagine that very few Cochrane reviews would include any evidence at all, especially given that most Cochrane reviews are done perfectly happily with published papers, whereas this one had the advantage of clinical study reports, which are generally far more reliable and comprehensive than published papers.

It is almost as if the authors have gone out of their way to exclude the evidence, which does not help to answer important questions about the efficacy of neuraminidase inhibitors.

It is also noteworthy that no specific reasons were given for exclusion of studies from stage I of the process: we are only told that "insufficient information was available". In the interests of transparency, it would be better to know specifically what information was lacking.

May I suggest that the authors either explain the reason why they felt the need to use far stricter inclusion criteria than is normal in Cochrane reviews, or revisit their inclusion criteria so that the studies can be analysed.

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Adam Jacobs, Director, Dianthus Medical Limited

Reply

Adam Jacobs writes:

"The selection criteria in the review seem highly unusual. The authors describe a 2-stage process for including trials. In the first stage, they require that the trial reports they analyse have "external consistency". As far as I can tell, this means that they must be able to verify the contents of the report from an external source."

At page 11 of the review we provide the definition: "External consistency. Consistency of data as reported in regulatory documents, other versions of the same clinical study reports/unpublished reports and other references, to be established by cross-checking"

"This seems an extraordinarily high bar to set. I am not aware that it is part of standard Cochrane methodology. If it were applied across Cochrane reviews more generally, I imagine that very few Cochrane reviews would include any evidence at all, especially given that most Cochrane reviews are done perfectly happily with published papers, whereas this one had the advantage of clinical study reports, which are generally far more reliable and comprehensive than published papers".

And

"May I suggest that the authors either explain the reason why they felt the need to use far stricter inclusion criteria than is normal in Cochrane reviews, or revisit their inclusion criteria so that the studies can be analysed."

Our review is the first systematic review that we are aware of to be completely based on regulatory information. As our basic element of data synthesis was different, we had to develop new methods which we did transparently and are described in the review. It was a fact that we had received partial clinical study reports for the same trials from both Roche and EMA. We felt the need to ensure these reports were consistent. Whether our methods were an "extraordinarily high bar" or a reasonable bar or too low a bar is a judgement readers can make for themselves.

The background history which informed our methodology is explained in the review itself. At pages 4 and 5 of the review we write:

"In 2009, a reader posted a comment in response to the (then current) 2006 version of this review (Jefferson 2006). He pointed out that the review had endorsed the claim regarding a reduction in complications based on the uncritical inclusion of the Kaiser meta-analysis (Doshi 2009). The reader pointed out that only two of the 10 'Kaiser trials' had been published (Nicholson 2000; Treanor 2000) and the information provided by the Kaiser text about the remaining eight was insufficient for their appraisal. Our subsequent efforts to retrieve and review the eight unpublished trials (representing 2691 patients) were unsuccessful, raising the possibility that the findings of our previous review were not an accurate estimate of the benefits and safety of the drug. In addition, we found clear evidence of possible publication bias (see below) amid concern that some evaluations have not been available to scrutiny by the scientific community (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009)."

"This review is focused on healthy adults and children. It represents the amalgamation of two long-standing Cochrane reviews on the effects of NIs for influenza in healthy adults (Jefferson 2010a, also published as Jefferson 2009a) and children (Matheson 2007). The reviews were combined to pool our collective expertise and time in extracting and assessing data from clinical study reports, which in the case of some oseltamivir trials, report both adult and paediatric outcomes. Cochrane reviews of NIs in both children and adults generated intense interest from clinicians and media during the influenza outbreak declared a pandemic by the WHO in 2009. The Cochrane review of NIs in healthy adults highlighted the high risk of publication bias (Jefferson 2010a). In 2009, a reader posted a comment in response to the (then current) 2006 version of this review (Jefferson 2006). He pointed out that the review had endorsed the claim regarding a reduction in complications based on the uncritical inclusion of the Kaiser meta-analysis (Doshi 2009). The reader pointed out that only two of the 10 'Kaiser trials' had been published (Nicholson 2000; Treanor 2000) and the information provided by the Kaiser text about the remaining eight was insufficient for their appraisal. Our subsequent efforts to retrieve and review the eight unpublished trials (representing 2691 patients) were unsuccessful, raising the possibility that the findings of our previous review were not an accurate estimate of the benefits and safety of the drug. In addition, we found clear evidence of possible publication bias (see below) amid concern that some evaluations have not been available to scrutiny by the scientific community (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009).

Our attempts to reconcile published and unpublished evidence by contacting the manufacturer and study authors failed (the latter were unable to provide us with the necessary data; some were not in possession of the data and others may have been restricted by confidentiality agreements). Together with the *British Medical Journal* (BMJ) we ascertained that ghostwriters had been involved, which means the named authors may not have been in full control of the trial publications (Cohen 2009). We also identified several key differences in licensed indications for oseltamivir between regulatory systems (mainly between the US, Europe and Japan) and under-reporting of harms. The differences are detailed elsewhere (Doshi 2009) but of particular concern was the insistence of the FDA that oseltamivir has not been shown to reduce complications (FDA 2011a). The FDA has also not allowed an indication for interference of viral transmission within households (the key concept behind post-exposure prophylaxis). This undermined our confidence in published data and in the findings of our previous Cochrane reviews. In the background of all this were suggestions that NIs may not be as safe as previously assumed, with associations between oseltamivir use and neuropsychiatric adverse reactions of particular concern (Hama 2008)."

Adam Jacobs writes:

"It is almost as if the authors have gone out of their way to exclude the evidence, which does not help to answer important questions about the efficacy of neuraminidase inhibitors."

A page 5 of the review we write:

"During the preparation of the 2010 review and of the current review, we realised that there were multiple sources and different levels of granularity of clinical trial data (see 'The Scope of Clinical Trial Data' table in Jefferson 2011). We decided that clinical study reports and regulatory comments were likely to provide the least biased, most complete and most insightful set of data for our review".

And

"We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled phase III treatment trials of oseltamivir have never been published. This includes M76001, the biggest treatment trial ever undertaken on oseltamivir (with just over 1400 people of all ages). Exclusion of unpublished data changed our previous findings regarding oseltamivir's ability to reduce complications of influenza (Doshi 2009; Jefferson 2009a)."

Our attempts at identifying and retrieving all available evidence from regulators and manufacturers since 2009 are documented at <http://bmj.com/tamiflu>.

Adam Jacobs writes:

"It is also noteworthy that no specific reasons were given for exclusion of studies from stage I of the process: we are only told that "insufficient information was available". In the interests of transparency, it would be better to know specifically what information was lacking."

In Table 9 (page 186) we list all studies included in Stage 1 and report details of what data for each were available to us. For, example for trial MV22940 we know that it is likely to be a randomised trial assessing effects of oseltamivir on post exposure prophylaxis but no other data are available to us. In these circumstances we cannot proceed to assessment until the information is available, as explained in the text of the review. However these studies are not excluded but are marked as pending assessment.

We invite Adam Jacobs to read the review and the references which document the history of the review, background and rationale for withdrawing the original review and developing the current version. We also invite Mr Jacobs to clarify what business relation his firm has if any with Roche, GSK and BioCryst Ltd.

It is possible that future Cochrane reviews will include an increasing proportion of regulatory information to minimize the effects of reporting bias. This type of speculation is however beyond the scope of the review.

Contributors

Cochrane Neuraminidase Inhibitors Review Team, 5 March 2013

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Dr Matthew Thompson, Clinical Reader, Department of Primary Care Health Sciences, University of Oxford, UK

Feedback from Harri Hemilä, 6 May 2013

Summary

Comment: Oseltamivir (Tamiflu) shortens the duration of influenza-like illness by 13% (95% CI 8% to 18%)

In studies measuring dichotomous outcomes, relative risk (RR) is a standard measure for comparing study groups. The purpose of using RR is to adjust for baseline variability in the occurrence of disease. It is easier to compare two trials on the basis of their RR estimates than on the basis of their absolute effects.

The relative effect should also be calculated for continuous outcomes. Although the duration of disease may vary randomly in placebo groups, there are also biological reasons why diseases in different placebo groups differ in their severity and duration. For example, in Analysis 1.1 of this review, the duration of influenza-like illness in the placebo group of trial WV15671 is 35% shorter than in the placebo group of trial WV15819/WV15876/WV15978 ($Z = 6.5$; $P = <0.00001$; 125h/192h). Such very large baseline differences are not explained by chance. Differences in the study populations, influenza seasons, study protocols, etc. are plausible explanations for the baseline variation. The above-mentioned baseline difference is much greater than any of those between the oseltamivir (Tamiflu) and placebo groups in the five trials of Analysis 1.1. As for dichotomous outcomes, the baseline variability of continuous outcomes can be adjusted for by calculating the effect in percentages, i.e., the relative effect. Furthermore, the percentage effect is informative for an average reader because the reader may form an opinion on whether, for example, a 10% or 20% average decrease in the duration is worth the cost and effort of the treatment. Separate from the absolute effect in days, the percentage effect shows whether the effect is small or large.

Therefore the effect of oseltamivir should be calculated also as a percentage effect. I calculated the relative effects for the five trials listed in Analysis 1.1, pooled them using the fixed effect inverse variance method of RevMan, and found that the average effect of oseltamivir is a 13% (95% CI 8 to 18%) decrease in the duration of influenza-like illness.

Furthermore, the relative effect estimate makes it possible to compare the effects of treatments for related conditions. Influenza-like illness has substantial overlap with the common cold. In our Cochrane review on vitamin C and the common cold we calculated that ≥ 1 g/day of vitamin C shortens colds in adults by 8% (95% CI 4 to 12%) and in children by 18% (95% CI 9 to 27%) [1]. Another meta-analysis found that a high dose of zinc (>75 mg/day) as zinc acetate lozenges decreased the duration of colds by 42% (95% CI 35 to 48%) and as zinc lozenges made with other salts by 20% (95% CI 12 to 28%) [2]. The mechanism of the effect of vitamin C and zinc lozenges is not understood; however, there is no reason to assume that their effects are specific, for example, to the rhinovirus. If vitamin C and zinc lozenges have effects on diverse respiratory viruses, they might also have an effect on influenza viruses. In mice, influenza infection decreased vitamin C concentration in bronchoalveolar lavage fluid [3]. In mice, vitamin C deficiency increased lung pathology caused by influenza infection [4]. An early study with influenza patients reported that the occurrence of pneumonia was 80% lower (2 vs. 10 cases) in the vitamin C group, suggesting that vitamin C might also have an effect on influenza in humans [5,6]. If the effects of vitamin C and zinc lozenges on influenza-like illness are of the same magnitude as their effects on the common cold, then the effects of these treatments compare reasonably with oseltamivir. The comparison of the percentage effects of oseltamivir, vitamin C and zinc lozenges may be useful when considering how future research resources concerning the treatment of respiratory virus infections might be allocated. In this respect, the type of effect measure has a much wider importance than just its use in evaluating the effectiveness of oseltamivir as an issue of its own.

Thus the relative effect estimate adjusts for baseline variations between trials, it is informative for most readers because people are familiar with percentages, and it makes it easier to compare different treatments for related conditions. For these reasons I would like to encourage the authors to calculate and report the relative effect estimates for oseltamivir in the next revision of the review.

References

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- [2] Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review. Open Respir Med J 2011;5:51-8. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/>

[3] Buffinton GD, Christen S, Peterhans E, Stocker R. Oxidative stress in lungs of mice infected with influenza A virus. *Free Rad Res Commun* 1992;16:99-110 <http://www.ncbi.nlm.nih.gov/pubmed/1321077>, <http://dx.doi.org/10.3109/10715769209049163>

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[5] Kimbarowski JA, Mokrow NJ. Colored precipitation reaction of the urine according to Kimbarowski as an index of the effect of ascorbic acid during treatment of viral influenza [in German]. *Deutsche Gesundheitswesen* 1967;22:2413-8. <http://www.ncbi.nlm.nih.gov/pubmed/5614915>, Translation: <http://www.mv.helsinki.fi/home/hemila/T4.pdf>

[6] Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. *Cochrane Database Syst Rev* 2007;CD005532. <http://dx.doi.org/10.1002/14651858.CD005532.pub2>

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Harri Hemilä

Department of Public Health, University of Helsinki

Reply

Thank you for your suggestion and comprehensive argument why you think it is important. Indeed in our 2006 and 2009 updates of A047 (the previous review on antivirals for influenza in otherwise healthy adults), we pooled hazard ratios and reported relative effects for time to alleviation of symptoms. However GSK, the manufacturer of zanamivir, made the comment that hazard ratios may not be appropriate due to non-proportional hazards. Therefore for A159 we reported absolute treatment effects for time to alleviation of symptoms but not relative effects. We agree with your argument and will report absolute and relative effects for time to alleviation of symptoms and other outcomes in the next update of 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children' due at the end of 2013.

Contributors

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ

Review amendments, 16 May 2013

Summary

As reported in the current version of our review, we will complete the review of regulatory information which arrived after our original time lock. We will assess additional evidence from oseltamivir Module 2s, evidence on adverse events following exposure to neuraminidase inhibitors (NIs) and clinically relevant outcomes.

A rationale and description of our methods follows.

Evidence from Module 2s (Ms2) of oseltamivir trials

1. Summary and background

This part of the document will describe our efforts to determine whether the additional information included within Module 2s (Ms2) of clinical study reports (CSRs) would change the risk of bias assessment, identify additional useful or relevant information, and conclusions of the overall body of evidence contained within our existing review. A second aim is to construct and test a tool that could be used to extract, organise and appraise study information contained in such modules.

The items which are most commonly found in the M2 of the oseltamivir trials are: Certificates of Analysis (a report on the colour, composition and content of active and control substance capsules, blank Case Report Forms (case notes for each participant), follow-up cards/diary cards (on which each participant recorded information such as symptoms), informed consent text and participant contract (to be administered to and signed by each participant), lists of investigators in the trial, investigation review board, ethics committees and study sites' addresses, the Reporting Analysis Plan (Roche's term for the Statistical Analysis Plan or SAP detailing the types of data analyses to be carried out), randomisation list (used to allocate participants and the study Protocol with its amendments when appropriate or available).

1.2 Methods

We received 12 CSR Ms2 from 31 studies requested from EMA by July 2011. Before we reviewed Ms2 we knew they contained protocols, with their amendments, certificate of analyses, blank case report forms, randomisation and participating centres' lists. However, we had no precise idea whether this was a comprehensive list or whether further items would be identified once we started reviewing. We also noted that the same info was reported elsewhere in the CSRs (for example in the core report) but in a different level of detail. A good example of

this is the statistical analysis section of the core report which is a few pages long chapter, compared to the Statistical Analysis Plan (SAP), which is a self contained document included in M2. In addition we were not aware of the existence of any readily available tool to allow us to extract, organise and appraise the information contained in the Ms2.

As consequence we decided to develop our own tool. Our plan is to do this by identifying the types of items contained in the Ms2 available to us and their location in the Ms2. The outline content of all items identified will be checked in the Ms2 because of the potential for differing titles for the same item. For example we have already noticed that Research Analysis Plan (RAP) is sometimes called Data Analysis Plan (DAP) or Statistical Analysis Plan (SAP). Another example are the Protocol Amendment Histories and Protocol Modification History Document. These represented different ways of identifying the same item and need to be given a single identifier. Items such as Data Reporting and Analysis Manual (DRAM) are only cited in one M2. We will also conduct a pilot to identify with certainty which items are present more frequently. We will make a list of what we thought were most present and important items contained in the Ms2 and create a grid based on the sequence of development of the trial design and analysis plan. For example, we want to track whether the reporting of the trial study design in the relevant section of the protocol and its amendments (in M2) is consistent with that described in the core report (in M1). We will also make an initial extraction frame to reconstruct the timeline of the study documents, summarising the number of protocol changes and their dates in sequence. This has the purpose of giving an overview of the main timeline points of the key items of study design and analysis.

We will then pilot our extraction sheet and make changes following discussion with all authors. We will extract the data in the same groups we worked in the original review.

We will define the impact of adding M2 information by measuring the change in risk of bias (ROB) assessment in our review as well as reporting our summary description and appraisal of each trial before and after addition of the data and comparing it with the manufacturer's assessment.

The detailed questions addressed by our analysis are:

1. Does addition of M2 to M1 change the risk of bias evaluation compared to M1 alone?
2. Does reading M2 and M1 in CSRs change the risk of bias evaluation compared to using published papers?
3. Is the current risk of bias tool adequate for assessing trials based on reading M2 then M1 in the CSRs?
4. Does reading M2 and M1 in the CSRs identify additional useful relevant information for systematically reviewing a trial programme?

We will primarily use descriptive methods to answer the questions. To answer question 1 we will compare the risk of bias in our 2012 review with risk identified after addition of M2 information to our current review using a 3 by 3 contingency table. We will repeat this procedure to answer question 2, by comparing risk of bias in our 2009 *BMJ* review to our current assessment. This analysis will be based on the subset of trials that were published and included in our 2009 review.

To answer question 3 we will list all the components of other risk of bias in the current review and compared these with previous reviews (2012 and 2009).

To answer the final question we will provide a summary of the items that were identified in our assessment of the trials using the new M2 tool. This will allow us to summarise discrepancies between what was planned in the protocol, what was carried out (RAP, protocol amendments), what was reported in M1, and what was reported in the published papers. The focus would be on the trial programme of research i.e. issues that appeared consistently over the trials.

Adverse events

2. Summary and background

This document outlines how we will conduct the analysis of adverse events as part of the wider Cochrane review of neuraminidase inhibitors (NIs) for prophylaxis and treatment of influenza in healthy adults and children (A159).

We use the term 'adverse events' throughout this document rather than harms or adverse reactions as these latter terms imply causality which may or may not be appropriate.

In keeping with the methods of our previous review we will not use data from journal publications for this proposed analysis. We now have access to multiple clinical study reports (CSRs) for both oseltamivir and zanamivir. To our knowledge this is the first time some of these data have been available outside manufacturers and regulators, and allows for the exploration of events in more detail than is possible using the limited information on safety reported in journal publications. This potentially allows us to address some of the concerns that have arisen in the post marketing period about the possible relationship between neuraminidase inhibitors, oseltamivir in particular, and neuropsychiatric and other harms. The documents available to us contain listings and summaries of adverse events recorded in the trials including narrative summaries of serious adverse events and adverse events leading to study withdrawal.

The adverse events are classified by relationship to the study drug and also, by intensity (mild, moderate, severe, life-threatening and death). The duration of events is reported and they are also lumped into body systems such as gastrointestinal, neurological, etc.

2.1 Methods

All CSRs of oseltamivir and zanamivir will be included in our analysis. CSRs for prophylaxis, for treatment of adults and for treatment of children will be analysed separately. Adverse events will be initially descriptively compared over the entire treatment and follow-up period but then potentially stratified by on-treatment and off-treatment periods if it appears there may be a difference between treatment groups.

2.2 Adverse events for comparison

2.2.1 Common events

For common events of any intensity with an overall incidence of 2% or more we will compare the incidence between treatment groups. The cut-off of 2% is based on a power analysis where assuming 4000 patients in total (this is approximately how many patients we have access to in oseltamivir treatment trials of adults as well as in oseltamivir prophylaxis trials of adults), we will have 80% power to detect an odds ratio of 1.75 with 5% level of significance.

2.2.2 Uncommon events

Due to a lack of data to compare uncommon events we will compare events lumped into body systems between treatment groups. If we find evidence of a difference in incidences between groups lumped into a body system we will conduct further analysis if appropriate. This further analysis is to determine whether the difference in incidence is due to any common events included in that body system. For example, in the case of neurological body system, if we found evidence of a difference between treatment groups we would remove all common neurological events such as headaches and repeat the analysis.

2.3 Severe, serious events and events leading to study withdrawal

As well as the analysis described in section 2.2 above we will also conduct a subgroup analysis of just the events with severe intensity, serious events and events leading to study withdrawal. We will use the same definitions of "severe" and "serious" as specified in the CSRs. However we will check the classifications using all the information available in the CSRs including line listings of events, narratives provided for serious events and also for events leading to study withdrawal. Any disagreements with the original classifications will be recorded and any reclassifications will be assessed in a sensitivity analysis. Given it is unlikely there will be sufficient events to conduct separate statistical analysis at the level of body system we will compare the overall distribution of events by body system between treatment groups.

2.4 Incidence of adverse events in the CSRs

As a further check on the validity of the data on adverse events contained in the CSRs we will conduct descriptive comparisons of the incidence of adverse events in the prophylaxis and treatment trials.

This is because of the unclear methods of collecting and classifying adverse events in the trials. A potential adverse event could have been classified as a symptom of influenza, an efficacy outcome (such as complication of influenza) or an adverse event. Hence an informal comparison of the incidence of adverse events in the trials where participants had influenza (or influenza-like-illness) and the trials where participants did not have influenza may help show where adverse events could have been under-reported. We will take into account factors such as age of participants and duration of treatment exposure for these informal analyses. In addition if it is clear that an adverse event was not reported as an adverse event but was included elsewhere in the CSR (e.g. in the efficacy section), we will include that data in our adverse event analyses.

We will also construct a table showing the definitions specified in each CSR for classifying potential adverse events as adverse events, complications or symptoms of influenza.

2.5 Antibody titre

We have already reported that antibody production was lower in the oseltamivir group than in the placebo group in the systematic review of treatment trials of oseltamivir (2012). We will update this analysis by including additional oseltamivir trials as well as assess antibody production in the zanamivir trials.

We will assess antibody production in the prophylaxis trials of oseltamivir and zanamivir by the following methods.

We will first identify the participants who had influenza-like illness (ILI) or pyrexia. If the proportion is similar between active group and placebo group, the proportion of participants who had four times or higher increase of antibody will be compared between groups.

2.6 Dose-response analysis

A number of trials included two or more active treatment arms with different doses of study medication given to participants in each of the arms. For these trials we will investigate the dose-response relationship for common adverse events (as defined above).

2.7. Details of analysis

Initial analysis will be descriptive only where we will report the numbers and percentages of events by treatment group. If there is a potential difference in the pooled percentages between treatment groups (e.g. if there is more than a two standard error difference between percentages) then we will conduct formal meta-analysis. If indicated we may also conduct additional analyses taking into account event intensity and/or duration.

2.8 Limitation and exploratory analysis

The methods presented above are those that we have pre-specified prior to formal analysis of the data. A limitation of these methods is that we may fail to detect differences in rare adverse events because these events will be compared along with other types of events within body systems. Therefore in the process of conducting our formal analysis we may generate further hypotheses or conduct additional exploratory analyses. If this is the case then we will clearly label these analyses as exploratory and interpret the findings accordingly.

Types of outcome measures

3. Background

For most people, influenza is a self limiting illness. However the disease can at times lead to serious complications such as pneumonia and hospitalisations, and if treatment with neuraminidase inhibitors can reduce the risk of severe outcomes, this would be an important public health benefit. Another potentially important public health benefit would be the ability of antivirals to interrupt person to person transmission of influenza. Current evidence for these outcomes is scarce or inconclusive. A positive balance of effects on complications and viral spread versus harm profile is the main reason for using NIs in a public health context, especially the orally administered oseltamivir.

All analysis will be based on the intention-to-treat (ITT) or safety populations as our prior review discovered compelling evidence that the ITTI (the subpopulation deemed to be influenza-infected) populations were not balanced between treatment groups in the Roche oseltamivir trials. In addition, estimates from the ITT population will be more generalisable to clinical practice where routine testing for influenza is not common in many countries (and even where used, remains of variable accuracy). Analysis will be conducted separately for prophylaxis trials, treatment trials of adults and treatment trials of children.

The list of outcomes given below includes all potential outcomes that we believe are clinically important. However a number of them may not be formally comparable in this review because there are insufficient numbers of events (e.g. mortality) or they were not adequately measured or reported (e.g. drug resistance).

3.1 Outcome measures for treatment studies

Complications~
Harms*
Symptom relief
Hospitalisation
Viral excretion
Drug resistance
Mortality

3.2 Outcome measures for prophylaxis studies

Influenza-like-illness^
Complications~
Harms*
Hospitalisation
Viral excretion
Drug resistance
Mortality

~Complications (secondary illnesses) include pneumonia, bronchitis, otitis media, sinusitis or other respiratory tract infection after influenza-like illness. Initially we will construct a table to illustrate the design methodology used for each study. The table will include the following variables:

Study/trial ID
Where complications are first defined in the CSR (e.g. "as secondary endpoint in 3rd version of protocol six months into trial and two months prior to trial unblinding")
Definition of "complication" including types of events, population and time period at risk
How complications were measured (see diagnosis methods criteria shown below)
Availability of complications data for the ITT population

We will then stratify our analysis by method of diagnosis with three possible criteria:

- a. Lab-confirmed diagnosis (e.g. based on radiological or microbiologically confirmed evidence of infection).
- b. Clinical diagnosis without laboratory confirmation (diagnosed by a doctor after a clinical examination).
- c. Other type of diagnosis such as self-reported by patient

*A separate section provides the details of our proposed analysis of harms.

^The main outcome of interest is any symptomatic influenza-like-illness (ILI). However, we will also conduct separate analyses of influenza (symptomatic and asymptomatic) and non-influenza ILI.

Reply

TJ

Contributors

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ

Feedback from Peter Gross, Hackensack University Medical Center, USA, 17 April 2014

Summary

Can Cochrane compare their results on influenza neuraminidase inhibitors with the reduction in symptoms when penicillin is given for strep throat? I think they may be comparable. That would be an important perspective.

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Dear Dr Gross, the Cochrane Collaboration and specifically our ARI Group could certainly design a review looking at the comparative evidence of the effects of neuraminidase inhibitors versus penicillin for sore throat. Both reviews are in the ARI Group's Module, so it would have to be an indirect comparison review. I am not sure there are any of those in the Cochrane Database of Systematic Reviews, but there's always a first time for everything as our regulatory evidence review shows.

It would have to be a new review, with a new protocol, perhaps with new authors.
Would you be interested?

All the clinical study reports for the two neuraminidase inhibitors we looked at are at: <http://dx.doi.org/10.5061/dryad.77471> and a short introduction at: blog post <http://blog.datadryad.org/2014/04/17/tamiflu-data/>

With best wishes,
Tom Jefferson on behalf of the authors

Contributors

Peter Gross

Roche feedback on 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children', 16 October 2014

Summary

<https://editorial-unit.cochrane.org/cochrane-review-neuraminidase-inhibitors-influenza>

Reply

We have received feedback from Roche and the full document is accessible via the above link, hosted on the Cochrane Editorial Unit's (CEU) website. The review authors submitted their reply to the Roche feedback on 23 March 2015, and this has been posted on the CEU website.

Contributors

Submitted by Barry Clinch,¹ James Smith,² Andy Kenwright,¹ Bernadette Surujbally,³ Joanne Harding¹

¹Roche Products Ltd, Welwyn Garden City, UK; ²F. Hoffmann La-Roche Ltd, Basel, Switzerland; ³BStats Solutions Ltd, Hertfordshire, UK

Feedback from Ryuko Hatano, 28 August 2017

Summary

Dear Sir/Madam: Greetings from Japan.

We are members of the Association of Victims of Tamiflu-related Encephalopathy, a group of victims whose children or other family members had serious reactions after taking Tamiflu, including sudden death, accidental death due to abnormal behaviours, and serious sequelae with disability. In this letter, we would like to respectfully request your group to establish the causality between Tamiflu and abnormal behaviours, sudden death or sequelae.

We have learnt that the WHO's essential medicines list was amended and Tamiflu was moved from the core to the complementary list, and that its use be restricted to severe illness due to confirmed or suspected influenza virus infection in critically ill hospitalized patients. Moreover, the next Expert Committee might consider Tamiflu for deletion, unless new information supporting the use in seasonal and pandemic outbreaks is provided.

We understand that the systematic review your group issued in April 2014 and the opinion you submitted to the WHO have served as the major evidence that promoted the amendment and future possible deletion of Tamiflu from the essential medicines model list. We, all the members of the Association of Victims, deeply appreciate you for conducting such an important systematic review which influenced the policy of WHO.

We know the outline of the results of your systematic review because Dr. Rokuro Hama, a Japanese doctor who is one of the members of the Cochrane team translated some important parts of the review into Japanese and uploaded it on his website: <http://www.npojip.org/sokuho/140410.html>

According to the translation, the results of the systematic review is summarized as follows:

- 1) Tamiflu reduced the time to first alleviation of symptoms in adults by 0.7 day (from 7 to 6.3 days). There was no effect in asthmatic children who are the real target of efficacy, although healthy children of Tamiflu group alleviate symptoms one day earlier than placebo group.
- 2) Tamiflu reduced the production of antibody against influenza.
- 3) Tamiflu did not decrease hospitalization.
- 4) There was no evidence that Tamiflu reduce influenza like illness.
- 5) Tamiflu induced harmful effects such as nausea, vomiting, headache, neurologic symptoms, kidney disorders, diabetic/hyperglycemia and pain in extremities. Zanamivir had no such adverse effects.
- 6) In particular, neuro-psychiatric symptoms were significantly more reported in Tamiflu group than in the placebo group in the prophylaxis trials. Dose-response relationship was also seen in the treatment trials.

"Abnormal behaviour" has been listed as one of the adverse reactions to Tamiflu in the Japanese label of Tamiflu since 2004. Hence, we believe that the accidental deaths due to abnormal behaviours after using Tamiflu should be recognized as death cases caused by side effects of Tamiflu, and that they should be relieved by the government. We submitted the applications for damage relief to the Pharmaceuticals and Medical Devices Agency (PMDA), but they rejected them, stating that "there is no association with Tamiflu use".

We also believe that the sudden deaths during sleep may be the consequences of side effects of Tamiflu because animals died suddenly after the administration of Tamiflu in animal experiments. Therefore, we applied damage relief for the sudden death cases as well, but PMDA rejected them with the same reason.

We, 14 families filed cases against PMDA to cancel the decision. Three families (one sudden death and two accidental deaths after abnormal behavior) lost the cases at the Supreme Court. The court accepted the claim of PMDA: the causes of both sudden death and accidental death due to abnormal behaviors were caused by influenza related encephalopathy and not by Tamiflu use because Tamiflu has no effect on brain and there is no evidence suggesting causality in animal, clinical and epidemiologic studies.

However, sensory function, cognitive function and consciousness of rats are disturbed and the mortality of rats from sudden death rises as the doses of Tamiflu increases as shown in the review article on the mechanisms of sudden-onset type of reactions to Tamiflu (Hama et al. 2016). High dose of Tamiflu stops animals' respiration, followed by cardiac arrest (Kimura and Haji et al. 2013). It induces low body temperature (Ono et al. 2013).

There are some epidemiologic studies which suggest association between Tamiflu use and delirium or unconsciousness (Fujita et al. 2010). There is also an epidemiologic study in which sudden deteriorations leading to death within 12 hours after Tamiflu use were far more frequently reported than after Relenza use (Hama et al. 2011). All these findings suggest close association, but the judges neglected them and concluded that there was "no causal association" based solely on the claims of PMDA.

We ourselves witnessed extremely abnormal course of dying or developing sequelae in our precious children or other family members. Based on these experiences we are convinced that there is no cause for these events other than Tamiflu. However, we are merely lay people, and we have no scientific means to prove it by ourselves. If your group could establish the causality between Tamiflu and abnormal behaviours, sudden death or sequelae, it would be greatly appreciated. If needed, all the members of our group are willing to provide any information about our family cases.

Thank you very much for your understanding and kind assistance in advance.

Yours sincerely,

All members of the Association of Victims of Tamiflu-related Encephalopathy

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment

Ms. Ryuko Hatano

Affiliation: The Association of Victims of Tamiflu -related Encephalopathy

Role: Representative

Reply

Dear Ms Hatano,

Thank you for your query. We sympathize with your position. However, unfortunately we do not have enough information to respond to your specific request to “establish the causality between Tamiflu and abnormal behaviours, sudden death or sequelae.” The following explains why we cannot address your specific requests, and offers some thoughts on possibly relevant information that we can speak to based on our Cochrane Review.

Our systematic Review published in 2014 did not conduct a statistical test on every type of adverse event that was recorded in the clinical trials that we studied. Doing so may have led to false positives and false negative as well, undermining the reliability of any associations that we might have otherwise been able to detect. Therefore, as we write in the Review, our approach was to meta-analyse “(1) all serious adverse events; (2) all adverse events leading to study withdrawal; (3) all withdrawals; (4) all adverse events within a clinical study report’s defined body system; as well as (5) a small group of common adverse events as defined in the FDA drug label for oseltamivir.” (p.7).

Importantly, “There were too few events to meta-analyse (1) deaths; (2) serious adverse events by body system; and (3) any events that had an overall incidence of less than 0.5%. We did not meta-analyse outcomes with fewer than 10 events in total” (p.7).

“Abnormal behaviours”, “sudden death” or “sequelae” per se did not have an overall incidence of greater than 0.5%, and therefore we did not conduct statistical tests on them.

Our Review however, did conduct statistical tests and make causal inferences regarding other adverse events that may be possibly relevant to your concerns.

We wrote, with respect to oseltamivir being used for the prevention of influenza, that “oseltamivir caused headaches and psychiatric harms in adult prophylaxis trials” (p.38).

The degree to which the risk of psychiatric harms is increased is somewhere between 1 additional psychiatric adverse event for every 36 to 1538 persons that received oseltamivir for the prevention of influenza (p.3).

While our Review “failed to identify a clear association between oseltamivir and psychiatric harms” (p.38) in clinical trials in which oseltamivir was being used for the treatment of influenza, this does not rule out the possibility that a causal relationship exists. It only states that we did not detect one. We wrote: “The question of why oseltamivir treatment trials failed to identify a clear association between oseltamivir and psychiatric harms, although a weak dose-dependent association was observed, is a moot point. It is possible that influenza-like illness and influenza symptoms masked the harms in those who were already symptomatic and therefore recruited in the treatment trials (and influenza-type symptoms were excluded as adverse events to be reported). The reporting issue of compliharms may have helped to mask such events. Alternatively, it could be that these events are rare in the populations studied and that there was insufficient power to detect an association. The CI [confidence interval] was wide (0.43 to 2.03) and does not rule out a doubling in risk due to treatment - as was found in the prophylaxis trials. It is also possible that the risk of psychiatric harm increases with increasing dose (as the data from trials WV15670 and WV15671 suggest) and increasing duration of treatment (as the prophylaxis trials suggest)” (p.38).

In our Review, we discuss other studies, including three prospective cohort studies in Japan, that you may wish to review (p.38), although we did not formally analyze these studies in our systematic review. A careful analysis of these studies, and other studies we did not mention in this reply, would be required to answer your question about the causal link between Tamiflu and deaths.

We hope the above is helpful in responding to your query.

Regards

Contributors

(in alphabetical order)

Chris Del Mar

Peter Doshi

Rokuro Hama

Carl Heneghan

Jeremy Howick

Mark Jones

Kamal Mahtani

David Nunan
Igho Onakpoya
Elizabeth Spencer
Matthew Thompson

Feedback from Noritoshi Tanida, 14 September 2017

Summary

Dear authors of the Cochrane Acute Respiratory Infections Group, Neuraminidase Inhibitor Review Team.

I have learnt that the Association of Victims of Tamiflu-related Encephalopathy requested the Cochrane team to establish causality between Tamiflu and abnormal/psychiatric behaviours, sudden death or serious sequelae.

I know the victim's serious situations; the applications for damage relief to the Pharmaceuticals and Medical Devices Agency (PMDA) were turned down and they lost cases in law courts either. Both PMDA and law courts took the same position, saying "there was no serious side effects in Tamiflu."

Here, the importance of causality establishment is evident as to respond to the request by the victims' group. I remember that Cochrane collaboration started upon responding lay peoples' query. Hence, I also request the Cochrane team to focus on this issue and to establish causality between Tamiflu and abnormal/psychiatric behaviours, sudden death or sequelae.

In revising the systematic review report considering the establishment of causality between Tamiflu and serious side effects, I hope that the Cochrane Acute Respiratory Infections Group, Neuraminidase Inhibitor Review Team will formally include analyses on events of "injury and poisoning" especially "injury" with Tamiflu treatment.

I believe that all criteria for causal inference by Hill/US surgeon General are satisfied for both abnormal behaviour and sudden death.

I thank you in advance.
Sincerely Yours,

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment

Noritoshi Tanida (MD, PhD, DTM&H)

Affiliation: Former Professor of Department of Medical Humanities, School of Medicine, Yamaguchi University, Japan.

Reply

Dear Professor Tanida,

Thank you for your query. We received a similar request from Ms. Ryuko Hatano on Aug 28, 2017, regarding "abnormal behaviours, sudden death or sequelae."

As we explain in our response to that query, these events per se did not occur at a frequency greater than 0.5% and therefore we did not meta-analyze it. The same is true of "injury and poisoning." This also did not occur at a frequency greater than 0.5% and therefore we did not meta-analyze it.

Please see our response to her query for more information on our methods and findings.

Regards

Contributors

(in alphabetical order)

Chris Del Mar
Peter Doshi
Carl Heneghan
Jeremy Howick
Mark Jones
Kamal Mahtani
David Nunan
Igho Onakpoya
Elizabeth Spencer
Matthew Thompson

WHAT'S NEW

Date	Event	Description
4 January 2018	Amended	Removed Rokuro Hama's name from the Feedback reply to Nori-toshi Tanida's comment, as it had been included by mistake.

HISTORY

Protocol first published: Issue 1, 2011

Review first published: Issue 1, 2012

Date	Event	Description
20 December 2017	Feedback has been incorporated	Two feedback comments and replies have been added to the re-view.
27 March 2015	Feedback has been incorporated	The authors' response has been posted on the CEU website https://editorial-unit.cochrane.org/cochrane-review-neu-raminidase-inhibitors-influenza
14 January 2015	Amended	We removed 'healthy' from the review title because the adjective 'healthy' incorrectly describes the review's population. Several included trials are in people with chronic respiratory problems and those in a general population have participants with pre-ex-isting pathologies as well as healthy people.
1 December 2014	Feedback has been incorporated	Link to Feedback incorporated.
29 July 2014	Feedback has been incorporated	Feedback comment and reply added.
22 July 2013	New search has been performed	Searches updated. We received the last clinical study report in September 2013. Since the first publication of this review in Jan-uary 2012, we have completed the review of regulatory informa-tion that became available after our original time lock. We have assessed additional evidence from oseltamivir Module 2, evi-dence on adverse events following exposure to neuraminidase inhibitors and clinically relevant outcomes, and cross-referenced this with the individual listings contained in Modules 3 to 5. We now hold all the relevant full clinical study reports, which we are making publicly accessible with this review.
22 July 2013	New citation required and conclusions have changed	In this update we found further evidence that the mode of action of oseltamivir is likely to be centrally mediated. We then carried out a toxicity assessment and found that oseltamivir has mul-ti-system toxicity (renal, neurological, psychiatric, metabolic, gastrointestinal and immune system). The effects of both drugs are modest. Evidence of oseltamivir toxicity is reasonably firm. Zanamivir toxicity is low. Neither drug should be used routinely. The beneficial effects on influenza viruses are slight or difficult to identify.
15 May 2013	Amended	Amendments to data analyses from oseltamivir trials Module 2; clinical outcomes and adverse events added in the 'Feedback' section and 'Published notes' sections

Date	Event	Description
14 May 2013	Feedback has been incorporated	Feedback comment and reply added to the review
8 March 2013	Feedback has been incorporated	Feedback and reply added to the review
28 January 2013	Amended	New feedback comment and reply posted
7 September 2012	Amended	Conflict of interest statement updated for a feedback submitter
9 February 2012	Feedback has been incorporated	Feedback comments added to review
4 May 2011	Feedback has been incorporated	Feedback from three contributors has been added to the review

CONTRIBUTIONS OF AUTHORS

TJ, PD, CDM, MT, MJ and CH were authors of the separate relevant Cochrane reviews. The protocol for the **2012** review was written by TJ, PD and CDM. All authors contributed to the writing of this protocol and devised the approach strategies to the data sources. CH provided logistical support. For the 2012 review, all authors reconstructed clinical trials using the CONSORT statement-based extraction template, TJ reviewed regulatory material and TJ, MJ, CH, RH and CDM applied the inclusion criteria. CDM supervised the process and arbitrated when necessary. MJ carried out the statistical analyses. RH reviewed the Japanese data together with MJ and PD. TJ reviewed the FDA files. CDM and MT screened the electronic searches. TJ prepared the final text and all authors contributed to the final draft. Toby Lasserson contributed editorial support.

For the **2014** review TJ, PD, CDM, MT, RH, MJ and CH amended the protocol. TJ and PD applied the inclusion criteria to the oseltamivir clinical study reports. CH and IO applied the inclusion criteria to the zanamivir clinical study reports. MJ supervised the process and arbitrated when necessary. MJ carried out the statistical analyses. RH reviewed the Japanese data together with MJ and PD. TJ, PD, CH, IO, ES, DN and JH extracted the clinical study reports. CDM and MT screened the electronic search updates. TJ prepared the final text and all authors contributed to the final draft.

DECLARATIONS OF INTEREST

All review authors have applied for and received competitive research grants. TJ, PD, CDM, MT, RH, MJ and CH are co-recipients of the NIHR grant to carry out this review (<http://www.nets.nihr.ac.uk/projects/hta/108001>). In addition:

Prof Jefferson receives royalties from his books published by Blackwell and Il Pensiero Scientifico Editore, Rome. Dr Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 pharmaceutical products. In 2011-2013 Dr Jefferson acted as an expert witness in a litigation case related to oseltamivir phosphate; Tamiflu [Roche] and in a labour case on influenza vaccines in healthcare workers in Canada. In 1997-99 Dr Jefferson acted as consultant for Roche, in 2001-2 for GSK and in 2003 for Sanofi-Synthelabo for pleconaril (an anti-rhinoviral which did not get approval from FDA). Dr Jefferson is a consultant for IMS Health.

Dr Doshi received EUR 1500 from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir.

Prof Del Mar was a Board member of two companies to commercialise research at Bond University, part of his responsibilities as Pro-Vice Chancellor (Research) until 2010, receives fees for editorial and guideline developmental work and royalties from books, and is in receipt of institutional grants from NHMRC (Aus), NIHR (UK) and HTA (UK) and from a private donor (for support of the editorial base of the Cochrane ARI Group).

Dr Hama receives royalties from two books published in 2008 titled "Tamiflu: harmful as was afraid" and "In order to escape from drug-induced encephalopathy". Dr Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir and gefitinib.

Dr Howick has received expenses and payments from Johns Hopkins and the American Society for Neurophysiological Monitoring as an EBM consultant. Dr Howick has received funding from the Wellcome Trust, the Medical Research Council of the UK, the Economics and Social Science Research Council of the UK and he is currently a National Institute for Health Research non-clinical research fellow. He has received payment from the Canadian Medical Association Journal for writing a book review and receives royalties from the publication of his book from Blackwell/Wiley.

Dr Heneghan receives payment for running educational courses at the University of Oxford and University of Oxford ISIS consulting services for external teaching and training. He also receives royalties for books (Evidence Based Toolkit series by Blackwell BMJ Books).

Dr Onakpoya has no additional interests to disclose.
Dr Thompson has no additional interests to disclose.
Dr Jones has no additional interests to disclose.
Dr Spencer has no additional interests to disclose.
Dr Nunan has no additional interests to disclose.
Dr Mahtani has no additional interests to disclose.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

The review has been prepared with support from a NIHR (UK) grant 10/80/01

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have made a number of changes to the text of A159 during the process of turning the protocol into the review. This reflects our evolving understanding of the issues, during the relatively long period when work on the review was underway.

We have changed the review title to reflect the nature of the evidence. The old title was: *Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports*.

We have also re-written the objective twice, tightening up the text to bring it in line with our initial intentions and clarifying its meaning. The old objectives were: "To review clinical study reports (CSRs) identified from published and unpublished randomised controlled trials (RCTs) and relevant regulatory data on effectiveness and harms of NIs for influenza in all age groups" and "To review published and unpublished clinical study reports and other relevant regulatory data on effectiveness and harms of NIs for influenza in all age groups (and compare them with our published review)."

We changed the emphasis of the objectives on unpublished study reports as we had decided from the start to concentrate on regulatory information. Similarly, comparison of published versus unpublished data is an important and worthwhile effort, but the original objective possibly misled readers as to its importance in our work. We had always conceptualised it as a low-priority task we could carry out only if we had time following our review of unpublished data. We have also avoided using acronyms, which we thought cumbersome and confusing to the reader.

Our initial intention was to review clinical study reports and regulatory comments making up what we have subsequently called 'regulatory information'. The edits do not reflect a change in intent but our slowly evolving understanding of the problems we faced and our solutions to address these problems. As one of many examples, the transition from a world in which studies were identified by names and years (Nicholson 2000), to one in which the same trial is identified by a series of letters and numbers (WV15670), was not easy.

While the review was underway, we identified several unforeseen issues, such as placebo content and the effect of oseltamivir on antibodies. To test the relevant hypotheses we carried out post-protocol analyses, which had not been present in the original protocol but were derived from our protocol-stated intention to assess programmes and not single trials. These are now reported in their entirety in [Appendix 10](#).

In May 2013, we added amendments to the review for: data analyses from oseltamivir trials Module 2s, clinical outcomes and adverse events added in the [Feedback](#) section. In the text we explain the rationale and methods applying to regulatory information received after our 2011 time lock, which could not be implemented in time for the current review (see also [Appendix 2](#)). For the 16 May 2013 amendments see [Feedback](#).

NOTES

Since the January 2012 version of A159, we have now completed the review of regulatory information which became available after our original time lock. We have assessed additional evidence from oseltamivir Module 2s, evidence on adverse events following exposure to NIs and clinically relevant outcomes, and cross-referenced this with individual listings contained in Modules 3 to 5. We now hold all the relevant full clinical study reports, which we are making publicly accessible with this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [adverse effects] [*therapeutic use]; Drug Evaluation; Enzyme Inhibitors [adverse effects] [*therapeutic use]; Europe; Health Status; Influenza, Human [*drug therapy] [*prevention & control]; Japan; Legislation, Drug; Neuraminidase [*antagonists & inhibitors]; Oseltamivir [adverse effects] [*therapeutic use]; Pneumonia [prevention & control]; Publication Bias; Randomized Controlled Trials as Topic; United Kingdom; United States; Zanamivir [adverse effects] [*therapeutic use]

MeSH check words

Adult; Child; Humans



Published in final edited form as:

Lancet Respir Med. 2014 May ; 2(5): 395–404. doi:10.1016/S2213-2600(14)70041-4.

Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data

A full list of authors and affiliations appears at the end of the article.

Summary

Background—Neuraminidase inhibitors were widely used during the 2009–10 influenza A H1N1 pandemic, but evidence for their effectiveness in reducing mortality is uncertain. We did a meta-analysis of individual participant data to investigate the association between use of neuraminidase inhibitors and mortality in patients admitted to hospital with pandemic influenza A H1N1pdm09 virus infection.

Methods—We assembled data for patients (all ages) admitted to hospital worldwide with laboratory confirmed or clinically diagnosed pandemic influenza A H1N1pdm09 virus infection. We identified potential data contributors from an earlier systematic review of reported studies addressing the same research question. In our systematic review, eligible studies were done between March 1, 2009 (Mexico), or April 1, 2009 (rest of the world), until the WHO declaration of the end of the pandemic (Aug 10, 2010); however, we continued to receive data up to March 14, 2011, from ongoing studies. We did a meta-analysis of individual participant data to assess the association between neuraminidase inhibitor treatment and mortality (primary outcome), adjusting for both treatment propensity and potential confounders, using generalised linear mixed

Correspondence to: Prof Jonathan Nguyen-Van-Tam, Clinical Sciences Building, University of Nottingham, City Hospital, Nottingham NG5 1PB, UK, jvt@nottingham.ac.uk.

Contributors

JSN-V-T, PRM, SGM, SV, and JL-B conceived and designed the study. All authors, apart from SGM, SV, and JL-B, contributed to acquisition and local preparation of constituent datasets. SGM, SV, PRM, and JL-B contributed to dataset amalgamation and standardisation, design of statistical analyses, and data analysis. JSN-V-T, PRM, SGM, SV, and JL-B interpreted the data and wrote the paper. All authors contributed to critical examination of the paper for important intellectual content and approval of the final report. Each author acts as the guarantor of data from their individual study centre; JSN-V-T and PRM act as overall guarantors for the pooled analysis and the report.

*Joint first-authors

†Names listed at end of paper; affiliations in appendix

Declaration of interests

Between October, 2007, and September, 2010, JSN-V-T did ad-hoc paid consultancy and lecturing for several influenza vaccine manufacturers (Sanofi Pasteur MSD, Sanofi Pasteur, GlaxoSmithKline, Baxter AG, Solvay, Novartis) and manufacturers of neuraminidase inhibitors (F Hoffmann-La Roche: oseltamivir [Tamiflu] and GlaxoSmithKline: zanamivir [Relenza]). He is a former employee of SmithKline Beecham (now part of GlaxoSmithKline), Roche Products (UK), and Sanofi Pasteur MSD, all before 2005. He has no outstanding interests related to shares, share options, or accrued pension rights in any of these companies. He is in receipt of current or recent research funding, related to influenza vaccination from GlaxoSmithKline and AstraZeneca and non-financial support (travel) from Baxter AG. His brother became an employee of GlaxoSmithKline in January, 2014. JL-B is Statistical Editor of the Cochrane Skin Group. PRM is the recipient of the unrestricted educational grant for research in the area of pandemic influenza from F Hoffman-La Roche, used to fund this work. She has also received travel grants from F Hoffman-La Roche and its subsidiaries to attend clinical seminars to present this work. RB has received financial support from CSL, Sanofi, GlaxoSmithKline, Novartis, Roche, and Wyeth to do research and present at scientific meetings. Any funding received is directed to an NCIRS research account at The Children's Hospital at Westmead, NSW, Australia, and is not personally accepted by RB. All other named authors declare that they have no competing interests.

modelling. We assessed the association with time to treatment using time-dependent Cox regression shared frailty modelling.

Findings—We included data for 29 234 patients from 78 studies of patients admitted to hospital between Jan 2, 2009, and March 14, 2011. Compared with no treatment, neuraminidase inhibitor treatment (irrespective of timing) was associated with a reduction in mortality risk (adjusted odds ratio [OR] 0·81; 95% CI 0·70–0·93; $p=0\cdot0024$). Compared with later treatment, early treatment (within 2 days of symptom onset) was associated with a reduction in mortality risk (adjusted OR 0·48; 95% CI 0·41–0·56; $p<0\cdot0001$). Early treatment versus no treatment was also associated with a reduction in mortality (adjusted OR 0·50; 95% CI 0·37–0·67; $p<0\cdot0001$). These associations with reduced mortality risk were less pronounced and not significant in children. There was an increase in the mortality hazard rate with each day's delay in initiation of treatment up to day 5 as compared with treatment initiated within 2 days of symptom onset (adjusted hazard ratio [HR] 1·23] [95% CI 1·18–1·28]; $p<0\cdot0001$ for the increasing HR with each day's delay).

Interpretation—We advocate early instigation of neuraminidase inhibitor treatment in adults admitted to hospital with suspected or proven influenza infection.

Funding—F Hoffmann-La Roche.

Introduction

The neuraminidase inhibitors, oral oseltamivir and inhaled zanamivir, were the predominant medical countermeasure available from emergence of the influenza A H1N1pdm09 virus in early 2009, until the first release of monovalent H1N1 vaccines in October, 2009.

Prescribing data from seven countries (Australia, Canada, France, Germany, Japan, UK, USA) suggest at least 18·3 million individuals received oseltamivir between May 1, 2009, and Dec 31, 2009.¹ Country-specific policies for use of neuraminidase inhibitors during the 2009–10 pandemic varied from no use, to targeted use in at-risk patients (most countries), to treatment of all patients with clinical illness (UK). Most use of neuraminidase inhibitors worldwide was in the form of oseltamivir—eg, 97·5% of neuraminidase inhibitors used in the USA.²

There is little pre-pandemic evidence pertaining to the effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza; most evidence comes from observational studies of treatment of seasonal influenza, often in highly specific groups of patients.^{3–9} Thus, in 2009–10, neuraminidase inhibitors were used on the basis of rational deduction that they would reduce mortality due to influenza A H1N1pdm09 virus infection rather than on strong pre-existing evidence, although data from treatment of human influenza A H5N1 cases suggested this reduction in mortality might be possible.^{10,11} Japanese clinicians used neuraminidase inhibitors widely to treat all people presenting with clinical influenza in 2009–10 and recorded the lowest pandemic mortality rate of any developed country.^{12–14} Although a similar treat-all policy existed in the UK in 2009, uptake of neuraminidase inhibitors in patients admitted to hospital with influenza A H1N1pdm09 was low.¹⁵

Two systematic reviews and meta-analyses have examined the effectiveness of neuraminidase inhibitors in reducing mortality due to influenza. Both suggest substantial

reductions in mortality by two-thirds to three-quarters compared with no treatment.^{16,17} However, limitations are apparent, such as the heterogeneity of studies included and inadequate adjustment for potential confounding. Importantly, neither was able to adjust for the likelihood of a patient receiving antiviral treatment (propensity)—a crucial consideration when antiviral drugs might have been prioritised towards the sickest patients—and neither was able to use a pooled analysis approach with individual participant data.¹⁸

Methods

Study design and identification of datasets

The Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) research consortium was set up in October, 2011, and is coordinated by the Health Protection and Influenza Research Group at the University of Nottingham, Nottingham, UK. The aim of the collaboration is to do individual participant data meta-analyses of the effectiveness of antiviral use on outcomes of public health importance during the 2009–10 influenza pandemic. Members of the PRIDE research consortium are listed in appendix pp 1–6.

The initial identification of potential data contributors was done on the basis of a systematic search of 11 databases (date of last search April 19, 2012) for observational studies (case series, case-control, and cohort studies) and randomised controlled trials done between March 1, 2009 (Mexico), or April 1, 2009 (rest of the world), until the WHO declaration of the end of the pandemic (Aug 10, 2010), assessing the association between neuraminidase inhibitor treatment and clinical outcomes (mortality, influenza-related pneumonia, admission to critical care, length of stay in hospital and admission to hospital). We searched Ovid Medline (reports from 1996 onwards) and Embase (1980 onwards) using a comprehensive search strategy. We also searched CINAHL, CAB Abstracts, ISI Web of Science, PubMed, UK PubMed Central, Scopus, WHO regional indexes, LILAC, and J-STAGE databases using Boolean logic and core search terms relating to pandemic influenza (including influenza A virus OR H1N1 subtype OR swine origin influenza AH1N1 virus) AND exposure of interest—ie, antiviral drugs (including neuraminidase inhibitors OR oseltamivir OR zanamivir OR peramivir) AND clinical outcome measures (including pneumonia, or critical care/intensive care, or mortality). We identified further studies from reference lists of relevant articles and through contact with subject area experts (via JSN-V-T). All search results were limited to human beings with no language restrictions. Our detailed search strategy is reported elsewhere.¹⁷

On the basis of this search, we contacted 401 potential data contributors, identified during the conduct of our previously reported systematic review;¹⁷ these potential contributors included several corresponding authors from different papers but potentially related to the same source dataset, as an all-inclusive approach. We recruited additional centres through our network of global collaborators, publicity at conferences attended, and by word of mouth. Centres fulfilling the minimum dataset requirement (appendix pp 7–8) were eligible for inclusion. We requested data for both laboratory confirmed and clinically diagnosed pandemic influenza A H1N1pdm09 cases, but allowed centres to provide individual patient data extending to March 14, 2011 (third pandemic wave cases). Clinically diagnosed cases that could not be confirmed by virology were diagnosed on the basis of clinical signs and

symptoms that, in the opinion of the attending physician, were judged to be representative of influenza-like illness, in the absence of any other more likely diagnosis. We deliberately accepted diagnoses made on clinical judgment rather than specifying a set of clinical criteria, since case definitions of influenza-like illness vary within and between countries. This study was granted exemption from full ethical review by the University of Nottingham Medical School Research Ethics Committee, provided that each contributing centre held its own institutional review board approval for data collection and sharing.

Data standardisation, exposures, outcomes, and covariates

A common data dictionary was developed and individual datasets standardised according to these definitions (appendix pp 9–15) before pooling for analysis.

The primary outcome variable was mortality, defined as death occurring during admission to hospital or individual study follow-up period for the generalised linear mixed regression models and as death occurring within 30 days of illness onset in the Cox regression models. Use of neuraminidase inhibitors (exposure) was defined and compared as follows: neuraminidase inhibitor treatment (irrespective of timing) versus none; early neuraminidase inhibitor treatment (starting treatment ≤ 2 days after symptom onset) versus later (initiation > 2 days after symptom onset); early neuraminidase inhibitor treatment versus none; and later neuraminidase inhibitor treatment versus none. Additionally, we created a continuous exposure variable, representing time (in days) between symptom onset and treatment initiation (0 meaning treatment commenced on day of symptom onset). Covariates in the final multivariable models were “inpatient treatment with oral or intravenous antibiotics” and “inpatient treatment with systemic corticosteroids” prescribed during the admission to hospital for influenza along with treatment propensity scores. We were unable to adjust for dose or duration of such treatments because of the scarce availability of these data across the individual datasets.

Propensity scoring

We calculated propensity scores for the likelihood of neuraminidase inhibitor treatment for each patient within individual datasets using multivariable logistic regression for binary treatment variables and generalised propensity score estimation for the continuous time to treatment variable as described by Hirano and Imbens.¹⁹ For each separate study dataset we calculated propensity scores (likelihood of treatment) for each of the four main exposure measures: neuraminidase inhibitor at any time (yes or no), early versus late neuraminidase inhibitor, early versus no neuraminidase inhibitor, and later (> 2 days) versus no neuraminidase inhibitor. Covariates were then included as follows, irrespective of significance: age, sex, comorbidity (yes or no), a proxy indicator of severe disease (yes or no), which were, in order of preference, severe respiratory distress; shortness of breath; unweighted symptom score; or, if none of these indicators were available, we used one of the following measures of severity: AVPU (alert, voice, pain, unresponsive) mental status examination score, Glasgow Coma Scale score, Sequential Organ Failure Assessment score, or CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥ 65 years) pneumonia severity scores, if these were available, entered as a continuous variable. We added the following variables when available to create an extended model, using a parsimonious

approach that retained only significant covariates in the final model: obesity, smoking, pregnancy, asthma, chronic obstructive pulmonary disease, lung disease, heart disease, immunosuppression, neurological disease, renal disease, and diabetes. We rejected variables with more than 25% missing data. Some variables used for the propensity score calculation, such as comorbidity (binary) and illness severity at presentation (binary), were derived at individual study level only and were not appropriate for inclusion in the pooled dataset analysis because of the heterogeneity in definition of these variables between studies.

The appropriateness of the propensity derivation models was assessed graphically by comparing the distribution of estimated propensity scores across treatment groups for each individual dataset.²⁰ Propensity scores were then categorised into quintiles for each individual dataset.

Statistical analysis

We used a generalised linear mixed model to account for clustering of effects by study using the *xtmelogit* command in Stata (version 12). We included “study” as a random intercept to account for differences in baseline crude mortality rate at each site. We adjusted the model for treatment propensity, inpatient antibiotics, and systemic corticosteroids. We included missing data in covariates as a separate dummy category. The overall analysis included patients of all ages with laboratory or clinically diagnosed influenza A H1N1pdm09. We did prespecified stratified analyses for adults and children (<16 years), pregnant women (irrespective of age), laboratory confirmed influenza A H1N1pdm09 cases, and patients admitted to critical care units. Additionally, for a subset of our sample for whom exact onset and treatment initiation times were available, we investigated the association between time to initiation of antiviral treatment and mortality within 30 days of illness onset using a time-dependent Cox regression shared frailty model (to account for clustering by study) adjusted for propensity score and inpatient treatment with antibiotics or systemic corticosteroids. Antiviral treatment was modelled as a time-dependent covariate to overcome immortal time bias (ie, survivor bias). Results from the generalised linear mixed model are expressed as relative risks of mortality using odds ratios (ORs) and hazard ratios (HRs) for the Cox regression analysis with 95% CIs. We used Stata (version 12) for all analyses.

The protocol²¹ for this study was registered with the PROSPERO register of systematic reviews, number CRD42011001273.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The funder has not and will never have access to the data. Each collaborator had access to the raw data from his or her centre. SGM, SV, PRM, JL-B, and JSN-V-T had access to the pooled dataset. The corresponding author (JSN-V-T) had full access to all the data in the study and the final responsibility for the decision to submit for publication.

Results

We received replies from 128 (32%) of 401 centres contacted; of these 77 (60%) confirmed willingness to participate and the remainder declined (36 [28%] had no data; three [2%] agreed initially but later withdrew because of lack of capacity for data extraction, institutional review board restrictions preventing sharing of individual participant data, or failure to obtain government approval for data sharing; 12 [9%] had agreed in principle, but were unable to share data within project timescales). No data were requested from nor provided by pharmaceutical companies. After exclusion of duplicate responses (same source dataset), and addition of three further datasets provided through informal contact with domain experts, 80 research groups from 38 countries in six WHO regions contributed anonymised data for 168 117 patients, of whom 24416 had laboratory results indicative of noninfluenza A H1N1 disease. Among the remaining 143 701 laboratory confirmed or clinically diagnosed (without standard study-wide case definition) influenza A H1N1pdm09 cases, 106 138 were outpatients and 2593 had missing information for hospital admission. The remaining 34 970 inpatients were eligible for inclusion (figure 1).

Of the 34 970 inpatients eligible for inclusion, 2095 (6%) had missing information for mortality status, and 3584 (10%) for exposure to neuraminidase inhibitors; 57 (<1%) were unsuitable for inclusion for other reasons (figure 1). Ultimately, we included 29 234 records from 78 studies (two studies provided only outpatient data and were excluded from analysis) of patients admitted to hospital between Jan 2, 2009, and March 14, 2011: 25 001 (86%) laboratory confirmed; 9218 (32%) children; and 1600 (5%) aged 65 years or older. Appendix p 16 show the incidence of cases by month. Full characteristics of the pooled dataset are listed in table 1 with absolute risks of mortality for various exposure categories and subgroups summarised in appendix p 16. Baseline characteristics of each constituent dataset are presented in appendix pp 17–21.

Patients without neuraminidase inhibitor treatment data and therefore excluded from analysis were more likely to be older, to have presented to hospital later, less likely to have a laboratory confirmed diagnosis, and more likely to be treated with antibiotics than were patients included in the analysis (appendix pp 26–27). However, they were less likely to be smokers, obese, or to have an underlying comorbidity. Additionally, their hospital stay was shorter, and they were less likely to have severe outcomes (admission to critical care unit or death), or influenza-related pneumonia (appendix pp 26–27).

After adjustment for propensity score and corticosteroid and antibiotic treatment, the likelihood of mortality in patients treated with a neuraminidase inhibitor was 0·81 (95% CI 0·70–0·93), compared with no treatment (table 2). The OR did not change substantially when only laboratory confirmed cases were included (adjusted OR 0·82 [95% CI 0·70–0·95]). Similarly, we identified significant associations with a reduced mortality risk in adults, pregnant women, and critically ill adult patients (table 2). However, there was no significant association between neuraminidase inhibitor treatment and mortality in children aged 0–15 years (table 2). Post-hoc analyses restricted to children up to 1 year of age and up to 5 years of age did not change this finding (appendix p 27).

Early neuraminidase inhibitor treatment compared with later treatment initiation was associated with an overall significant reduction in mortality risk (adjusted OR 0·48 [95% CI 0·41–0·56]; table 3). The ORs remained essentially unchanged when only laboratory confirmed cases were considered, but risk reduction was higher in pregnant women (table 3). Notably, there was again no significant association between early treatment and mortality in children after adjustment (table 3).

Neuraminidase inhibitor treatment within 2 days of symptom onset compared with none was also associated with a significant reduction in mortality in all patients (adjusted OR 0·50 [95% CI 0·37–0·67]; table 3), with significant risk reductions also noted among laboratory confirmed cases, adults, pregnant women, and adult patients admitted to critical care (table 3). However, there was no significant association with a lower mortality risk in children aged 0–15 years (table 3).

With regard to neuraminidase inhibitor treatment started more than 2 days after symptom onset compared with none, we identified no significant association with mortality in all patients (adjusted OR 1·20 [95% CI 0·93–1·54]), nor in laboratory confirmed cases, adults, pregnant women, or children (table 4). However, we noted an associated mortality risk reduction of about a third (adjusted OR 0·65 [95% CI 0·46–0·93]) in adult patients admitted to critical care.

Information about exact timing of neuraminidase inhibitor treatment from symptom onset was available for 65% (12284 of 18803) of those receiving such treatment. After taking into account clustering by study, propensity score quintiles, and in-hospital treatment with antibiotics or systemic corticosteroids, when antiviral use was modelled as a time-dependent covariate to overcome potential immortal time bias (ie, survivor bias), neuraminidase inhibitor treatment was significantly associated with decreased hazard rate of mortality over a 30-day follow-up period (adjusted HR 0·51 [95% CI 0·45–0·58], $p<0·0001$) as compared with no antiviral treatment. When only treated cases were included, there was an increase in the hazard with each day's delay in initiation of treatment up to day 5 as compared with treatment initiated within 2 days of symptom onset (adjusted HR 1·23 [95% CI 1·18–1·28], $p<0·0001$ for the increasing HR with each day's delay). The unadjusted and adjusted survival curves comparing survival by time to treatment initiation are shown in figure 2 and appendix pp 28–29.

Discussion

Our results show that neuraminidase inhibitor treatment was associated with reduced mortality in adult patients admitted to hospital with influenza A H1N1pdm09 virus infection. Neuraminidase inhibitor treatment of influenza A H1N1pdm09 at any stage of illness compared with none revealed an associated reduction in the likelihood of mortality (table 2). We identified an associated likelihood of lower mortality when comparing early versus later initiation of treatment and when comparing early treatment with none (table 3, panel). Although we included 4233 patients (14%) without laboratory confirmed influenza A H1N1pdm09, restriction to laboratory-confirmed cases produced near identical estimates, suggesting that the data are not confounded by misclassification bias attributable to other

causes (tables 2, 3). Additionally, we noted much the same findings in adults, pregnant women, and adult patients needing admission to critical care. The finding regarding critical care suggests that neuraminidase inhibitors were associated with mortality reduction across the spectrum of severity in adult patients admitted to hospital with influenza A H1N1pdm09. These findings accord closely with previous studies^{16,17} but have increased precision and reduced estimates of effectiveness consistent with more complete adjustment for confounders and treatment propensity. They are also consistent with ecological data.²³⁻²⁵

We were consistently unable to show any association of neuraminidase inhibitor treatment with mortality reduction in children. Possible explanations include lower case fatality proportion in paediatric patients (thus reduced statistical power),^{26,27} higher influenza A H1N1pdm09 viral load in children²⁸ than adults leading to reduced drug effectiveness, suboptimum dosing in very young children,²⁹ secondary bacterial infections (eg, meticillin-resistant *Staphylococcus aureus*), confounding by indication³⁰ (children might have been more likely to have had antivirals prescribed if they had more severe disease or if they failed to respond to other treatments), or a combination of these factors. Since it has been suggested that younger children might be admitted with milder disease compared with older children and adults (precautionary physician behaviour), that the pharmacokinetics and pharmacology of oseltamivir might be different in very young children,²⁹ and that influenza pathogenesis might differ by age,³⁰ we did post-hoc sensitivity analyses separately in children up to 1 year of age and up to 5 years of age, but our findings did not change (appendix p 27). However, we note that these results contrast with those of Louie and colleagues,³² who recently showed a two-thirds reduction in mortality among children treated with neuraminidase inhibitors admitted to hospital with influenza (OR 0.36 [95% CI 0.16–0.83]).

The finding that no treatment was better than late treatment is probably explained by confounding due to illness severity at the point of treatment initiation (ie, confounding by indication). Untreated patients probably had milder disease and patients treated later in the course of their illness might have had delays in hospital admission, delays in diagnosis after admission, or delays in being considered for neuraminidase inhibitor treatment (treatment only started once their condition deteriorated), or combinations of these factors. We advocate early consideration of a diagnosis of influenza in patients admitted to hospital with respiratory infection during periods of known influenza activity, and early instigation of neuraminidase inhibitor treatment based on rapid laboratory confirmation or clinical suspicion.

Our analyses examining the effect of later treatment versus none are especially relevant to the continued clinical debate about the value of delayed therapy. Combining all subgroups of patients, we did not identify any protective association with treatment delayed more than 2 days after symptom onset (table 4). This finding could be explained by confounding by indication. However, we noted that in adult patients admitted to critical care, delayed treatment was associated with reduced likelihood of mortality compared with no treatment (table 4), suggesting that delayed therapy might still be worthwhile in severely ill patients; this finding is plausible since, within this subgroup, treated and untreated patients (who all needed admission to critical care) are likely to have been more balanced in terms of illness

severity thereby overcoming confounding by this factor to some extent. Additionally, some patients admitted to critical care might have had prolonged influenza A H1N1pdm09 virus replication in the lower respiratory tract, which might benefit from later initiation of neuraminidase inhibitor treatment. To gain further understanding about overall timing-dependent benefit, we modelled time to start of antiviral treatment using a time-dependent Cox regression model, which showed a significant detrimental survival benefit associated with delay in treatment beyond 2 days after symptom onset ($p < 0.0001$), albeit with overlapping 95% CIs when time to treatment was modelled as a categorical variable; the latter finding suggests that potential differences in treatment benefit between starting on day 3 after symptom onset through to more than 5 days after symptom onset cannot be further clarified through our data. This finding could seem to conflict with the findings in table 4 comparing later neuraminidase inhibitor treatment to no neuraminidase inhibitor treatment but is not surprising, because by comparing only treated patients in figure 2, we possibly eliminated some of the confounding due to indication, which allowed us to identify the potential survival benefits conferred by later treatment, albeit detrimental in proportion to treatment delay.

One of the strengths of this study is the very large number of patients from geographically diverse clinical centres and source populations. We made exhaustive efforts to identify suitable datasets from around the world, but nevertheless cannot comment on the extent to which bias might have been introduced by failing to include centres that did not respond (we cannot say if they had suitable data or not), or that declined to share data; in a worst case scenario, it is possible that less than 20% of potential sites contributed to this analysis. Furthermore, comparatively few cases were from the WHO African (0.1%) and South-East Asia (0.7%) regions, which might limit the extent to which our findings can be generalised.

A clear limitation of our study is that we were unable to adjust specifically for disease severity in our multilevel models because of the heterogeneity of severity measures used across individual datasets. However, we made every effort to include relevant data including severity measures, within each propensity score, but there is still likely to be some residual confounding, particularly due to illness severity at presentation. Likewise, we attempted to control for study-level biases, such as treatment policies, and healthcare seeking behaviour, using multilevel models but there might be residual confounding. A further limitation of our dataset is that 10% of the patients had missing data for exposure to neuraminidase inhibitors and were excluded from the analysis; the characteristics of these patients are compared with those with data for neuraminidase inhibitor exposure in appendix pp 26–27; these patients were more likely to be older, to have presented to hospital later, less likely to have a laboratory confirmed diagnosis, and more likely to be treated with antibiotics.

The decision to adjust for treatment with antibiotics and corticosteroids was taken after consultation with clinical colleagues within the PRIDE study collaboration. This decision results from widespread clinical practice to treat patients admitted to hospital with respiratory illness with corticosteroids and antibiotics. There is particular uncertainty about the possible effect of corticosteroids on the course of severe influenza infection.^{33,34} Therefore, it was necessary to separate out the possible effects of antivirals from these other commonly used treatments. We did not do specific analyses to establish the potential effect

of antibiotic or corticosteroid use on mortality, but recognise that these factors both warrant further research. Although we were able to adjust for inpatient antibiotics and systemic corticosteroid use, we were unable to adjust for pandemic H1N1 vaccination since 35% (8284 of 23633) of our case series were admitted to hospital before the first availability of vaccine in October, 2009, and 71% (10 967 of 15 349) of data for vaccination status were missing among those admitted after that juncture; however, the available data suggest uptake was no higher than 8% during the study period.

This meta-analysis of individual patient data offers the most rigorous assessment of mortality benefits of neuraminidase inhibitor treatment during the 2009–10 pandemic that is likely to be possible using retrospective observational data. The greatest likelihood of reduced mortality seems to be attributable to treatment started within 2 days of symptom onset. These data offer evidence of the effectiveness of neuraminidase inhibitors during the 2009–10 pandemic and are superior to extrapolations from earlier data on seasonal influenza; they could retrospectively vindicate prepandemic neuraminidase inhibitor antiviral stockpiling decisions made by governments worldwide. Treatment guidance policies should increase emphasis on early empirical neuraminidase inhibitor treatment of adult patients admitted to hospital after presenting with proven or clinically suspected influenza A H1N1pdm09 virus infection. However, most adult patients with suspected or confirmed influenza are not admitted to hospital within 48 h of illness onset. Therefore, the implications of these findings, although based on patients admitted to hospital with influenza A H1N1pdm09, encourage early initiation of neuraminidase inhibitor treatment in outpatients who are appreciably unwell with suspected or confirmed influenza, or at increased risk of complications, including those with influenza A H3N2 or influenza B. Further studies are needed in children to confirm the adequacy of present dose regimens and duration of therapy in terms of clinical efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel: Research in context**Systematic review**

Two systematic reviews and meta-analyses have examined the effectiveness of neuraminidase inhibitors in reducing mortality due to influenza. Hsu and colleagues¹⁶ considered reported observational data, mainly for seasonal influenza, and concluded that oral oseltamivir might reduce mortality (odds ratio [OR] 0·23 [95% CI 0·13–0·43]). In our own systematic review, we included only reported data from the 2009–10 influenza A H1N1 pandemic (all observational) and showed that early neuraminidase inhibitor treatment versus none reduced mortality by two thirds (OR 0·35 [95% CI 0·18–0·71]).¹⁷ We applied search terms relating to pandemic influenza (including “Influenza A Virus” OR “H1N1 Subtype” OR “swine origin influenza AH1N1 virus”), AND exposure of interest—ie, antiviral drugs (including “neuraminidase inhibitors” OR “oseltamivir” OR “zanamivir” OR “peramivir”) AND clinical outcome measures (including “pneumonia”, “critical or intensive care”, “mortality”) to 11 databases (search range from Jan 1, 2009, to Aug 10, 2010; last search on April 19, 2012) without imposing language restrictions. Importantly, both studies acknowledged limitations such as the heterogeneity of studies included and inadequate adjustment for potential confounding. Moreover, neither was able to adjust for the likelihood of a patient receiving antiviral treatment (propensity)—a crucial consideration when antiviral drugs might have been prioritised towards the sickest patients.

Interpretation

By using a meta-analysis of individual patient data, which permits a uniform approach to potential confounding and adjustment for treatment propensity, and through the assembly of a very large international dataset, our study adds substantially to the evidence that neuraminidase inhibitors administered to adults admitted to hospital with influenza A H1N1pdm09 reduced mortality, especially when started promptly. Since placebo-controlled randomised controlled trials of neuraminidase inhibitors are not ethically feasible during a pandemic, the evidence we have assembled is likely to be the best that will be available. The US Centers for Disease Control and Prevention recommend neuraminidase inhibitor treatment as early as possible for any patient with confirmed or suspected influenza who is hospitalised; has severe, complicated or progressive illness; or is at higher risk for influenza complications.²² Neuraminidase inhibitors are also widely prescribed in Japan, but elsewhere their use is far less common. Although a similar treat-all policy existed in the UK in 2009, uptake of neuraminidase inhibitors inpatients admitted to hospital with influenza A H1N1pdm09 virus was low.¹⁵ We advocate early instigation of neuraminidase inhibitor treatment in adults admitted to hospital with suspected or proven influenza infection.

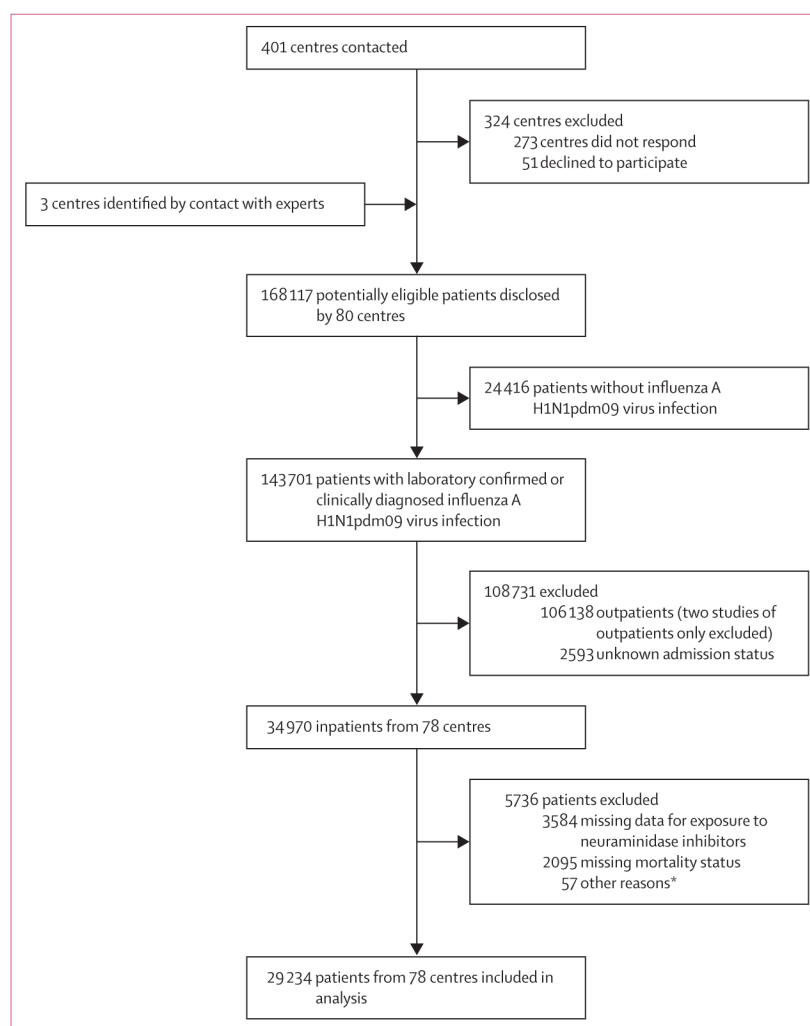


Figure 1: Study flow diagram

*47 overlapping data; one onset of illness before March 1, 2009 (Mexico); nine missing data for key variables.

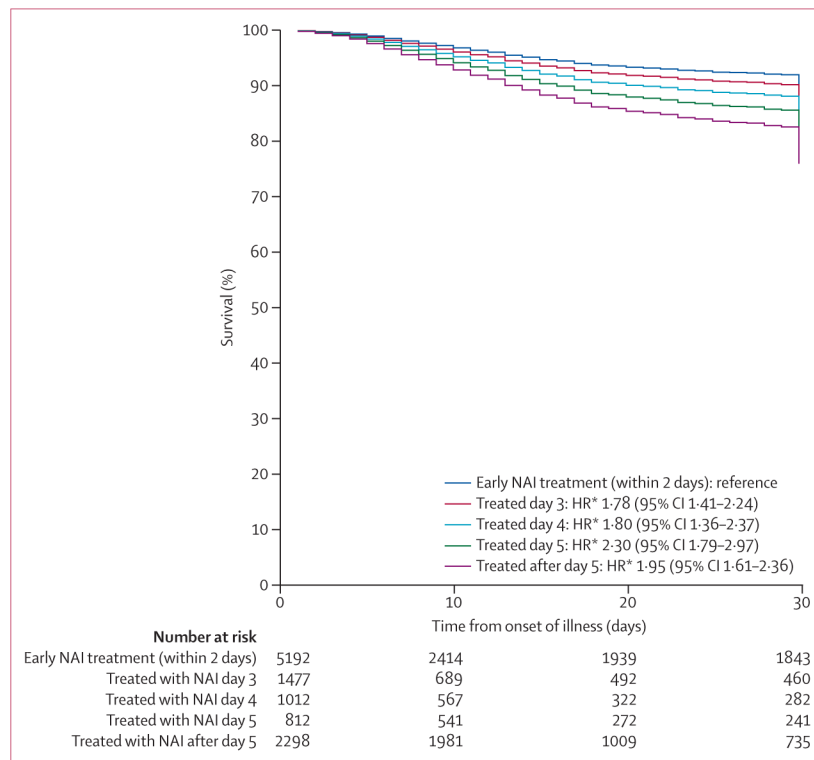


Figure 2: Survival by time to treatment

HR=hazard ratio. NAI=neuraminidase inhibitor. *Cox regression shared frailty model (adjusted for treatment propensity and in hospital steroid or antibiotic use).

Table 1:

Characteristics of pooled dataset of patients admitted to hospital with influenza A H1N1pdm09 virus infection included in mortality analysis

	All patients	Deceased	Survived
Number of patients [*]	29 234 (100%)	2784 (10%)	26 450 (90%)
Number of male cases (n=29 226) [†]	14 431 (49%)	1433 (51%)	12 998 (49%)
Age in years (n=29 034) [†]	26 (11–44)	40 (26–54)	25 (10–42)
Adults (≥16 years)	19 816 (68%)	2450 (88%)	17 366 (66%)
Children (<16 years)	9218 (32%)	325 (12%)	8893 (34%)
Obese [‡] (n=22 527) [†]	2607 (9%)	517 (19%)	2090 (8%)
Smoking (n=19 066) [†]	2406 (8%)	285 (10%)	2121 (8%)
Pregnant women [§]	2166/9513 (23%)	177/951 (19%)	1989/8562 (23%)
WHO region (n=29 234) [†]			
African	41 (<1%)	14 (1%)	27 (<1%)
Americas	14 186 (49%)	1477 (53%)	12 709 (48%)
Eastern Mediterranean	5262 (18%)	518 (19%)	4744 (18%)
European	7272 (25%)	680 (24%)	6592 (25%)
South-East Asia	210 (1%)	14 (1%)	196 (1%)
Western Pacific	2263 (8%)	81 (3%)	2182 (8%)
Influenza A H1N1pdm09 diagnosis (n=29 234) [†]			
Laboratory confirmed	25 001 (86%)	2486 (89%)	22515 (85%)
Clinically diagnosed	4233 (14%)	298 (11%)	3935 (15%)
Comorbidities ^{†¶}			
Any comorbidity (n=28 672)	11 011 (38%)	1471 (53%)	9540 (36%)
Asthma (n=20 518)	2820 (10%)	134 (5%)	2686 (10%)
COPD (n=17 081)	1012 (3%)	171 (6%)	841 (3%)
Other chronic lung disease (n=17 853)	2479 (8%)	272 (10%)	2207 (8%)
Heart disease (n=18 419)	1624 (6%)	317 (11%)	1307 (5%)
Renal disease (n=19 860)	710 (2%)	151 (5%)	559 (2%)
Liver disease (n=12 264)	295 (1%)	81 (3%)	214 (1%)
Cerebrovascular disease (n=9803)	304 (1%)	34 (1%)	270 (1%)

	All patients	Deceased	Survived
Neurological disease (n=13 598)	1013 (3%)	136 (5%)	877 (3%)
Diabetes (n=24 764)	2087 (7%)	418 (15%)	1669 (6%)
Immunosuppression (n=25 268)	1803 (6%)	346 (12%)	1457 (6%)
Pandemic H1N1 vaccination (n=4382) ^{††}	347/15 349 (2%)	27/1604 (2%)	320/13 745 (2%)
Time from symptom onset to hospital admission in days (n=23 769) [†]	2(1–5)	4(2–6)	2 (1–4)
Antiviral agents used			
No NAI treatment	10 431 (36%)	959 (34%)	9472 (36%)
Any NAI	18 803 (64%)	1825 (66%)	16 978 (64%)
Oral oseltamivir ^{**}	17 309/18 803 (92%)	1675/1825 (92%)	15 634/16 978 (92%)
Intravenous or inhaled zanamivir ^{**}	435/18 803 (2%)	52/1825 (3%)	383/16 978 (2%)
Intravenous peramivir ^{**}	49/18 803 (<1%)	28/1825 (2%)	21/16 978 (<1%)
NAI (regimen unknown) ^{**}	1251/18 803 (7%)	140/1825 (8%)	1111/16 978 (7%)
NAI and non-NAI ^{**}	94/18 803 (<1%)	18/1825 (1%)	76/16 978 (<1%)
NAI combination therapy ^{**}	238/18 803 (1%)	69/1825 (4%)	169/16 978 (1%)
Early NAI (≤2 days of symptom onset) (n=13 254) ^{†***}	5995/18 803 (32%)	358/1825 (20%)	5637/16 978 (33%)
Later NAI (>2 days after symptom onset) (n=13 254) ^{†***}	7259/18 803 (39%)	942/1825 (52%)	6317/16 978 (37%)
Time from symptom onset to antiviral treatment in days (n=12 284) [†]	3(1–5)	4 (2–7)	3(1–5)
Other in-hospital treatment [†]			
Antibiotics (n=20 362)	13 230 (45%)	1096 (39%)	12 134 (46%)
Corticosteroids (n=9982)	2745 (9%)	453 (16%)	2292 (9%)
Hospital length of stay in days (n=22 366) [†]	5(2–9)	7 (2–15)	5 (2–8)
Other patient outcomes [†]			
Influenza-related pneumonia ^{†††} (n=16 551)	7225 (25%)	1035 (37%)	6190 (23%)
Admission to critical care (n=24 435)	6848 (23%)	1957 (70%)	4891 (18%)

Data are n (%) or median (IQR). COPD=chronic obstructive pulmonary disease. NAI=neuraminidase inhibitor.

* All percentages have been calculated using these denominators unless otherwise specified.

[†] Missing data; n shows number of cases with data.

^{††} Reported as clinically obese or using WHO definition for obesity (BMI ≥30 kg/m² in adults aged ≥20 years).

§ Proportions were calculated as a percentage of pregnant patients among female patients of reproductive age (13–54 years); the broader age range was selected in preference to the WHO definition (15–44 years) after consultation with data contributors to reflect the actual fertility experience of the sample.

¶ For definition of comorbidity, see appendix pp 9–11.

// Denominators for pandemic vaccine based on patients admitted after Oct 1, 2009 (when vaccine potentially available).

*** Percentages calculated as a proportion of the sample receiving NAI therapy.

†† Clinically or radiologically diagnosed pneumonia.

Table 2:

Neuraminidase inhibitor treatment (at any time) versus none

	Crude analysis			Adjusted* analysis		
	OR (95% CI)	p value		OR (95% CI)	p value	
Laboratory confirmed or clinically diagnosed, all ages; n=29 234	0.92 (0.81–1.05)	0.21		0.81 (0.70–0.93)	0.0024	
Laboratory confirmed cases, all ages; n=25 001	0.94 (0.81–1.09)	0.42		0.82 (0.70 to 0.95)	0.0104	
Adults (≥16 years); n=19 816	0.82 (0.70–0.95)	0.0071		0.75 (0.64–0.87)	0.0002	
Children (<16 years); n=9218	1.02 (0.73–1.42)	0.90		0.82 (0.58–1.17)	0.28	
Pregnant women; n=2166	0.47 (0.24–0.90)	0.0228		0.46 (0.23–0.89)	0.0215	
Critical care patients						
Adults (≥16 years); n=5103	0.74 (0.57–0.95)	0.0187		0.72 (0.56–0.94)	0.0155	
Children (<16 years); n=1725	0.84 (0.52–1.37)	0.49		0.70 (0.42–1.16)	0.17	

OR=odds ratio.

* Adjusted for treatment propensity (by quintile), corticosteroid use, and antibiotic use.

Table 3:
Early neuraminidase inhibitor treatment (≤ 2 days after onset) versus later (> 2 days) or none

	Crude analysis		Adjusted* analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Early treatment versus later treatment				
Laboratory confirmed or clinically diagnosed, all ages; n=13 254	0.36 (0.31–0.41)	<0.0001	0.48 (0.41–0.56)	<0.0001
Laboratory confirmed cases, all ages; n=12 992	0.36 (0.31–0.41)	<0.0001	0.48 (0.41–0.56)	<0.0001
Adults (≥ 16 years); n=9270	0.37 (0.32–0.44)	<0.0001	0.45 (0.38–0.54)	<0.0001
Children (< 16 years); n=3899	0.53 (0.35–0.80)	0.0026	0.67 (0.44–1.03)	0.07
Pregnant women; n=917	0.20 (0.09–0.46)	0.0002	0.27 (0.11–0.63)	0.0026
Critical care patients				
Adults (≥ 16 years); n=3385	0.64 (0.51–0.79)	<0.0001	0.62 (0.49–0.77)	<0.0001
Children (< 16 years); n=683	1–12 (0.63–1.99)	0.69	1.15 (0.64–2.06)	0.64
Early treatment versus none				
Laboratory confirmed or clinically diagnosed, all ages; n=16 425	0.54 (0.40–0.72)	<0.0001	0.50 (0.37–0.67)	<0.0001
Laboratory confirmed cases, all ages; n=13 200	0.53 (0.39–0.71)	<0.0001	0.48 (0.36–0.66)	<0.0001
Adults (≥ 16 years); n=10 607	0.39 (0.28–0.55)	<0.0001	0.38 (0.27–0.54)	<0.0001
Children (< 16 years); n=5696	1.08 (0.61–1.93)	0.79	0.85 (0.47–1.53)	0.59
Pregnant women; n=1303	0.16 (0.04–0.64)	0.0099	0.16 (0.04–0.67)	0.0118
Critical care patients				
Adults (≥ 16 years); n=1608	0.30 (0.19–0.45)	<0.0001	0.31 (0.20–0.47)	<0.0001
Children (< 16 years); n=572	0.88 (0.40–1.91)	0.74	0.76 (0.34–1.67)	0.49

OR=odds ratio.

* Adjusted for treatment propensity (by quintile), corticosteroid use, and antibiotic use.

Table 4:

Later neuraminidase inhibitor treatment (>2 days) versus none

	Crude analysis		Adjusted* analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Laboratory confirmed or clinically diagnosed, all ages; n=17 670	1.27 (1.00-1.61)	0.0497	1.20 (0.93-1.54)	0.15
Laboratory confirmed cases, all ages; n=14 409	1.25 (0.98-1.59)	0.07	1.17 (0.92-1.51)	0.21
Adults (≥16 years); n=12 269	1.01 (0.77-1.32)	0.94	1.01 (0.76-1.33)	0.96
Children (<16 years); n=5282	1.34 (0.78-2.31)	0.29	1.29 (0.75-2.21)	0.36
Pregnant women; n=1302	0.72 (0.26-2.01)	0.53	0.70 (0.24-2.06)	0.51
Critical care patients				
Adults (≥16 years); n=2977	0.61 (0.43-0.86)	0.0045	0.65 (0.46-0.93)	0.0183
Children (<16 years); n=644	0.65 (0.32-1.36)	0.25	0.75 (0.35-1.57)	0.44

OR=odds ratio.

* Adjusted for treatment propensity quintiles, corticosteroid use and antibiotic use.



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Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza^a

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Abstract

These clinical practice guidelines are an update of the guidelines published by the Infectious Diseases Society of America (IDSA) in 2009, prior to the 2009 H1N1 influenza pandemic. This document addresses new information regarding diagnostic testing, treatment and chemoprophylaxis with antiviral medications, and issues related to institutional outbreak management for seasonal influenza. It is intended for use by primary care clinicians, obstetricians, emergency medicine providers, hospitalists, laboratorians, and infectious disease specialists, as well as other clinicians managing patients with suspected or laboratory-confirmed influenza. The guidelines consider the care of children and adults, including special populations such as pregnant and postpartum women and immunocompromised patients.

Keywords

seasonal influenza; diagnostic testing; treatment; chemoprophylaxis; institutional outbreaks

EXECUTIVE SUMMARY

Seasonal influenza A and B virus epidemics are associated with significant morbidity and mortality each year in the United States and worldwide. One study estimated that during 2010–2016, the seasonal incidence of symptomatic influenza among all ages in the United States was approximately 8% and varied from 3% to 11% [1]. Most people recover from uncomplicated influenza, but influenza can cause complications that result in severe illness and death, particularly among very young children, older adults, pregnant and postpartum women within 2 weeks of delivery, people with neurologic disorders, and people with certain chronic medical conditions including chronic pulmonary, cardiac, and metabolic disease, and those who are immunocompromised [2–8]. During 2010–2018, seasonal influenza epidemics were associated with an estimated 4.3–23 million medical visits, 140 000–960 000 hospitalizations, and 12 000–79 000 respiratory and circulatory deaths each year in the United States [9]. A recent modeling study estimated that 291 243–645 832 seasonal influenza-associated respiratory deaths occur annually worldwide [10].

Use of available diagnostic modalities and proper interpretation of results can accurately identify patients presenting with influenza. Timely diagnosis may decrease unnecessary laboratory testing for other etiologies and use of antibiotics, improve the effectiveness of infection prevention and control measures, and increase appropriate use of antiviral medications [11, 12]. Early treatment with antivirals reduces the duration of symptoms and risk of some complications (bronchitis, otitis media, and pneumonia) and hospitalization, and may decrease mortality among high-risk populations [13–16]. Annual vaccination is the best method for preventing or mitigating the impact of influenza, but in certain situations, chemoprophylaxis with antiviral medications can be used for preexposure or postexposure prevention and can help control outbreaks in certain populations.

These clinical practice guidelines are an update of the guidelines published by the Infectious Diseases Society of America (IDSA) in 2009 [17]. The guidelines consider the care of children, pregnant and postpartum women, and nonpregnant adults and include special considerations for patients who are severely immunocompromised such as hematopoietic stem cell and solid organ transplant recipients. The target audience includes primary care clinicians, obstetricians, emergency medicine providers, hospitalists, and infectious disease specialists. The guidelines may be also useful for occupational health physicians and clinicians working in long-term care facilities. It adds new information on diagnostic testing, use of antivirals, and considerations of when to use antibiotics and when to test for antiviral resistance, and presents evidence on harm associated with routine use of corticosteroids.

The panel followed a process used in the development of previous IDSA guidelines that included a systematic weighting of the strength of recommendations and quality of evidence based upon the US Public Health Service Grading System for ranking recommendations in clinical guidelines as utilized in the previous 2009 guidelines (Table 1) [17]. Summarized below are the recommendations. A detailed description of background, methods, evidence summary, and rationale that support each recommendation, and research needs are included in the full document.

Because prevention and control of influenza is a dynamic field, clinicians should consult the website of the Centers for Disease Control and Prevention (CDC) for the latest information about influenza vaccines, influenza tests, and approved antiviral medications.

DIAGNOSIS

Which Patients Should Be Tested for Influenza?

Recommendations

Outpatients (including emergency department patients).

1. During influenza activity (defined as the circulation of seasonal influenza A and B viruses among persons in the local community) (see Figure 1):
 - Clinicians should test for influenza in high-risk patients, including immunocompromised persons who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (eg, cough without fever) if the testing result will influence clinical management (*A-III*).
 - Clinicians should test for influenza in patients who present with acute onset of respiratory symptoms with or without fever, and either exacerbation of chronic medical conditions (eg, asthma, chronic obstructive pulmonary disease [COPD], heart failure) or known complications of influenza (eg, pneumonia) if the testing result will influence clinical management (*A-III*) (see Table 3).
 - Clinicians can consider influenza testing for patients not at high risk for influenza complications who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (eg, cough without fever) and who are likely to be discharged home if the results might influence antiviral treatment decisions or reduce use of unnecessary antibiotics, further diagnostic testing, and time in the emergency department, or if the results might influence antiviral treatment or chemoprophylaxis decisions for high-risk household contacts (see recommendations 40–42) (*C-III*).
2. During *low* influenza activity without any link to an influenza outbreak:
 - Clinicians can consider influenza testing in patients with acute onset of respiratory symptoms with or without fever, especially for immunocompromised and high-risk patients (*B-III*).

Hospitalized Patients.

3. During influenza activity:
 - Clinicians should test for influenza on admission in all patients requiring hospitalization with acute respiratory illness, including pneumonia, with or without fever (*A-II*).

- Clinicians should test for influenza on admission in all patients with acute worsening of chronic cardiopulmonary disease (eg, COPD, asthma, coronary artery disease, or heart failure), as influenza can be associated with exacerbation of underlying conditions (*A-III*).
 - Clinicians should test for influenza on admission in all patients who are immunocompromised or at high risk of complications and present with acute onset of respiratory symptoms with or without fever, as the manifestations of influenza in such patients are frequently less characteristic than in immunocompetent individuals (*A-III*).
 - Clinicians should test for influenza in all patients who, while hospitalized, develop acute onset of respiratory symptoms, with or without fever, or respiratory distress, without a clear alternative diagnosis (*A-III*).
4. During periods of low influenza activity:
- Clinicians should test for influenza on admission in all patients requiring hospitalization with acute respiratory illness, with or without fever, who have an epidemiological link to a person diagnosed with influenza, an influenza outbreak or outbreak of acute febrile respiratory illness of uncertain cause, or who recently traveled from an area with known influenza activity (*A-II*).
 - Clinicians can consider testing for influenza in patients with acute, febrile respiratory tract illness, especially children and adults who are immunocompromised or at high risk of complications, or if the results might influence antiviral treatment or chemoprophylaxis decisions for high-risk household contacts (see recommendations 41–43) (*B-III*).

What Specimen(s) Should Be Collected When Testing Patients for Influenza?

Recommendations

5. Clinicians should collect upper respiratory tract specimens from outpatients for influenza testing as soon after illness onset as possible, preferably within 4 days of symptom onset (*A-II*).
- Nasopharyngeal specimens should be collected over other upper respiratory tract specimens to increase detection of influenza viruses (*A-II*).
 - If nasopharyngeal specimens are not available, nasal and throat swab specimens should be collected and combined together for influenza testing over single specimens from either site (particularly over throat swabs) to increase detection of influenza viruses (*A-II*).
 - Mid-turbinate nasal swab specimens should be collected over throat swab specimens to increase detection of influenza viruses (*A-II*).

- Flocked swab specimens should be collected over non-flocked swab specimens to improve detection of influenza viruses (*A-II*).
- 6. Clinicians should collect nasopharyngeal (optimally, as for outpatients), mid-turbinate nasal, or combined nasal–throat specimens from hospitalized patients without severe lower respiratory tract disease for influenza testing as soon as possible (*A-II*).
- 7. Clinicians should collect endotracheal aspirate or bronchial-veolar lavage fluid specimens from hospitalized patients with respiratory failure receiving mechanical ventilation, including patients with negative influenza testing results on upper respiratory tract specimens, for influenza testing as soon as possible (*A-II*).
- 8. Clinicians should not collect or routinely test specimens for influenza from nonrespiratory sites such as blood, plasma, serum, cerebrospinal fluid, urine, and stool (*A-III*).
- 9. Clinicians should not collect serum specimens, including single or paired sera, for serological diagnosis of seasonal influenza virus infection for clinical management purposes (*A-III*).

What Test(s) Should Be Used to Diagnose Influenza?

Recommendations

10. Clinicians should use rapid molecular assays (ie, nucleic acid amplification tests) over rapid influenza diagnostic tests (RIDTs) in outpatients to improve detection of influenza virus infection (*A-II*) (see Table 6).
11. Clinicians should use reverse-transcription polymerase chain reaction (RT-PCR) or other molecular assays over other influenza tests in hospitalized patients to improve detection of influenza virus infection (*A-II*) (see Table 6).
12. Clinicians should use multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized immunocompromised patients (*A-III*).
13. Clinicians can consider using multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized patients who are not immunocompromised if it might influence care (eg, aid in cohorting decisions, reduce testing, or decrease antibiotic use) (*B-III*).
14. Clinicians should not use immunofluorescence assays for influenza virus antigen detection in hospitalized patients except when more sensitive molecular assays are not available (*A-II*), and follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative immunofluorescence test results (*A-III*).
15. Clinicians should not use RIDTs in hospitalized patients except when more sensitive molecular assays are not available (*A-II*), and follow-up testing with

RT-PCR or other molecular assays should be performed to confirm negative RIDT results (*A-II*).

16. Clinicians should not use viral culture for initial or primary diagnosis of influenza because results will not be available in a timely manner to inform clinical management (*A-III*), but viral culture can be considered to confirm negative test results from RIDTs and immunofluorescence assays, such as during an institutional outbreak, and to provide isolates for further characterization (*C-II*).
17. Clinicians should not use serologic testing for diagnosis of influenza because results from a single serum specimen cannot be reliably interpreted, and collection of paired (acute/convalescent) sera 2–3 weeks apart are needed for serological testing (*A-III*).

TREATMENT

Which Patients With Suspected or Confirmed Influenza Should Be Treated With Antivirals?

Recommendations

18. Clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza, irrespective of influenza vaccination history, who meet the following criteria:
 - Persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization (*A-II*).
 - Outpatients of any age with severe or progressive illness, regardless of illness duration (*A-III*).
 - Outpatients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients (*A-II*).
 - Children younger than 2 years and adults ≥ 65 years (*A-III*).
 - Pregnant women and those within 2 weeks postpartum (*A-III*).
19. Clinicians can consider antiviral treatment for adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history, who are either:
 - Outpatients with illness onset ≤ 2 days before presentation (*C-I*).
 - Symptomatic outpatients who are household contacts of persons who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised (*C-III*).
 - Symptomatic healthcare providers who care for patients who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised (*C-III*).

For Patients Who Are Recommended to Receive Antiviral Treatment for Suspected or Confirmed Influenza, Which Antiviral Should Be Prescribed, at What Dosing, and for What Duration?

Recommendations

20. Clinicians should start antiviral treatment as soon as possible with a single neuraminidase inhibitor (NAI) (either oral oseltamivir, inhaled zanamivir, or intravenous peramivir) and not use a combination of NAIs (*A-I*).
21. Clinicians should not routinely use higher doses of US Food and Drug Administration-approved NAI drugs for the treatment of seasonal influenza (*A-II*).
22. Clinicians should treat uncomplicated influenza in otherwise healthy ambulatory patients for 5 days with oral oseltamivir or inhaled zanamivir, or a single dose of intravenous peramivir (*A-I*).
23. Clinicians can consider longer duration of antiviral treatment for patients with a documented or suspected immunocompromising condition or patients requiring hospitalization for severe lower respiratory tract disease (especially pneumonia or acute respiratory distress syndrome [ARDS]), as influenza viral replication is often protracted (*C-III*).

In a Patient With Suspected or Confirmed Influenza, When Should Bacterial Coinfection of the Upper or Lower Respiratory Tract Be Considered, Investigated, and Treated?

Recommendations

24. Clinicians should investigate and empirically treat bacterial coinfection in patients with suspected or laboratory-confirmed influenza who present initially with severe disease (extensive pneumonia, respiratory failure, hypotension, and fever), in addition to antiviral treatment for influenza (*A-II*).
25. Clinicians should investigate and empirically treat bacterial coinfection in patients who deteriorate after initial improvement, particularly in those treated with antivirals (*A-III*).
26. Clinicians can consider investigating bacterial coinfection in patients who fail to improve after 3–5 days of antiviral treatment (*C-III*).

If a Patient With Influenza Does Not Demonstrate Clinical Improvement With Antiviral Treatment or Demonstrates Clinical Deterioration During or After Treatment, What Additional Testing and Therapy Should Be Considered?

Recommendation

27. Clinicians should investigate other causes besides influenza virus infection in influenza patients who fail to improve or deteriorate despite antiviral treatment (*A-III*).

When Should Testing Be Done for Infection With an Antiviral-resistant Influenza Virus?

Recommendations

28. Influenza NAI resistance testing can be considered for:
 - Patients who develop laboratory-confirmed influenza while on or immediately after NAI chemoprophylaxis (*C-III*).
 - Patients with an immunocompromising condition and evidence of persistent influenza viral replication (eg, after 7–10 days, demonstrated by persistently positive RT-PCR or viral culture results) and remain ill during or after NAI treatment (*B-III*).
 - Patients with laboratory-confirmed influenza who inadvertently received subtherapeutic NAI dosing (*C-III*).
 - Patients with severe influenza who do not improve with NAI treatment and have evidence of persistent influenza viral replication (eg, after 7–10 days) (*C-II*).
29. Clinicians should remain informed on current CDC and World Health Organization surveillance data on the frequency and geographic distribution of NAI-resistant influenza viruses during influenza season, and with the latest CDC antiviral treatment recommendations (*A-III*).

Should Adjunctive Therapy Be Administered to Patients With Suspected or Confirmed Influenza?

Recommendations

30. Clinicians should not administer corticosteroid adjunctive therapy for the treatment of adults or children with suspected or confirmed seasonal influenza, influenza-associated pneumonia, respiratory failure, or ARDS, unless clinically indicated for other reasons (*A-III*).
31. Clinicians should not routinely administer immunomodulation using immunoglobulin preparations such as intravenous immunoglobulin for treatment of adults or children with suspected or confirmed seasonal influenza (*A-III*).

ANTIVIRAL CHEMOPROPHYLAXIS IN COMMUNITY SETTINGS

Who Should Be Considered for Antiviral Chemoprophylaxis to Prevent Influenza in the Absence of Exposure or an Institutional Outbreak (Preexposure Chemoprophylaxis)?

Recommendations—Antiviral drugs should not be used for routine or widespread chemoprophylaxis outside of institutional outbreaks; antiviral chemoprophylaxis can be considered in certain situations:

32. Clinicians can consider antiviral chemoprophylaxis for the duration of the influenza season for adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza and for whom influenza

vaccination is contraindicated, unavailable, or expected to have low effectiveness (eg, persons who are severely immunocompromised) (*C-II*).

33. Clinicians can consider antiviral chemoprophylaxis for the duration of the influenza season for adults and children aged ≥ 3 months who have the highest risk of influenza-associated complications, such as recipients of hematopoietic stem cell transplant in the first 6–12 months posttransplant and lung transplant recipients (*B-II*).
34. Clinicians can consider short-term antiviral chemoprophylaxis in conjunction with prompt administration of inactivated influenza vaccine for unvaccinated adults and children aged ≥ 3 months who are at high risk of developing complications from influenza in whom influenza vaccination is expected to be effective (but not yet administered) when influenza activity has been detected in the community (*C-II*).
35. Clinicians can consider short-term antiviral chemoprophylaxis for unvaccinated adults, including healthcare personnel, and for children aged ≥ 3 months who are in close contact with persons at high risk of developing influenza complications during periods of influenza activity when influenza vaccination is contraindicated or unavailable and these high-risk persons are unable to take antiviral chemoprophylaxis (*C-III*).
36. Clinicians can consider educating patients and parents of patients to arrange for early empiric initiation of antiviral treatment as an alternative to antiviral chemoprophylaxis (*C-III*).

Which Antiviral Drugs Should Be Used for Preexposure Chemoprophylaxis for Influenza?

Recommendation

37. Clinicians should use an NAI (oral oseltamivir or inhaled zanamivir) if preexposure chemoprophylaxis for influenza is administered rather than an adamantane antiviral (*A-II*).

What Is the Duration of Preexposure Antiviral Chemoprophylaxis to Prevent Influenza?

Recommendations

38. Clinicians should administer preexposure antiviral chemoprophylaxis for adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza (eg, severely immunocompromised persons such as hematopoietic stem cell transplant recipients) for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness, as soon as influenza activity is detected in the community and continued for the duration of community influenza activity (*A-II*).
39. Clinicians should test for influenza and switch to antiviral treatment dosing in persons receiving preexposure antiviral chemoprophylaxis who become symptomatic, preferably with an antiviral drug with a different resistance profile if not contraindicated (*A-II*).

Which Asymptomatic Persons Exposed to Influenza Should Be Considered for Postexposure Antiviral Chemoprophylaxis in a Noninstitutional Setting?

Recommendations

40. Clinicians can consider postexposure antiviral chemoprophylaxis for asymptomatic adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza (eg, severely immunocompromised persons) and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness, after household exposure to influenza (*C-II*).
41. Clinicians can consider postexposure antiviral chemoprophylaxis (in conjunction with influenza vaccination) for adults and children aged ≥ 3 months who are unvaccinated and are household contacts of a person at very high risk of complications from influenza (eg, severely immunocompromised persons), after exposure to influenza (*C-II*).
42. Clinicians can consider educating patients and arranging for early empiric initiation of antiviral treatment as an alternative to postexposure antiviral chemoprophylaxis (*C-III*).

When Should Postexposure Antiviral Chemoprophylaxis Be Started?

Recommendations

43. If chemoprophylaxis is given, clinicians should administer postexposure antiviral chemoprophylaxis as soon as possible after exposure, ideally no later than 48 hours after exposure (*A-III*).
44. Clinicians should not administer once-daily postexposure anti-viral chemoprophylaxis if >48 hours has elapsed since exposure. Full-dose empiric antiviral treatment should be initiated as soon as symptoms occur, if treatment is indicated (*A-III*).

How Long Should Postexposure Antiviral Chemoprophylaxis Be Given?

Recommendations

45. Clinicians should administer postexposure antiviral chemoprophylaxis in a nonoutbreak setting for 7 days after the most recent exposure to a close contact with influenza (*A-III*).
46. Clinicians should test for influenza and switch to antiviral treatment dosing in persons receiving postexposure antiviral chemoprophylaxis who become symptomatic, preferably with an antiviral drug with a different resistance profile if not contraindicated (*A-III*).

Which Antiviral Drugs Should Be Used for Postexposure Chemoprophylaxis?

Recommendation

47. Clinicians should administer an NAI (inhaled zanamivir or oral oseltamivir) if postexposure chemoprophylaxis for influenza is given, rather than an adamantane antiviral (*A-II*).

INSTITUTIONAL OUTBREAK CONTROL

When Is There Sufficient Evidence of an Influenza Outbreak in a Long-term Care Facility or Hospital to Trigger Implementation of Control Measures Among Exposed Residents or Patients and Healthcare Personnel to Prevent Additional Cases of Influenza?

Recommendations

48. Active surveillance for additional cases should be implemented as soon as possible when one healthcare-associated laboratory-confirmed influenza case is identified in a hospital or one case of laboratory-confirmed influenza is identified in a long-term care facility (*A-III*).
49. Outbreak control measures should be implemented as soon as possible, including antiviral chemoprophylaxis of residents/patients, and active surveillance for new cases, when 2 cases of healthcare-associated laboratory-confirmed influenza are identified within 72 hours of each other in residents or patients of the same ward or unit (*A-III*).
50. Implementation of outbreak control measures can be considered as soon as possible if one or more residents or patients has suspected healthcare-associated influenza and results of influenza molecular testing are not available on the day of specimen collection (*B-III*).

Which Residents/Patients Should Be Considered to Have Influenza and Be Treated With Antivirals During an Influenza Outbreak in a Long-term Care Facility or Hospital?

Recommendations

51. When an influenza outbreak has been identified in a long-term care facility or hospital, influenza testing should be done for any resident/patient with one or more acute respiratory symptoms, with or without fever, or any of the following without respiratory symptoms: temperature elevation or reduction, or behavioral change (*A-III*).
52. Empiric antiviral treatment should be administered as soon as possible to any resident or patient with suspected influenza during an influenza outbreak without waiting for the results of influenza diagnostic testing (*A-III*).

To Control an Influenza Outbreak in a Long-term Care Facility or Hospital, Should Antiviral Chemoprophylaxis Be Administered to Exposed Residents/Patients?

Recommendation

53. Antiviral chemoprophylaxis should be administered as soon as possible to all exposed residents or patients who do not have suspected or laboratory-confirmed influenza regardless of influenza vaccination history, in addition to implementation of all other recommended influenza outbreak control measures, when an influenza outbreak has been identified in a long-term care facility or hospital (*A-III*).

During an Influenza Outbreak at a Long-term Care Facility, Should Antiviral Chemoprophylaxis Be Administered to Residents Only on Affected Units or to All Residents in the Facility?

Recommendation

54. Antiviral chemoprophylaxis should be administered to residents on outbreak-affected units, in addition to implementing active daily surveillance for new influenza cases throughout the facility (*A-II*).

Which Healthcare Personnel Should Receive Antiviral Chemoprophylaxis During an Institutional Outbreak?

Recommendations

55. Clinicians can consider antiviral chemoprophylaxis for unvaccinated staff, including those for whom chemoprophylaxis may be indicated based upon underlying conditions of the staff or their household members (see recommendations 40–44) for the duration of the outbreak (*C-III*).
56. Clinicians can consider antiviral chemoprophylaxis for staff who receive inactivated influenza vaccine during an institutional influenza outbreak for 14 days postvaccination (*C-III*).
57. Clinicians can consider antiviral chemoprophylaxis for staff regardless of influenza vaccination status to reduce the risk of short staffing in facilities and wards where clinical staff are limited and to reduce staff reluctance to care for patients with suspected influenza (*C-III*).

How Long Should Antiviral Chemoprophylaxis Be Given to Residents During an Influenza Outbreak in a Long-term Care Facility?

Recommendation

58. Clinicians should administer antiviral chemoprophylaxis for 14 days and continue for at least 7 days after the onset of symptoms in the last case identified during an institutional influenza outbreak (*A-III*).

INTRODUCTION

These clinical practice guidelines are an update of the guidelines published by the Infectious Diseases Society of America (IDSA) in 2009 [17], just prior to the recognition of the emergence of influenza A(H1N1) pdm09 virus as the cause of the 2009 H1N1 pandemic. Since then, new rapid molecular diagnostic assays became available, new risk factors for severe disease were recognized, and a parenteral neuraminidase inhibitor (NAI), peramivir, was approved for use in the United States. In addition, many observational studies in hospitalized patients with seasonal influenza A or B virus infection have been conducted, including studies of influenza A(H1N1) pdm09 virus infections, that have addressed the effectiveness of antiviral treatment and adjunctive therapies. Additional information is also available about the emergence of antiviral resistance. However, only a small proportion of the new data arises from randomized controlled clinical trials.

The purpose of this guideline's recommendations is to provide clinicians with evidence-based recommendations for the diagnosis and treatment of seasonal influenza, including use of commercially available influenza diagnostic tests, use of approved antiviral agents for treatment and chemoprophylaxis of influenza, and use of antibiotics or other adjunctive measures for treatment of complications associated with influenza. The recommendations also address the use of diagnostic tests and antiviral agents for the control of institutional influenza outbreaks. The care of specific patient populations is addressed, including children, pregnant and postpartum women, and persons who are severely immunocompromised such as hematopoietic stem cell and solid organ transplant recipients. The target audience includes primary care clinicians, obstetricians, emergency medicine providers, hospitalists, and infectious disease specialists.

The guidelines do not provide recommendations on infection prevention and control (IPC) measures for seasonal influenza in all healthcare settings; these are available on the Centers for Disease Control and Prevention (CDC) website [18]. Influenza outbreaks outside of healthcare settings (eg, daycare, schools, and workplaces) are not addressed; public health authorities should be consulted for outbreaks in these settings. The guidelines do not provide recommendations on diagnosis or treatment of human infections with novel influenza A viruses of animal origin following exposure to poultry or pigs (eg, avian influenza A viruses, or swine-origin [variant] viruses); current recommendations for IPC, specimen collection, diagnosis, and treatment of novel influenza A virus infections are available on the CDC website [19, 20]. The guideline also does not provide specific recommendations for the supportive clinical management of critical illness resulting from complications of influenza virus infection. Influenza vaccination is not addressed because annual influenza vaccination recommendations are published by the Advisory Committee on Immunization Practices (available on the CDC website and published in the *Morbidity and Mortality Weekly Report*) and the Committee on Infectious Diseases of the American Academy of Pediatrics.

METHODOLOGY

Guidelines Panel Composition

For this update, the IDSA chose 2 co-chairs to lead the process and convened a multidisciplinary panel of 16 experts in infectious diseases and the management of patients with influenza. In addition, the Pediatric Infectious Diseases Society, the American Academy of Pediatrics, the American College of Emergency Physicians, the Society for Healthcare Epidemiology of America, and the American College of Obstetricians and Gynecologists provided representatives with specific expertise in pediatrics, emergency medicine, healthcare epidemiology, and obstetrics and gynecology.

Disclosure and Management of Potential Conflicts of Interest

All prospective panelists were required to disclose any actual, potential, or perceived conflicts of interest (COI) prior to inclusion in the panel. The disclosures were used to categorize the panelists as (i) cleared for full participation, (ii) allowed to participate with recusal from certain aspects of guidelines development, or (iii) disqualified from participation. The co-chairs remained free of any financial COI during the entire guidelines development process, which meant avoidance of any relationship with pharmaceutical or device companies with products in development or being marketed for influenza or pneumonia. Furthermore, all panelists were precluded from participating in any marketing-related activities (eg, lectures or advisory boards directly funded by a pharmaceutical or device company with interests related to the guideline subject[s]). Panelists were required to disclose to the IDSA and the chairs any new activities that had the potential to be viewed as a COI prior to engaging in the activity. Assignments of panelists to specific clinical questions were made as to minimize any COI concerns. At the beginning of each meeting, whether face-to-face or by teleconference, panelists were required to disclose any new potential COI or prior relevant COI to the subject matter to be discussed.

Clinical Questions and Evidence Review

Following approval by the IDSA's Standards and Practice Guideline Committee (SPGC), an initial list of clinical questions was developed by the panel based on the 2009 guidelines and clinical problems requiring guidance. The panel committee prioritized the clinical questions and divided them into subgroups based on diagnostics, treatment, and prevention and control. Each of these subgroups was addressed by its dedicated subcommittee.

Two health science librarians designed literature searches to address each of the questions. Searches were limited to studies performed between January 2009 and March 2014 and published in English. Databases searched included PubMed/Medline, Embase, and the Cochrane Database for Systematic Reviews. The searches focused on human studies and, while not an exhaustive list, included such search terms as "influenza" or "influenza and virus," "influenza and infection," "influenza and treatment," "influenza and prophylaxis," "influenza and chemoprophylaxis," and "influenza and outbreak." A subsequent literature search was developed and updated through July 2017. To supplement the librarians' electronic searches, panelists also contacted experts and conducted updated literature searches, examined reviews of conference proceedings, manually checked reference lists,

and examined regulatory agency websites for relevant articles published through January 2018. While the optimal “gold standard” randomized controlled trial evidence was often not available, the aim was to ensure that the guidelines panel considered the most up-to-date evidence to address the clinical questions within its scope. For both the initial and the updated evidence search, the titles and abstracts of identified citations were screened, and potentially relevant citations were subjected to a full-text review, using predefined inclusion and exclusion criteria. Where necessary, screening of retrieved articles was conducted in duplicate and independently. Panel judgments were made throughout the guidelines based on consensus.

Development of Clinical Recommendations

Formal evidence summaries for specific treatment and chemoprophylaxis questions were prepared by the panel members. The current guideline development process included a systematic weighting of the quality of the evidence and the grade of recommendations based upon the US Public Health Service Grading System (Table 1) for ranking recommendations in clinical guidelines as utilized in the previous 2009 guidelines [17]. The adopted grading system as per Table 1 ranged from the optimal category and grade for a recommendation of “A-I” (which meant that the panel judged that there was good evidence to support a recommendation for [should always be offered] or against [should never be offered] use, and evidence emerged from >1 properly conducted randomized controlled trial) to the lowest category and grade, which was “C-III” (meaning that there was poor evidence to support a recommendation and the judgment was based on evidence from opinions of respected authorities, as well as based on clinical experience, descriptive studies, or reports of expert committees). The summaries of study evidence were discussed and reviewed by panel committee members, and judgments were made based on the emerging evidence coupled to clinical expertise and experience. The analyses were completed in parallel with drafting of updated recommendations. Once the analyses were completed, recommendations were reviewed and revised as appropriate by the panel.

The panel had 4 face-to-face meetings and conducted teleconferences over 5 years. All members of the panel participated in the preparation of the guidelines and approved the final recommendations. Feedback was obtained from external peer reviewers. The Pediatric Infectious Diseases Society, the Society for Healthcare Epidemiology of America, and the American College of Obstetricians and Gynecologists reviewed and endorsed the guideline. The IDSA SPGC and the IDSA Board of Directors reviewed and approved the guidelines prior to dissemination.

Revision Dates

At annual intervals, the SPGC will determine the need for revisions to the guideline based on an examination of current literature evidence and the likelihood that any new data will have an impact on the recommendations. If necessary, the entire expert panel will be reconvened to discuss potential changes. Any revision to the guideline will be submitted for review and approval to the IDSA SPGC and Board of Directors.

BACKGROUND

Definitions

“Influenza season” refers to the surveillance period when influenza activity typically occurs, such as during October through May, in the United States. “Influenza activity” is defined as the circulation of seasonal influenza A and B viruses among persons in the local community. “High influenza activity” is defined as increased circulation of seasonal influenza A and B viruses, such as peak weeks of circulation of seasonal influenza A and B viruses during the colder fall, winter, and spring months in the United States. “Low influenza activity” is defined as low or lack of circulation of seasonal influenza A and B viruses, such as during the warm summer months in the United States. “Acute respiratory illness” is defined as infection of either the upper or lower respiratory tract with respiratory symptoms, with or without fever. “Influenza-like illness” (ILI) is defined as acute respiratory illness with fever and either cough or sore throat. “Influenza” refers to symptomatic illness caused by seasonal influenza A or B virus infection. “Respiratory distress” is defined as difficulty in breathing that is usually associated with an increased respiratory rate and use of accessory muscles of breathing. “Laboratory-confirmed influenza” is defined as acute respiratory illness with laboratory testing evidence of influenza virus infection.

Scope

The scope of the guidelines pertains to diagnostic testing and treatment of illness caused by infection with influenza A and B viruses circulating among humans during seasonal epidemics and does not address asymptomatic infections. The guidelines also address diagnostic testing and use of antivirals for management of institutional influenza outbreaks. Background information about signs and symptoms of influenza, complications, groups considered to be at high risk of complications, and influenza tests are included in the next section. The guidelines do not address sporadic infections with influenza C virus, and do not address sporadic human infections with novel influenza A viruses of animal origin.

Seasonal Influenza Background Information—Influenza is caused by infection of the respiratory tract with influenza A, B, or C viruses. Seasonal epidemics of influenza A and B viruses occur each fall, winter, and spring in the United States, while influenza C virus infections occur sporadically. Seasonal influenza A or B virus infections can cause a wide range of manifestations, from asymptomatic infection, uncomplicated illness with or without fever (Table 2), to complications that may result in severe disease (Table 3). One study estimated that during 2010–2016, the seasonal incidence of symptomatic influenza among all ages in the United States was approximately 8% and varied from 3% to 11% [1]. Most people recover from influenza without sequelae, but some persons are considered to be at increased risk for severe and fatal influenza, including children aged <5 years (but especially <2 years), adults aged ≥65 years, pregnant and postpartum women, people with certain chronic medical conditions including pulmonary, cardiac, and metabolic disease, people with immunosuppression, people with extreme obesity, residents of nursing homes, and American Indians and Alaska Natives [2–8] (Table 4). Elderly persons have the highest mortality rates attributable to influenza [8]. Among the high-risk groups, persons considered

to be at very high risk of complications from influenza include those who are severely immunocompromised (eg, hematopoietic stem cell transplant [HSCT] recipients).

During the 2010–2016 influenza seasons, seasonal influenza epidemics were associated with an estimated 4.3–16.7 million medical visits, 140 000–710 000 hospitalizations, and 12 000–56 000 respiratory and circulatory deaths each year in the United States [9]. A recent modeling study estimated a range of 291 243–645 832 seasonal influenza-associated respiratory deaths occurring annually worldwide [10]. Substantial practice variation exists in the diagnosis and treatment of influenza [21–23]. Appropriate diagnosis of influenza and timely use of antiviral medications may decrease unnecessary testing for other etiologies and associated empiric antibiotic use [11, 12], duration of symptoms, hospitalization, the need for critical care, and mortality [13–16].

Influenza vaccine effectiveness varies by age, host immune status, and the match between circulating and vaccine virus strains [24]. Because influenza vaccine effectiveness is widely variable, ranging from very low to approximately 40%–60% in well-matched seasons (<https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm>) [25], a history of current season influenza vaccination does not exclude a diagnosis of influenza.

Typical signs and symptoms of uncomplicated influenza are listed in Table 2. However, atypical presentations of influenza virus infection, with or without fever, should also be considered along with the patient's underlying health and immune function (eg, fever without source in infants; new-onset neurologic signs and symptoms [seizures, altered mental status], more commonly in infants and young children, but possible in adults; new-onset cardiovascular events [heart failure, myocardial infarction or ischemia, cerebrovascular accident] in adults; and exacerbation of chronic medical conditions, with or without fever [particularly cardiac, pulmonary, or neurologic disease], more commonly in adults than in children) (Table 5). Influenza should also be considered in children and adults with pneumonia, and those with severe, complicated, or progressive (worsening) acute respiratory illness, but with no documented alternative diagnosis, and those with an epidemiological link to case(s) of influenza or an influenza outbreak year-round (Table 5).

Influenza is associated with a variety of signs and symptoms that may vary by age, underlying chronic disease, complications, host immune status, and influenza virus type or influenza A virus subtype. Abrupt onset of fever with cough is most predictive of uncomplicated influenza in adult outpatients, with a sensitivity of >70% during the influenza season [26–29]. A retrospective, cross-sectional study in a single urban US emergency department found that the best predictive model for identifying influenza for all ages consisted of cough (diagnostic odds ratio [DOR], 5.87), fever (DOR, 4.49), rhinorrhea (DOR, 1.98), and myalgias (DOR, 1.44) [30]. In a prospective systematic sampling study, fever (temperature $\geq 38^{\circ}\text{C}$) and cough were significantly associated with reverse-transcription polymerase chain reaction (RT-PCR)-confirmed influenza [29]. A prospective study of adults aged 28–50 years across 2 influenza seasons in Taiwan reported that fever and cough had the best sensitivity (86%), while fever, cough, and sneezing had the best specificity (77%) for influenza [31].

While the abrupt onset of fever with cough is a good indicator of influenza, signs and symptoms may vary for patients with different underlying conditions. In a retrospective study of clinical predictors of influenza in hospitalized patients, fever with cough or sore throat had a sensitivity of 43% for patients without asthma, and only 21% for asthmatic patients [32]. A prospective study of >500 influenza patients in North Carolina reported that emergency department patients commonly reported cough, nasal congestion, fever, fatigue/malaise, headache, poor appetite, sore throat, and myalgias/muscle aches, whereas hospitalized patients reported shortness of breath and wheezing [33].

Infants and young children with influenza may not always have fever and may present with a wide range of signs and symptoms [34], making an influenza diagnosis more difficult [29]. Infants and young children may present with fever and suspected sepsis [35, 36]. Diarrhea can occur in up to 28% of infants and young children with influenza [37–39]. A prospective study found that fever >38°C, chills, headache, malaise, and sore eyes were significantly associated with a positive RT-PCR test result for influenza virus in children younger than 15 years [29]. Fever ($\geq 38^\circ\text{C}$), headache, cough, and absence of abnormal breathing sounds in pediatric patients had a positive predictive value of 57.1% [29]. In a retrospective, cross-sectional study, adding rhinorrhea to the fever and cough case definition achieved a better balance between sensitivity (85%) and specificity (47%) among children aged <5 years [30]. In another prospective study among pediatric outpatients aged ≤ 13 years with respiratory infections, fever was the only reliable predictor of culture-confirmed influenza virus infection [40].

Influenza is an important cause of community-acquired pneumonia in adults [41]. Invasive bacterial coinfection may occur (with *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* [group A streptococci], and others) [42–45]. Secondary bacterial pneumonia due to methicillin-resistant *S. aureus* (MRSA) is becoming more prevalent and has been a more common finding in recent pediatric influenza-associated deaths [42, 46–48].

Influenza virus infection of the respiratory tract can result in severe nonpulmonary complications (eg, myocarditis [42, 49], rhabdomyolysis [50–61], encephalitis [53–57], and hypovolemic shock with hyperthermia or hypothermia [46, 58–62]). Myocarditis and encephalitis were the most frequently described extrapulmonary complications associated with influenza in adults in a recent comprehensive review [63]. Exacerbation of chronic disease (eg, coronary artery disease, chronic pulmonary disease, asthma, heart failure) with influenza virus infection can result in severe illness [49, 63–69]. Influenza can trigger acute myocardial infarction [70].

Elderly persons with influenza may present without fever and milder systemic symptoms than younger patients, but with higher frequencies of altered mental status [71–75]. Data from a prospective surveillance study indicated that in patients aged ≥ 65 years hospitalized with acute cardiopulmonary illnesses, the clinical symptoms of cough and/or sore throat combined with a lowered oral temperature threshold ($\geq 37.3^\circ\text{C}$ or 99.0°F) increased sensitivity and specificity of influenza diagnosis [76]. Another prospective study found that cough (odds ratio [OR], 6.4; 95% confidence interval [CI], 3.2–13.0) and feverishness

and/or triage temperature $\geq 37.2^{\circ}\text{C}$ (OR, 3.0; 95% CI, 2.0–4.7) were most predictive of influenza among adults aged ≥ 60 years in the emergency departments of 6 hospitals [77].

Immunocompromised patients may also present without typical findings of influenza. In a study of adult transplant patients, the CDC criteria of ILI, defined as fever and either cough or sore throat, were poorly predictive of RT-PCR-positive cases [78]. In a report of an influenza outbreak in an ambulatory stem cell transplant center, only 7% had signs and symptoms that met the CDC ILI definition; only a minority had fever [79].

Nosocomial acquisition of influenza is a consideration in persons who experience an onset of fever 48 hours or more after hospital admission during the influenza season [80–84]. However, any hospitalized patient may be in the incubation period for influenza virus infection when admitted and become symptomatic during the first few days of hospitalization for other illnesses or injuries. During influenza season, even in the absence of fever, the presence of new onset or worsening or unexplained cough in a hospitalized patient should prompt testing for influenza [32].

In a 2015 prospective study among 504 hospitalized or emergency department patients with laboratory-confirmed influenza, only 29% were clinically diagnosed with influenza [33]. Certain factors made an influenza diagnosis more likely, including having a high-risk condition, being in an inpatient setting, and not having a bacterial infection diagnosis. In the same study of laboratory-confirmed influenza patients, receiving a diagnosis of bacterial infection decreased the likelihood of an influenza diagnosis by 3-fold [33].

During low influenza activity (eg, summer months in the United States), a diagnosis of influenza should be considered for ill international travelers or their ill contacts [85–88] because influenza viruses circulate year-round among persons living in the tropics and during winter periods in temperate climates of the Southern Hemisphere [89, 90]. In addition, influenza should be considered in persons with acute febrile respiratory symptoms who have recently spent time in settings linked to an influenza outbreak. These may include organized tour groups [91], international mass gatherings [92–94], summer camps [95, 96], cruise ships [87, 91, 97–101], and military ships [102].

Clinicians should consider novel influenza A virus infection in the differential diagnosis in travelers who have recently returned from countries affected by poultry outbreaks of avian influenza and who have febrile respiratory symptoms and a recent history of direct or close exposure to poultry (well-appearing, sick or dead birds, or visiting a live poultry market [103, 104]). If novel influenza A virus infection is suspected, clinicians should seek prompt consultation with the local and state health departments for possible testing for novel influenza A virus infection, with laboratory confirmation at the CDC. Updated information on avian influenza is available at the CDC's avian influenza website [19] and the World Health Organization's (WHO) avian influenza website [105]. Novel influenza A virus infection should also be suspected in persons with febrile respiratory illness and a history of recent direct or close contact with pigs, such as at animal exhibits at agricultural fairs [106, 107]. Swine influenza A viruses are endemic among pigs worldwide, including the United States. Human infection with swine influenza A viruses is referred to as "variant virus

infection.” Updated information on variant influenza virus infections is available at the CDC’s variant influenza viruses website [20].

Influenza testing should be performed when the results are anticipated to influence clinical management (impact decision to initiate antiviral therapy, other diagnostic testing, antibiotic use, or IPC measures) or public health response (eg, outbreak identification and interventions). The decision to test is related to the level of suspicion for influenza, local influenza activity, and the sensitivity and specificity of available influenza tests. The appropriate respiratory tract specimen to collect depends upon the approved specimens for the specific influenza test used, patient acceptability, and disease severity. The choice of influenza test depends upon the clinical setting and test performance (Table 6). Clinicians should be aware of the prevalence of influenza viruses among the patient population being tested to help inform the pretest probability of influenza, understand the limitations of influenza tests, and properly interpret the results, particularly negative results (Table 7). Molecular assays that detect influenza virus nucleic acids have the best performance characteristics. Detection of influenza viruses in respiratory specimens by molecular assays is suggestive, but cannot confirm, that infectious virus is present; only isolation of influenza viruses by viral culture can confirm that viable virus is present. A wide range of influenza tests is available for diagnostic purposes:

- i. Rapid influenza molecular assays are a relatively new kind of highly sensitive molecular point-of-care influenza diagnostic test for rapid (15–30 minutes) detection of influenza A and B viral RNA in respiratory specimens, with higher sensitivity than rapid influenza diagnostic tests (RIDTs) that detect influenza viral antigens.
- ii. RT-PCR is a highly sensitive and highly specific testing modality for detection of influenza A and B viral RNA in respiratory specimens, though the results may take 4–6 hours or more once testing is started, and RT-PCR may not be available at all clinical sites. Some of the newer cartridge-based RT-PCR assays can yield results in 60–80 minutes. RT-PCR can be useful as a confirmatory test and identify influenza virus types and influenza A virus subtypes.
- iii. Multiplex RT-PCR assays target a panel of microorganisms using multiplex RT-PCR. Multiplex respiratory pathogen panels range from narrow, targeting influenza A and B viral and RSV RNA, to broad, targeting more than a dozen respiratory viruses and other pathogens in respiratory specimens. Turnaround times to results range from 1 to 8 hours. These assays are preferred for immunocompromised patients and may be useful for other hospitalized patients.
- iv. Immunofluorescence assays include direct fluorescent anti-body or indirect fluorescent antibody staining for influenza virus antigen detection. They have higher sensitivity than RIDTs, but lower sensitivity and specificity compared with viral isolation in cell culture or RT-PCR. Results are available within 2–4 hours after specimen submission. Performance of these assays depends heavily on laboratory expertise and the quality of the specimen collected (ie, specimens must include respiratory epithelium cells; requires a florescent microscope and an experienced laboratory technician).

- v. RIDTs can identify influenza A and B viral nucleoprotein antigens in respiratory specimens and rapidly (<15 minutes) provide results. Most are approved for bedside and office use. Compared with other types of tests (eg, RT-PCR), RIDTs are significantly less sensitive than other methods (false-negative results are not uncommon). RIDTs that utilize analyzer devices generally have higher sensitivity to detect influenza viral antigens than RIDTs without analyzer devices but have lower sensitivity than rapid molecular assays.

Additional tests are available and may have utility under certain circumstances (eg, institutional outbreaks), but are generally not useful for clinical diagnostic purposes. These include:

- i. Viral culture of respiratory specimens, using standard cell culture and shell vial culture, can provide specific information regarding circulating strains and subtypes of seasonal influenza A viruses and influenza B virus strains for public health purposes, especially to inform influenza vaccine strain selection, and is important during both low and high influenza activity. However, because results are not available in a timely manner, viral culture cannot inform clinical management of influenza patients, but can confirm negative test results from RIDTs and immunofluorescence assays, such as during an institutional outbreak, and to provide influenza virus isolates for further characterization.
- ii. Serologic testing results from a single serum specimen cannot be reliably interpreted, and collection of paired (acute/ convalescent) sera 2–3 weeks apart are needed for serological testing. Therefore, serologic testing cannot inform clinical management of influenza patients, but could be useful for seroepidemiology studies.

Recently, the US Food and Drug Administration (FDA) reclassified RIDTs from class I to class II devices, which requires approved tests to meet higher standards for clinical sensitivity and specificity. Most RIDTs and some rapid molecular assays are Clinical Laboratory Improvement Amendments (CLIA) “waived” tests that can be performed in clinical settings or by any clinical laboratory with a CLIA Certificate of Waiver. As the field of approved influenza diagnostics is dynamic, clinicians should consult the CDC website for information on FDA-cleared tests (<https://www.cdc.gov/flu/professionals/diagnosis/index.htm>).

To properly interpret test results, clinicians should understand the limitations of diagnostic tests with lower sensitivities to detect influenza viruses (eg, immunofluorescence assays, rapid antigen tests) and influenza activity among the population being tested. Antiviral treatment, when indicated, should not be delayed until the results of diagnostic testing are available for persons at high risk of complications, those with progressive disease, or patients being admitted to hospital. Interpretation of test results depends on multiple factors, including the level of influenza activity in the population being tested, pretest probability, whether influenza viruses are actively replicating or have recently infected the person being tested, the time from illness onset to specimen collection, the source and quality of respiratory specimen(s), the characteristics of a test, and whether proper procedures were used for specimen collection, transport, and testing [108]. Interpretation of test results relies

on the positive and negative predictive values of a test, which are influenced primarily by the prevalence of influenza viruses in the population tested and on the sensitivity and specificity of the test to detect influenza virus infection vs a “gold standard” test such as RT-PCR assay results [108, 109]. The sensitivity and specificity of an influenza test are fixed parameters, whereas the prevalence of circulating influenza viruses (level of influenza activity) changes over time with influenza activity (eg, in the United States, high influenza activity can occur during the fall, winter, and spring, whereas low influenza activity occurs during the summer).

Multiple studies have reported that rapid influenza diagnostic tests (antigen detection) have low to moderate sensitivity. One meta-analysis of observational studies of rapid influenza antigen testing of respiratory tract specimens (mostly upper respiratory tract specimens) compared to molecular assays or viral culture reported that rapid influenza antigen tests had moderate sensitivity (62%) and high specificity (98%) among all ages [110]. These studies were predominantly among out-patients with uncomplicated influenza. Sensitivity of rapid influenza antigen tests was lower in adults (approximately 54%) than children (approximately 67%), and lower for detection of influenza B viruses than for influenza A viruses [110]. An updated meta-analysis of observational studies of rapid influenza antigen tests reported pooled sensitivities of 54% and 53% to detect influenza A and influenza B virus antigens, respectively, and pooled specificities of 99%, compared with RT-PCR [111]. Low sensitivity to detect influenza A(H1N1)pdm09 virus was reported for some rapid antigen tests [112]. Other studies reported higher sensitivities for detection of influenza A(H3N2) than for A(H1N1)pdm09 and influenza B viruses compared with RT-PCR [113, 114]. One meta-analysis of observational studies of rapid influenza antigen tests to detect A(H1N1) pdm09 virus reported a sensitivity of 51% and specificity of 98% compared with RT-PCR [115]. One comparative study reported variability in the analytical sensitivity of different rapid influenza antigen tests to detect dilutions of influenza viruses [116]. Use of an analyzer device for rapid influenza diagnostic tests to detect influenza viral antigens (immunoassay or immunofluorescence assay) had moderately high pooled sensitivity (80% and 77%) compared with RT-PCR [111]. Higher sensitivity to detect influenza viruses in respiratory specimens has been reported for one rapid molecular assay (isothermal nucleic acid amplification) than for rapid antigen detection tests [117–119], and a meta-analysis of rapid molecular assays reported pooled sensitivities of 92% and 95% for detection of influenza A and B viruses, respectively, and pooled specificities of 99% [111].

The timing and site of respiratory specimen collection can affect influenza testing results. The sensitivity of influenza screening assays such as rapid diagnostic tests is somewhat higher when respiratory specimens are collected within 48–72 hours of illness onset due to reduction in influenza viral shedding after this period [120]. RT-PCR is more likely to still be positive later in illness. Viral shedding is more prolonged in infants, young children, and immunocompromised patients. Testing of lower respiratory tract specimens by RT-PCR in critically ill patients with respiratory failure can yield higher detection of influenza viruses compared with upper respiratory tract specimens [121, 122].

The high specificity among most influenza screening tests and molecular assays indicates that the frequency of false-positive results is generally very low, especially when influenza

activity is high in the patient population tested. The potential for a false-positive result is higher when influenza activity is very low (eg, when influenza viruses are not circulating among the population tested such as during summer months) for a patient without a known influenza epidemiological link (exposure to a person with influenza in areas where influenza activity is high [eg, opposite hemisphere or to tropical/subtropical areas] or to an influenza outbreak). A positive influenza test result in a person without known exposure to influenza during low influenza periods (low positive predictive value) could be a false positive. Collection of additional respiratory specimens for testing of influenza viruses by molecular assays should be considered for outpatients who are at high risk for influenza complications and hospitalized patients with suspected influenza, and antiviral treatment should be started promptly while molecular assay results are pending.

Persons who receive live attenuated influenza virus vaccine for intranasal administration can shed influenza vaccine virus strains in the upper respiratory tract for up to 7 days after intranasal vaccination and can test positive during this period [123–125]. Clinicians should also consider that a positive influenza test result does not exclude bacterial coinfection, and evaluation of the potential need for antibiotics, especially in patients with pneumonia, should be considered.

The choice of an antiviral drug for treatment or chemoprophylaxis should be based on the approved and recommended ages, route of administration, whether contraindications exist for the use of a particular product, and knowledge of antiviral resistance patterns. Antiviral resistance information is available in the weekly CDC influenza surveillance report (<https://www.cdc.gov/flu/weekly/index.htm>), and the latest information about approved antivirals is available on the CDC website (<http://www.cdc.gov/flu/professionals/index.htm>).

The risk of influenza-associated complications is not identical among all high-risk persons, and antiviral chemoprophylaxis is likely to have the greatest benefit among those at highest risk of influenza complications and death, particularly if influenza vaccination is contraindicated or not expected to be effective (eg, severely immunocompromised persons). If antiviral chemoprophylaxis is given to close contacts of high-risk persons while awaiting an immune response to influenza vaccination, it should be continued for 2 weeks after vaccination until an immune response is expected (6 weeks for children aged 6 months to <9 years not previously vaccinated and who require 2 doses). Antiviral chemoprophylaxis should not be given for 2 weeks after administration of live attenuated influenza virus vaccine. If pos-texposure antiviral chemoprophylaxis is administered, it should be given within 48 hours of exposure to a person with influenza.

DIAGNOSIS

Which Patients Should Be Tested for Influenza?

Recommendations

Outpatients (including emergency department patients).

1. During influenza activity (defined as the circulation of seasonal influenza A and B viruses among persons in the local community) (see Figure 1):

- Clinicians should test for influenza in immunocompromised and high-risk patients who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (eg, cough without fever) if the testing result will influence clinical management (*A-III*).
- Clinicians should test for influenza in patients who present with acute onset of respiratory symptoms with or without fever, and either exacerbation of chronic medical conditions (eg, asthma, chronic obstructive pulmonary heart disease [COPD], heart failure) or known complications of influenza (eg, pneumonia) if the testing result will influence clinical management (*A-III*) (see Table 3).
- Clinicians can consider influenza testing for patients not at high risk for influenza complications who present with influenza-like illness, pneumonia, or nonspecific respiratory illness (eg, cough without fever) and who are likely to be discharged home if the results might influence antiviral treatment decisions or reduce use of unnecessary antibiotics, further diagnostic testing, and time in the emergency department, or if the results might influence antiviral treatment or chemoprophylaxis decisions for high-risk household contacts (see recommendations 40–42) (*C-III*).

2. During low influenza activity without any link to an influenza outbreak:

- Clinicians can consider influenza testing in patients with acute, febrile respiratory tract illness, especially for immunocompromised and high-risk patients (*B-III*).

Hospitalized Patients.

3. During influenza activity:

- Clinicians should test for influenza on admission in all patients requiring hospitalization with acute respiratory illness, including pneumonia, with or without fever (*A-II*).
- Clinicians should test for influenza on admission in all patients with acute worsening of chronic cardiopulmonary disease (eg, COPD, asthma, coronary artery disease, or congestive heart failure), as influenza can be associated with exacerbation of underlying conditions (*A-III*).
- Clinicians should test for influenza on admission in all patients who are immunocompromised or at high risk of complications and present with acute onset of respiratory symptoms with or without fever, as the manifestations of influenza in such patients are frequently less characteristic than in immunocompetent individuals (*A-III*).
- Clinicians should test for influenza in all patients who, while hospitalized, develop acute onset of respiratory symptoms with or

without fever, or respiratory distress, without a clear alternative diagnosis (*A-III*).

4. During periods of low influenza activity:

- Clinicians should test for influenza on admission in all patients requiring hospitalization with acute respiratory illness, with or without fever, who have an epidemiological link to a person diagnosed with influenza, an influenza outbreak or outbreak of acute febrile respiratory illness of uncertain cause, or who recently traveled from an area with known influenza activity (*A-II*).
- Clinicians can consider testing for influenza in patients with acute, febrile respiratory tract illness, especially children and adults who are immunocompromised or at high risk of complications, or if the results might influence antiviral treatment or chemoprophylaxis decisions for high-risk household contacts (see recommendations 41–43) (*B-III*).

Evidence Summary

Although clinical diagnosis during influenza outbreaks has reasonable sensitivity and specificity, laboratory testing should be performed when the results may influence clinical management or infection prevention and control decisions. During periods of high influenza activity, influenza is typically diagnosed based on presenting illness signs and symptoms. Cough and fever provide the most predictive signs and symptoms when influenza viruses are circulating in the community [126]. However, influenza may be clinically indistinguishable from illness caused by other infectious etiologies (including bacterial and other viral infections such as respiratory syncytial virus, parainfluenza virus, human metapneumovirus, and adenovirus) [127]. Various case definitions and scoring systems designed to predict the likelihood of influenza have low specificity and predictability [30, 128–133].

An algorithmic approach may help optimize the use of influenza testing (Figure 1). If influenza testing of high-risk outpatients with suspected influenza to confirm influenza is not feasible, or if testing will not change clinical management decisions, a clinical diagnosis of influenza without testing can support empiric antiviral treatment decisions. Influenza testing is recommended for all hospitalized patients during influenza season with acute respiratory illness including pneumonia, respiratory failure, or exacerbation of a chronic condition (eg, asthma, coronary artery disease, COPD) [65–67] and for immunocompromised patients with any of the above or nonspecific respiratory symptoms or unexplained fever [134]. Influenza testing can help inform management and IPC measures in hospitalized patients. A test confirming influenza may reduce the unnecessary use of antibiotics (especially if the procalcitonin level is low, suggesting that bacterial infection is unlikely) and improve antibiotic stewardship. Also, influenza testing can be helpful in hospitalized patients to reduce unnecessary antiviral therapy if a highly sensitive influenza test (eg, molecular assay) does not confirm influenza (especially when another microbial etiology is identified).

One randomized clinical trial (RCT), performed at medical wards of 2 teaching hospitals in the United Kingdom, found no evidence that RT-PCR testing for influenza influenced

antibiotic prescribing or clinical outcome in adult patients; however, few study patients with RT-PCR-confirmed influenza were prescribed antiviral treatment [135]. The authors suggested this was in part due to the length of illness prior to admission (>48 hours) or unfamiliarity by physicians with RT-PCR. In contrast, several observational studies have reported benefits of influenza testing. In a retrospective study of data from the National Hospital Ambulatory Medical Care Survey, influenza testing resulted in fewer ancillary and other diagnostic tests (ie, chest radiography, blood culture, urinalysis, complete blood count) and more frequent use of antivirals [136]. Another study reported that rapid influenza diagnostic testing resulted in early receipt of antiviral treatment as compared with relying on the presence of risk factors alone [137]. In a retrospective study, rapid influenza testing led to a significant reduction in antibiotic use among hospitalized adults [12]. A study from 2 hospitals in Belgium during the 2015 influenza season reported that use of a rapid molecular assay in emergency departments helped avoid 10.7% of hospitalizations, 46.4% of antibiotic prescriptions, and 42.9% of additional investigations for influenza-positive patients, and helped facilitate prescription of oseltamivir and patient isolation [138]. In a prospective trial in the United Kingdom, use of a rapid multiplex polymerase chain reaction (PCR) test in patients hospitalized with acute respiratory illness increased appropriate use of anti-virals for patients with laboratory-confirmed influenza from 65% to 91% and decreased length of hospital stay by 1 day [139]. Use of a rapid RT-PCR-based influenza assay decreased unnecessary antiviral use among adult patients hospitalized for acute respiratory tract infection who tested negative for influenza [140].

A randomized controlled trial using a rapid influenza antigen test in a pediatric emergency department demonstrated that among young children with febrile acute respiratory illness, rapid testing resulted in fewer diagnostic tests, fewer antibiotic prescriptions, and decreased length of stay in the emergency department [11]. Use of a respiratory viral panel test for children admitted to the hospital with an acute respiratory tract illness resulted in shorter time to diagnosis, duration of antibiotic use, and length of inpatient stay [141]. One study used a decision analytic model to compare costs of care and outcomes using 4 different strategies for influenza testing in children (rapid multiplex PCR; traditional RT-PCR; direct-fluorescent antibody staining; and rapid antigen tests). Despite the increased cost, when considering the potential to reduce inappropriate antibiotic use and other costs of care, the most effective test was rapid multiplex PCR [142]. Other studies have reported that a confirmatory influenza test result reduced the use of unnecessary antibiotics and patient waiting time in outpatient clinics and emergency departments [136, 143–145].

Laboratory testing is important for immunocompromised patients since the manifestations of influenza virus infection in such patients are frequently less characteristic than in immunocompetent patients.

What Specimen(s) Should Be Collected When Testing Patients for Influenza?

Recommendations

5. Clinicians should collect upper respiratory tract specimens from outpatients for influenza testing as soon after illness onset as possible, preferably within 4 days of symptom onset (A-II).

- Nasopharyngeal (NP) specimens should be collected over other upper respiratory tract specimens to increase detection of influenza viruses (*A-II*).
 - If NP specimens are not available, nasal and throat swab specimens should be collected and combined together for influenza testing over single specimens from either site (particularly over throat swabs) to increase detection of influenza viruses (*A-II*).
 - Mid-turbinate nasal swab specimens should be collected over throat swab specimens to increase detection of influenza viruses (*A-II*).
 - Flocked swab specimens should be collected over non-flocked swab specimens to improve detection of influenza viruses (*A-II*).
6. Clinicians should collect NP (optimally, as for outpatients), mid-turbinate nasal, or combined nasal-throat specimens from hospitalized patients without severe lower respiratory tract disease for influenza testing as soon as possible (*A-II*).
 7. Clinicians should collect endotracheal aspirate or broncho-alveolar lavage (BAL) fluid specimens from hospitalized patients with respiratory failure receiving mechanical ventilation, including patients with negative influenza testing results on upper respiratory tract specimens, for influenza testing as soon as possible (*A-II*).
 8. Clinicians should not collect or routinely test specimens for influenza from nonrespiratory sites such as blood, plasma, serum, cerebrospinal fluid (CSF), urine, and stool (*A-III*).
 9. Clinicians should not collect serum specimens, including single or paired sera, for serological diagnosis of seasonal influenza virus infection for clinical management purposes (*A-III*).

Evidence Summary

In most persons, infectious influenza virus levels in the upper respiratory tract of persons with uncomplicated influenza peak during the first 1–2 days after illness onset, and decline to undetectable levels within a week [146, 147]. Collection of upper respiratory tract specimens from immunocompetent outpatients with influenza >3–4 days after illness onset may yield negative results because of substantially decreased influenza viral shedding, especially in older children and adults. Influenza viruses might be detectable in upper respiratory tract specimens for longer periods in some patients, particularly when molecular assays are used. Infants and young children and adults hospitalized with severe lower respiratory tract illness often shed influenza viruses for ≥ 1 week. Immunocompromised patients may have prolonged influenza virus replication and shed infectious influenza viruses for weeks to months, even when asymptomatic or without fever [134, 148].

The appropriate respiratory tract specimen to collect depends upon which influenza test is used and patient acceptability. Prospective evaluation of clinical specimens in patients with influenza A(H1N1)pdm09, A(H1N1), or A(H3N2) virus infections documented that the

highest viral load and best sensitivity are obtained from NP aspirate, followed by nasal or NP swab, and then throat swab specimens [149]. NP aspirate specimens are acceptable for multiple types of influenza tests [150], but are more cumbersome to obtain and less well tolerated by patients. Similar sensitivity in detecting respiratory viruses has been demonstrated for mid-turbinate nasal swab specimens compared with NP swabs [151]. For molecular assays, NP or mid-turbinate nasal swab specimens are the preferred upper respiratory tract specimens. However, mid-turbinate swabs may not be approved for all assays or accepted by all laboratories. Oropharyngeal specimens (eg, throat swabs) generally have a lower yield for detection of seasonal influenza viruses [152], but may still produce positive results, especially when molecular assays are used. Testing sputum specimens by RT-PCR can increase the detection of influenza viral RNA over combined nasal and throat swabs [153–155].

Some influenza diagnostic assays have been tested and FDA approved for respiratory specimens collected from specific sites, although published studies have utilized other respiratory specimens such as combined specimens or lower respiratory tract specimens. Clinicians should check both the approved clinical specimens for a specific assay and what specimens are accepted by clinical laboratories before collecting specimens. Some assays (eg, a few rapid influenza diagnostic tests) require the exact swab supplied with the test being used. Use of a flocked nasal swab (with fibers projecting outward) may increase the detection of influenza viruses over a nonflocked swab and have a similar yield as NP aspirate [156].

Testing of a combined specimen (a nasal swab and a throat swab placed together) can be used to increase test sensitivity over testing each swab separately. Testing combined specimens from 3 sites (combined nasal and throat swabs plus a nasal aspirate) was more sensitive for detecting influenza A(H1N1) pdm09 virus than any single sample [157]. Paired nasal-throat swabs are similar in sensitivity to NP aspirates in children when evaluated by molecular assay and are more readily tolerated [158]. Addition of a throat swab to a nasal specimen using molecular testing has been shown to slightly increase recovery of influenza viruses in pediatric patients in some studies [159], but not in others [160]. For the detection of influenza viruses by nonmolecular assays, combined specimens or NP aspirates should be considered. In the hospitalized patient, the use of flocked mid-turbinate nasal swabs, combined nasal plus throat swabs, or NP aspirates is recommended.

In critically ill patients with respiratory failure who are receiving mechanical ventilation, a lower respiratory tract specimen (endotracheal aspirate or BAL fluid) should be obtained for influenza testing. Lower respiratory tract specimens have much higher sensitivity for detection of influenza viruses in critically ill patients because influenza virus shedding may be lower or have stopped in the upper respiratory tract, whereas influenza viral replication in the lower respiratory tract may be higher and prolonged [121, 122, 161–163].

Seasonal influenza viruses infect the respiratory tract and typically are not associated with viremia. Influenza viral RNA has rarely been detected in blood, although detection in severely immunosuppressed persons and critically ill patients with influenza has been reported, but whether this represents viremia is unclear [164–166]. A large autopsy series of

100 fatal cases found no evidence of extrapulmonary influenza A(H1N1) pdm09 virus infection [167]. Therefore, except for research purposes or for special patient populations, there is no diagnostic utility to routinely collect whole blood, plasma, or serum specimens for seasonal influenza virus testing by any assay.

The pathogenesis of influenza-associated neurologic complications (including encephalopathy, encephalitis, acute disseminated encephalomyelitis, cerebral vascular accident, Guillain-Barré syndrome) is complex and may be related to inflammation of the nervous system caused by cytokine dysregulation triggered by influenza virus infection of the respiratory tract [168, 169]. Therefore, CSF testing for influenza for suspected seasonal influenza-associated central nervous system disease is not routinely recommended. Clinicians should test respiratory specimens for influenza if influenza-associated neurologic complications are suspected.

Renal failure can occur in critically ill influenza patients [63, 170, 171] but does not represent kidney infection, and evidence of seasonal influenza viruses has very rarely been reported in urine [172]; therefore, collection of urine for influenza testing is not recommended.

Influenza viral RNA or infectious virus has rarely been detected in stool, and such detection is of unknown clinical importance [38, 173–175]; therefore, testing of stool for influenza viruses is not recommended.

For serological diagnosis of seasonal influenza virus infection, paired acute and convalescent serum specimens must be collected and tested together, and cannot inform clinical management. There is no validated immunoglobulin M assay or other available serologic assay to diagnose seasonal influenza virus infection in a single serum specimen. Therefore, single serum or paired sera specimens should not be collected for influenza serology except for research purposes.

What Test(s) Should Be Used to Diagnose Influenza?

Recommendations

10. Clinicians should use rapid molecular assays (ie, nucleic acid amplification tests) over RIDTs in outpatients to improve detection of influenza virus infection (*A-II*) (see Table 6).
11. Clinicians should use reverse-transcription polymerase chain reaction (RT-PCR) or other molecular assays over other influenza tests in hospitalized patients to improve detection of influenza virus infection (*A-II*) (see Table 6).
12. Clinicians should use multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized immunocompromised patients (*A-III*).
13. Clinicians can consider using multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses, in hospitalized patients who

are not immunocompromised if it might influence care (eg, aid in isolation decisions, reduce other testing or antibiotic use) (*B-III*).

14. Clinicians should not use immunofluorescence assays for influenza virus antigen detection in hospitalized patients except when more sensitive molecular assays are not available (*A-II*), and follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative immunofluorescence test results (*A-III*).
15. Clinicians should not use RIDTs in hospitalized patients except when more sensitive molecular assays are not available (*A-II*), and follow-up testing with RT-PCR or other molecular assays should be performed to confirm negative RIDT results (*A-II*).
16. Clinicians should not use viral culture for initial or primary diagnosis of influenza because results will not be available in a timely manner to inform clinical management (*A-III*), but viral culture can be considered to confirm negative test results from RIDTs and immunofluorescence assays, such as during an institutional outbreak, and to provide isolates for further characterization (*C-II*).
17. Clinicians should not use serologic testing for diagnosis of influenza because results from a single serum specimen cannot be reliably interpreted, and collection of paired (acute/convalescent) sera 2–3 weeks apart are needed for serological testing (*A-III*).

Evidence Summary

There are multiple options for influenza diagnostic and confirmatory testing [108]. The ideal diagnostic test should produce rapid, accurate results with high sensitivity and high specificity to detect influenza viruses in respiratory specimens at reasonable cost. Each test has strengths and weaknesses and a thoughtful diagnostic approach is important (see information on influenza testing and clinical algorithms available on the CDC website: <https://www.cdc.gov/flu/professionals/diagnosis/index.htm>).

Rapid influenza molecular assays that detect influenza viral RNA utilizing different nucleic acid amplification technologies have recently been approved by the FDA. These rapid molecular assays generally have moderately high to high sensitivity (66%–99%) and high specificity (55%–99%), depending upon the virus type, compared with RT-PCR assays [111, 117, 176–184]. In some studies, sensitivity and specificity of rapid molecular assays were reported to be slightly lower for influenza B viruses than for influenza A viruses.

RT-PCR assays, whether real-time or multiplex, are highly sensitive and highly specific nucleic acid amplification tests for detection of influenza viral RNA. RT-PCR assays produce results in significantly less time than viral culture and are frequently used as a confirmatory test [126]. There are multiple assays approved by the FDA. These assays are also useful for testing individuals with suspected influenza during low influenza periods. Some commercially available molecular assays can distinguish between influenza A virus subtypes. Molecular techniques for influenza diagnosis continue to advance; additional and

updated information is available at the CDC's influenza website (<http://www.cdc.gov/flu/professionals/diagnosis/index.htm>).

Immunofluorescence assays require laboratory expertise and a fluorescent microscope, and take longer to produce results than RIDTs, rapid molecular assays, and some RT-PCR assays, but have generally better sensitivity and specificity than RIDTs [185, 186]. However, some immunofluorescence assays may be part of a respiratory panel and thus useful for the identification of other respiratory viruses.

RIDTs are primarily point-of-care immunoassays; one test is an immunofluorescent assay. RIDTs have utility in community- and hospital-based outpatient settings because of their rapid processing times. Some RIDTs utilize an analyzer device for standardizing results and improving test sensitivity to detect influenza viral antigens [111]. However, the sensitivities for RIDTs range from very low to moderate (ie, approximately 10%–70%), often yielding false-negative results, while specificities are high (ie, approximately 90%–99%), compared with RT-PCR or viral culture [110, 111, 115, 116, 187]. Therefore, RIDTs are not recommended for use in hospitalized patients with suspected influenza, and rapid influenza molecular assays may be a better alternative in outpatient settings.

TREATMENT

Which Patients With Suspected or Confirmed Influenza Should Be Treated With Antivirals?

Recommendations

18. Clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza, irrespective of influenza vaccination history, who meet the following criteria:
 - Persons of any age who are hospitalized with influenza, regardless of illness duration prior to hospitalization (*A-II*).
 - Outpatients of any age with severe or progressive illness, regardless of illness duration (*A-III*).
 - Outpatients who are at high risk of complications from influenza, including those with chronic medical conditions and immunocompromised patients (*A-II*).
 - Children younger than 2 years and adults aged ≥ 65 years (*A-III*).
 - Pregnant women and those within 2 weeks postpartum (*A-III*).
19. Clinicians can consider antiviral treatment for adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history, who are either:
 - Outpatients with illness onset ≤ 2 days before presentation (*C-I*).
 - Symptomatic outpatients who are household contacts of persons who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised (*C-III*).

- Symptomatic healthcare providers who routinely care for patients who are at high risk of developing complications from influenza, particularly those who are severely immunocompromised (*C-III*).

Evidence Summary

Influenza can result in a wide range of clinical signs, symptoms, and complications of variable severity, from self-limited upper respiratory tract illness, to life-threatening illness with respiratory failure and prolonged respiratory tract influenza virus replication. The clinical and virologic impact of NAI antiviral treatment of influenza is dependent on several factors: immune status of the host, underlying medical conditions, age, virus type or influenza A virus subtype, and illness duration and severity when antiviral treatment is started [13, 16, 188–199]. The relevant study population to assess clinical benefit of NAI treatment is patients with laboratory-confirmed influenza (intention-to-treat-infected). There is no evidence that NAIs have benefit for ill patients with-out influenza virus infection. Therefore, in studies of NAI treatment of patients with nonspecific ILI without documentation of influenza virus infection (intention-to-treat), clinical outcomes are biased toward lower efficacy or effectiveness [14] than in studies of treatment of laboratory-confirmed influenza.

Most RCTs of NAI treatment of outpatients with seasonal influenza were conducted before 2009, whereas most observational studies of NAI treatment were done during or after the 2009 H1N1 pandemic. Systematic reviews and meta-analyses of RCTs of early NAI treatment in generally healthy outpatients with uncomplicated laboratory-confirmed influenza reported clinical benefit in reducing illness duration in children and adults, and in reducing risk of hospitalization in adults [194, 200]. A meta-analysis of observational data for high-risk pediatric and adult outpatients with laboratory-confirmed influenza reported that NAI treatment reduced the risk of hospitalization for any cause [201]. Survival benefit of NAI treatment of hospitalized adult patients with laboratory-confirmed influenza was reported by one systematic review of the published systematic reviews of observational studies [202] and 2 meta-analyses of observational studies [13, 16], but not in another meta-analysis [203].

Randomized placebo-controlled clinical trials that established the efficacy of NAIs in reducing the duration of fever and symptoms by approximately 1–2 days were conducted among mostly non-high-risk adult and pediatric outpatients with uncomplicated laboratory-confirmed influenza, enrolled within 36–48 hours of illness onset [188–191, 204–206]. Greater clinical benefit was reported when NAI treatment was started very early; in both adults and children, NAI treatment started within 6 hours of illness onset reduced symptoms by about 4 days [26, 197, 207]. Systematic reviews and meta-analyses of RCTs indicate that early initiation (within 2 days of illness onset) of antiviral treatment can reduce the duration of fever and symptoms, especially in nonasthmatic children; decrease the risk of otitis media in children; and reduce the risk of lower respiratory tract complications requiring antibiotics and of hospitalization in adults [14, 194, 200].

Because high-risk outpatients with suspected or confirmed influenza are recommended for prompt antiviral treatment, placebo-controlled studies are generally not possible in many

countries, and the benefits of antiviral therapy in different high-risk groups to reduce complications have not been reported in completed prospective, randomized, placebo-controlled trials. However, an individual patient data meta-analysis of >3000 outpatients at high risk for complications with laboratory-confirmed influenza reported that NAI treatment significantly reduced the likelihood of hospital admission [201].

There are no fully enrolled prospective, randomized, placebo-controlled trials of oral oseltamivir or inhaled zanamivir in hospitalized influenza patients. A pooled meta-analysis of observational studies with individual-level data from >29 000 hospitalized patients (86% with laboratory-confirmed influenza, 14% clinically diagnosed with influenza) reported survival benefit of NAI treatment (primarily oseltamivir) in adults compared with no treatment, with significantly greater survival benefit with early (within 2 days of illness onset) compared with later initiation (>2 days after onset) of NAI treatment [16]. This study also reported that NAI treatment (including started >2 days after onset) vs no treatment had significant survival benefit in critically ill adults and in pregnant and postpartum women with influenza [16]. In contrast, when mortality was analyzed as the endpoint for children aged <16 years hospitalized with influenza, the meta-analysis reported that early vs later initiation of NAI treatment, and early initiation vs no treatment, did not have significant survival benefit, although the low number of deaths limited statistical power [16, 195]. Other observational studies of hospitalized influenza patients have reported that NAI treatment shortened the duration of hospitalization and reduced the risk of mechanical ventilation in children [196, 208], and improved survival in adults [199].

The majority of observational studies, individual patient-level pooled analyses, and meta-analyses of patients with laboratory-confirmed influenza have reported clinical benefit of NAI treatment (primarily oral oseltamivir) among hospitalized patients, including persons at high risk for influenza complications (Table 4), including when NAI treatment was started >48 hours after illness onset [13, 15, 16, 192–196, 198, 199, 209, 210]. However, a small number of observational studies and one meta-analysis of observational studies of hospitalized influenza patients reported that NAI treatment did not have survival benefit [203, 211, 212]. In studies showing a benefit, the greatest clinical benefit was reported when antiviral treatment was started within 2 days of illness onset, but benefit was noted even when treatment was started in most patients 4–5 days and up to 7 days after illness onset [15, 16, 193, 199, 209].

Although prompt antiviral treatment is recommended for high-risk outpatients with suspected or confirmed influenza, a study of high-risk persons during 2011–2016 reported that of those who presented to outpatient care within 2 days of onset of acute respiratory illness symptoms, only 15% were prescribed antiviral treatment, including 37% with RT-PCR-confirmed influenza [213]. In this study, 40% of high-risk persons presented for medical care within 2 days of illness onset. Another study reported that while the proportion of hospitalized influenza patients who received antiviral treatment increased during 2010–2011 to 2014–2015, the percentage was higher in adults than children, and only 56% were treated on the day of admission [214]. A study of hospitalized pediatric influenza patients reported that the proportion that received antiviral treatment increased from 20% to 69% overall during 2007–2015, but varied from 42% to 90% among 46 hospitals during 2014–

2015 [23]. Because the clinical benefit of NAI treatment is greatest the earlier that treatment is initiated, we recommend starting empiric antiviral treatment as soon as possible without waiting for influenza testing results when patients with suspected influenza are being admitted to the hospital.

Early antiviral treatment of influenza in outpatients reduces the likelihood of antibiotic use for physician-diagnosed complications and may reduce secondary bacterial coinfection (otitis media, pneumonia) [13, 191, 194, 200, 215]. Thus, antiviral treatment of influenza has the potential to decrease medical care costs and antibiotic-attributable adverse events, and potentially decrease bacterial resistance to antibiotics. Well-described risk factors for influenza complications allow clinicians to target patients who are most likely to benefit from prompt antiviral treatment of influenza (Table 4) [134, 170, 208, 216–221].

Data from the 2009 H1N1 pandemic highlighted the impact of A(H1N1)pdm09 virus infection on pregnant and postpartum women [222–224]. While risk of severe morbidity and mortality from influenza occurs throughout pregnancy, these risks are higher in the second and third trimesters [225–227]. During the 2009 H1N1 pandemic, of 30 maternal deaths in the United States, 7.1% occurred in the first trimester; 26.8% in the second trimester, and 64.3% in the third trimester [3]. One meta-analysis of seasonal and pandemic influenza studies reported that increased influenza-associated mortality risk occurs in the third trimester compared to the first or second trimesters, but also extends 4 weeks postpartum [228]. The etiology for this increase in disease severity may reflect normal physiologic changes of pregnancy including an altered immune system, decreased lung capacity as the uterus grows, increased heart rate and oxygen consumption, and increased colloid oncotic pressure.

Maternal morbidity associated with influenza includes a greater risk for hospitalization, intensive care unit (ICU) admission, and adult respiratory distress syndrome [3, 209, 229–233]. Some studies reported that influenza during pregnancy may lead to preterm labor and small for gestational age infants [224, 234–240]. However, other studies of infants born to women who had laboratory-confirmed influenza during pregnancy have not shown higher rates of prematurity, preterm labor, low birth weight, or lower Apgar scores compared with infants born to uninfected women [230, 241, 242]. One meta-analysis reported an association of maternal influenza to congenital birth defects including neural tube and heart defects [243]. In addition, influenza during pregnancy can precipitate spontaneous abortion [244, 245]. A study of the 2009 H1N1 pandemic in California reported that pregnant and postpartum women who received antiviral treatment >2 days after presentation were more likely to be admitted to the ICU or die compared to those treated ≤2 days after presentation [209]. A meta-analysis of data from hospitalized patients with A(H1N1)pdm09 virus infection worldwide reported that pregnant and postpartum women treated with NAIs within 2 days of admission were 20% less likely to die compared to those treated later [16].

Annual influenza vaccination can prevent influenza, but influenza vaccine effectiveness has ranged from low to moderate in preventing medically attended outpatient visits and hospitalizations, and may have lower effectiveness in immunocompromised patients, who may also experience prolonged influenza viral replication [134]. A history of current season

influenza vaccination does not exclude a diagnosis of influenza in either immunocompetent or immunocompromised patients. Therefore, antiviral treatment should be initiated as soon as possible in hospitalized patients, high-risk persons, and those with severe or progressive disease if influenza is suspected, irrespective of receipt of influenza vaccine.

No primary studies exist of the effectiveness of antiviral treatment of uncomplicated influenza in a non-high-risk person to prevent influenza in a household contact who is at high risk for influenza complications, including immunocompromised persons. However, data from a prospective, randomized, placebo-controlled trial in Bangladesh to assess the impact of antiviral treatment of an index case on household spread of influenza documented a small but significant decrease in the number of secondary cases [246]. Retrospective observational studies have suggested benefit of antiviral treatment in reducing transmission to household contacts [247, 248]. Therefore, early antiviral treatment of persons with uncomplicated influenza who have household members that are immunocompromised is recommended to provide potential benefit in reducing the risk of influenza in the household contacts. See recommendations 40–42 and Evidence summary for discussion of the role of postexposure prophylaxis in high-risk patients who are close contacts of influenza patients.

For Patients Who Are Recommended to Receive Antiviral Treatment for Suspected or Confirmed Influenza, Which Antiviral Should Be Prescribed, at What Dosing, and for What Duration?

Recommendations

20. Clinicians should start antiviral treatment as soon as possible with a single NAI (either oral oseltamivir, inhaled zanamivir, or intravenous peramivir) and not use a combination of NAIs (*A-I*).
21. Clinicians should not routinely use higher doses of FDA-approved NAI drugs for the treatment of seasonal influenza (*A-II*).
22. Clinicians should treat uncomplicated influenza in otherwise healthy ambulatory patients for 5 days with oral oseltamivir or inhaled zanamivir, or a single dose of intravenous peramivir (*A-I*).
23. Clinicians can consider longer duration of antiviral treatment for patients with a documented or suspected immunocompromising condition or patients requiring hospitalization for severe lower respiratory tract disease (especially pneumonia or acute respiratory distress syndrome [ARDS]), as influenza viral replication is often protracted (*C-III*).

Evidence Summary

Clinicians should maintain familiarity with local patterns of influenza activity in their communities throughout influenza season. Current and frequently updated information on antiviral resistance and approved antivirals is available on the CDC's influenza website (<http://www.cdc.gov/flu>).

Based on seasonal influenza virus susceptibility patterns observed through virologic surveillance from 2009 through 2017, the use of an NAI is recommended—either oral

oseltamivir, inhaled zanamivir, or intravenous (IV) peramivir for early treatment of uncomplicated influenza in pediatric and adult patients. Therapy should be started as soon as possible and generally should not be delayed while awaiting influenza test results.

The adamantane influenza antiviral agents, with activity only against susceptible influenza A viruses, are not recommended for treatment of influenza A given documented high levels of adamantane resistance among circulating influenza A viruses in recent years [249, 250].

Risks and benefits may differ between specific antiviral agents for various patient populations based on age, underlying medical conditions, immune function, severity of illness, and different influenza virus strains. Comparative prospective, controlled data on outcomes with different antiviral agents do not exist for most of these risk groups and conditions. One superiority-design RCT without a placebo arm did not demonstrate superiority of investigational IV zanamivir to oral oseltamivir in hospitalized patients with laboratory-confirmed influenza [251]. One RCT of monotherapy with oral oseltamivir or inhaled zanamivir compared with combination oral oseltamivir plus inhaled zanamivir treatment or placebo in adult outpatients with lab oratory-confirmed influenza reported that oral oseltamivir demonstrated both significant reduction in viral shedding at day 2 of treatment and significant reduction in the median time to resolution of illness symptoms compared with inhaled zanamivir [252]. In addition, oral oseltamivir had both significant virologic and clinical benefit compared with combination oseltamivir-zanamivir treatment, whereas the oseltamivir-zanamivir combination treatment had significant virologic, but not significant clinical, benefit compared with inhaled zanamivir [252]. One RCT reported that combination oral therapy with oseltamivir, amantadine, and ribavirin resulted in a significant but modest reduction in influenza viral shedding at treatment day 3, but was not associated with significant reduction in multiple clinical endpoints compared with oseltamivir monotherapy in adult outpatients with laboratory-confirmed influenza [253]. Based upon available evidence, recommendations are provided below for specific antiviral agents, route, dosing, and duration of therapy.

Oseltamivir treatment is associated with gastrointestinal symptoms. Meta-analyses of RCTs among outpatients with lab oratory-confirmed influenza reported that oseltamivir treatment vs placebo was significantly associated with vomiting (relative risk [RR], 1.63) in children [200] and nausea (RR, 1.6; risk difference, 3.7%) and vomiting (RR, 2.43; risk difference, 4.7%) in adults [194]. Similar findings were reported in a systematic review of oseltamivir RCTs in children and adults [254]. No significant differences were found in any serious adverse events or study withdrawal due to adverse events in these pediatric and adult RCTs [194, 200]. Although post-marketing reports of severe abnormal behavior in adolescents with influenza after starting oseltamivir treatment have been reported primarily in Japan, no differences in the estimated incidence of life-threatening abnormal behavior were identified among patients treated with 4 different NAIs, including oseltamivir, in Japan [255]. Another study that utilized national medical claims data reported that the estimated risk of severe abnormal behavior was lower for Japanese children prescribed oseltamivir than those who were not prescribed an NAI [256]. A case-crossover analysis of administrative data found no association with suicide for oseltamivir exposure or influenza diagnosis [257]. A self-controlled case series study in Japan could not exclude the possibility that severe abnormal

behavior was induced by influenza [258]. A meta-analysis of RCTs of inhaled zanamivir treatment reported no evidence of an increase in reported adverse events vs placebo in children or adults [259]. A combined analysis of data from one phase 2 RCT and one phase 3 RCT of peramivir treatment reported that the frequency of adverse events was similar to placebo [260].

Dosing and Duration

Adults—Drug dosing is standardized for oral oseltamivir and inhaled zanamivir (Table 8). Oseltamivir phosphate is metabolized to the active metabolite oseltamivir carboxylate by hepatic esterases and renally excreted; dosage adjustment for oseltamivir is indicated for reduced renal function. Zanamivir is administered as an orally inhaled powder, concentrated in the respiratory tract with limited systemic absorption that is excreted unchanged by the kidneys. Duration of therapy with oseltamivir and zanamivir for ambulatory adults with uncomplicated influenza is 5 days. In ambulatory adults with uncomplicated influenza, peramivir administered as a single IV dose is an alternative, but is costlier. In hospitalized adults, oseltamivir is the preferred antiviral drug because data are very limited on inhaled zanamivir in severely ill influenza patients.

Modifications in Special Populations

Pediatrics—Oseltamivir (tablets or oral suspension formulation) may be administered to all pediatric age groups with influenza, including premature infants [216]. Duration of therapy for ambulatory children with uncomplicated influenza is 5 days. Dosing is based upon age and weight; however, the FDA has not reviewed data on safety and efficacy of oseltamivir in neonates <2 weeks of age. Although only limited pharmacokinetic data are available for oseltamivir in neonates and premature infants, 3 mg/kg/ dose twice daily has been used in some studies, although one open-label adaptive design study reported that doses of 3.5 mg/ kg were needed to produce drug exposures approaching the efficacious exposure levels in adults [261, 262]. One study that utilized a pharmacokinetic model based upon data from samples collected from neonates treated with oseltamivir suggested use of lower oseltamivir doses in premature (1 mg/kg) and term infants (2 mg/kg) [263]. Documented increased morbidity and mortality of influenza in newborn and very young infants should be balanced by the anticipated benefits of therapy given the available limited pharmacokinetics and safety data in this very young population [6]. Zanamivir (inhalation) is FDA-approved for treatment of uncomplicated influenza in children aged ≥7 years. Dosing and duration of uncomplicated influenza is the same for all pediatric age groups (2 inhalations twice daily for 5 days).

Peramivir is the only FDA-approved IV antiviral drug and is approved for early treatment of uncomplicated influenza in outpatients aged ≥2 years. Peramivir single-dose pharmacokinetics were studied in children ranging in age from ≥28 days to <16 years during the 2009 H1N1 pandemic [264], and infants and children were treated on a compassionate use basis [265]. For infants and children with influenza who cannot tolerate oral therapy, IV peramivir can be considered. Intravenous zanamivir has been evaluated in adults [251] and children [266], but is not FDA approved and is not currently available.

Geriatrics—There are no published randomized controlled clinical trials of antiviral treatment of influenza in geriatric populations. Since some elderly individuals may not be able to correctly use the inhaler device to effectively deliver zanamivir, caution should be used in prescribing inhaled zanamivir in patients with cognitive or physical limitations [267].

Pregnancy—Influenza may be associated with increased risk of adverse outcomes to the fetus and an increased risk of maternal complications and death. Observational studies suggest that early antiviral treatment provides improved clinical outcomes compared with no therapy or late initiation of antiviral treatment in hospitalized pregnant women with influenza [16, 209, 268]. However, no randomized, prospective, controlled trials of antiviral treatment in pregnant or postpartum women have been conducted to date. Oseltamivir is preferred for treatment of influenza in pregnant women over inhaled zanamivir because of concerns about lower lung volumes resulting in reduced drug distribution and concerns about bronchospasm. Oseltamivir is also preferred over IV peramivir because of the dearth of pharmacokinetic or safety data for peramivir in pregnant women [222]. Pharmacokinetic studies of oseltamivir comparing pregnant and nonpregnant women found that pregnant women have a lower systemic exposure of oseltamivir carboxylate due to increased renal filtration and secretion [269]. Based on pharmacokinetic modeling, a 30% dose increase of oseltamivir phosphate was estimated to be needed to attain comparable systemic exposure of oseltamivir carboxylate to nonpregnant women (105 mg once daily for prophylaxis and 105 mg twice daily for treatment) [270]. Therefore, higher dosing of oseltamivir can be considered, especially for pregnant women who are hospitalized with influenza complications, although there are no safety data supporting higher doses in pregnancy. Any potential benefit of higher oseltamivir dosing should be weighed against the severity of disease and the potential for unknown toxicities, and this is best done in the context of a study. The lower systemic exposure might also compromise the effectiveness of once-daily oseltamivir chemoprophylaxis.

Both oseltamivir phosphate and the metabolite oseltamivir carboxylate have been demonstrated to cross the placenta [271–276]. The safety of oseltamivir during pregnancy has been evaluated in several cohort studies and there is no evidence that oseltamivir causes harm to women or their babies [275–278]. Although oseltamivir carboxylate is detectable at low concentrations in the breastmilk of lactating women who received oseltamivir [276], the benefits of oseltamivir treatment of influenza in the mother outweigh any potential risk of exposure in the infant. There is no need to discontinue breastfeeding due to the use of oral oseltamivir.

The safety of inhaled zanamivir has been evaluated in small cohort studies, which showed no harm to pregnant women and their exposed babies [279–281]. Systemic exposure is lower in pregnancy with inhaled zanamivir than oseltamivir, and has been recommended by some experts when chemoprophylaxis of influenza is prescribed for pregnant women [222]. Zanamivir is detectable at low concentrations in breastmilk of lactating women who received inhaled zanamivir [276]. There is no need to discontinue breastfeeding due to the use of inhaled zanamivir.

There are very limited data on the safety or effectiveness of IV peramivir in pregnancy [265, 282–284]. There are also very limited data on the safety or effectiveness of the investigational drug IV zanamivir in pregnancy [285, 286]. No recommendation can be made about the use of IV peramivir or IV zanamivir in pregnant women with influenza at this time. No information is available on the use of peramivir during breastfeeding.

Immunocompromised Patients—Influenza viral replication in the respiratory tract, including asymptomatic shedding, can be prolonged, and emergence of resistant variants during or after antiviral treatment can occur more frequently in immunocompromised patients than in immunocompetent patients [134, 287–289]. There are limited data to define the optimal duration of therapy for influenza in immunocompromised patients, but retrospectively collected data suggest that treatment can safely extend to 10 days or longer. Rebound in influenza viral replication has been observed in some patients treated for 5 days, and longer duration of treatment is advisable if the disease course is severe and influenza viral RNA remains detectable. There are no data to support the use of higher doses of oseltamivir in this population. Early initiation of antiviral therapy is associated with the best outcomes [290], although clinical benefit has been reported when starting treatment >48 hours after symptom onset [291, 292].

Critical Illness—Antiviral treatment should be started as soon as possible for critically ill patients with suspected or laboratory-confirmed influenza. Although the benefits of therapy are greatest if therapy is started within 48 hours of illness onset, there is evidence of clinical benefit with later initiation of therapy in critically ill adults [16]. Although critically ill patients may have a variety of complications that alter drug absorption and excretion (ie, altered gastrointestinal motility, renal dysfunction), most studies suggest that oral oseltamivir, when administered by nasogastric tube, results in adequate drug exposures [293]. For patients requiring extracorporeal membrane oxygenation, data suggest that no dosage adjustment of oseltamivir is needed, although dose reduction is generally needed for patients on continuous renal replacement therapy [294, 295]. Nebulization of the commercial formulation of zanamivir containing lactose should be avoided in intubated patients, given documented severe and fatal complications reported with this mode of administration [296, 297]. Patients with significant hypoxemia who are not receiving mechanical ventilation may not be able to reliably use the disk inhaler device needed to effectively deliver inhaled zanamivir.

Adequate studies have not been conducted to define which patients may benefit from therapy with an IV antiviral medication. Intravenous peramivir can be considered if there are contraindications to enteric administration of oseltamivir or if adequate bioavailability is in question. Of note, IV peramivir given once daily to hospitalized adults and children aged ≥7 years, in addition to standard of care, failed to show superiority vs placebo [298], although enrollment criteria did not exclude patients based on duration of illness. If IV peramivir is used for hospitalized patients, consideration should be given to administering a multiday dosing regimen, although the optimal regimen is unknown.

Prolonged viral replication and shedding in the upper and lower respiratory tracts may occur in critically ill patients with influenza viral pneumonia [161, 299]. Given the possibility of

clinical deterioration following an initial clinical response if antivirals are stopped prior to a substantial antiviral effect, continuing antiviral treatment may be beneficial beyond 5 days, but the appropriate treatment duration has not been defined. Virologic testing in patients with a prolonged clinical course may help guide duration of antiviral treatment. Most studies have failed to demonstrate a benefit of higher doses of oseltamivir, including one RCT in hospitalized children and adults, and nonrandomized studies in hospitalized and critically ill adults [300].

Obese Populations—The volume of distribution of the metabolite oseltamivir carboxylate is not significantly different in nonobese and obese patients, and obese (including extremely obese) patients appear to have similar plasma levels as nonobese patients. This suggests standard oseltamivir dosing irrespective of weight in adults [301, 302].

Patients With Underlying Lung Disease—Because of the potential for exacerbation of reactive airway disease in influenza patients with COPD, asthma, or bronchospasm, noninhaled antiviral treatment may be safer in these individuals, although controlled studies are not available. One placebo-controlled RCT of inhaled zanamivir in influenza patients with mild to moderate asthma or COPD found adequate tolerance and symptom benefit [303]. If inhaled zan-amivir is used, bronchodilators should be readily available in case bronchospasm occurs [304].

In a Patient With Suspected or Confirmed Influenza, When Should Bacterial Coinfection of the Upper or Lower Respiratory Tract Be Considered, Investigated, and Treated?

Recommendations

24. Clinicians should investigate and empirically treat bacterial coinfection in patients with suspected or laboratory-confirmed influenza who present initially with severe disease (extensive pneumonia, respiratory failure, hypotension, and fever), in addition to antiviral treatment for influenza (*A-II*).
25. Clinicians should investigate and empirically treat bacterial coinfection in patients who deteriorate after initial improvement, particularly in those treated with antivirals (*A-III*).
26. Clinicians can consider investigating bacterial coinfection in patients who fail to improve after 3–5 days of antiviral treatment (*C-III*).

Evidence Summary

Several respiratory syndromes can be associated with either bacterial or viral pathogen infections or coinfections, including community-acquired pneumonia, sinusitis, pharyngitis, and acute otitis media. Respiratory viral infection, including influenza virus infection, can be difficult to distinguish from bacterial infection. The patient's age, underlying medical conditions, clinical signs and symptoms, disease severity, time of the year, and known circulation of respiratory viruses in the community are important considerations for clinical management. Bacterial coinfection with influenza virus infection can be present at the time of medical evaluation or may develop later and manifest with clinical deterioration. Lower

respiratory tract bacterial coinfection with influenza carries significant morbidity [122, 305, 306]. Some investigators have attributed the majority of deaths during the 1918 H1N1 pandemic to bacterial coinfection [307]. Bacterial coinfection contributed to critical and fatal illness during the 2009 H1N1 pandemic [122, 167, 308–310]. It is likely that the risk of pneumonia with bacterial coinfection varies by influenza virus strain [307, 310].

Streptococcus pneumoniae is the most common bacterial coinfection associated with influenza and pneumonia [310–314], but *S. aureus*, including methicillin-resistant strains [48, 315–317], and *S. pyogenes* coinfections have also been reported in patients with pneumonia and influenza [167, 318, 319]. Early antiviral treatment of influenza can reduce the risk of otitis media in young children and the need for antibiotic therapy for lower respiratory tract complications [189, 191, 194]. For additional guidance, see IDSA guidelines on the management of community-acquired pneumonia, *S. aureus* infections, and rhinosinusitis.

Guidance for the diagnosis and treatment of bacterial infection among several special populations is available, including guidance for the management of neonatal bacterial sepsis [320], sepsis among pregnant woman, infections among solid organ transplant recipients [321], and patients with human immunodeficiency virus infection (see guidelines for prevention and treatment of opportunistic infections: <https://aidsinfo.nih.gov>). Guidance for hospitalized patients to assess and treat those at risk of hospital-acquired bacterial pneumonia and ventilator-associated pneumonia has also been published [322–324]. Given the higher incidence of *S. aureus* infections, including MRSA among patients with severe pneumonia complicating influenza, agents with activity against MRSA should be included in the empiric treatment regimen for critically ill patients. There are no data to support the safety or efficacy of antibiotic chemoprophylaxis to prevent bacterial complications in patients with influenza.

Unfortunately, there are few tools or diagnostic strategies that reliably differentiate influenza virus infection alone from influenza and bacterial coinfection. Procalcitonin (PCT) and C-reactive protein (CRP) have both been used in an attempt to differentiate between bacterial and viral pneumonia. Very low levels of PCT, but not low levels of CRP, have high negative predictive value for bacterial infection, although clinical judgement is indicated [305, 309, 325]. One systematic review and meta-analysis reported that PCT tests have high sensitivity, particularly for ICU patients, but low specificity to identify bacterial coinfection in influenza patients [326]. The diagnostic value for PCT to exclude bacterial coinfection among influenza patients was reasonably high in this study [326]. One meta-analysis of data from patients with acute respiratory infections enrolled in 26 RCTs reported that procalcitonin-guided antibiotic treatment reduced 30-day mortality, antibiotic exposures, and antibiotic-related adverse effects [327].

If a Patient With Influenza Does Not Demonstrate Clinical Improvement With Antiviral Treatment or Demonstrates Clinical Deterioration During or After Treatment, What Additional Testing and Therapy Should Be Considered?

Recommendation

27. Clinicians should investigate other causes besides influenza virus infection in influenza patients who fail to improve or deteriorate despite antiviral treatment (*A-III*).

Evidence Summary

There are limited data to inform when clinical response to antiviral treatment can be expected in patients with influenza. In patients who do not demonstrate clinical improvement after at least 2–3 days of antiviral treatment, especially when treatment is initiated early in the clinical course, consideration should be given to potential alternative explanations. Development of complications should also be considered in patients with clinical deterioration (Table 9). However, lack of clinical improvement while receiving adequate antiviral treatment can occur in severely ill patients with influenza. Evaluation and management should be individualized. Specific guidance on evaluation and management of specific problems is beyond the scope of these guidelines.

There are some patient population-specific issues to consider:

- Pediatric populations: Influenza morbidity and hospitalization rates are much higher in children aged <2 years than in older children and young adults, likely due to the immature immune system in young children and lack of previous exposure and immunity to circulating influenza viruses [328, 329]. Extrapulmonary complications of influenza such as myocarditis, myositis, and encephalitis can occur in previously healthy children.
- Pregnant women: Metabolism of oseltamivir is increased in pregnancy, reducing exposure to oseltamivir carboxylate by 30% compared to nonpregnant women [269, 270]. Some experts have suggested consideration of higher oseltamivir dosing. Deterioration to respiratory failure and ARDS in pregnant women with influenza may necessitate emergency cesarean delivery in the ICU [234].
- Immunocompromised patients: Lung transplant and HSCT recipients may be more susceptible to development of influenza viral pneumonia, in addition to bacterial and fungal coinfections. Management should include involvement of an infectious diseases physician competent in infectious diseases in transplant recipients, if available. Data on colonizing respiratory tract flora in lung transplant patients should help to inform empiric antibiotic coverage. Immunosuppressed patients, especially HSCT patients, who are treated with NAIs are more likely to experience emergence of antiviral resistance during or after therapy in part due to a poor host response, with prolonged influenza virus replication [134]. However, prolonged replication of influenza viruses in the respiratory tract can occur in such patients without emergence of antiviral resistance. Antiviral resistance is discussed in the next section. Clinicians should

be aware that adverse events associated with immunosuppressive agents may result in clinical deterioration in severely immunosuppressed patients. For example, pneumonitis has been reported with multiple immunosuppressive drugs, including in patients receiving mammalian target of rapamycin (mTOR) inhibitors such as sirolimus or everolimus [330, 331].

When Should Testing Be Done for Infection With an Antiviral-resistant Influenza Virus?

Recommendations

28. Influenza NAI resistance testing can be considered for:
 - Patients who develop laboratory-confirmed influenza while on or immediately after NAI chemoprophylaxis (*C-III*).
 - Patients with an immunocompromising condition and evidence of persistent influenza viral replication (eg, after 7–10 days, demonstrated by persistently positive RT-PCR or viral culture results) and remain ill during or after NAI treatment (*B-III*).
 - Patients with laboratory-confirmed influenza who inadvertently received subtherapeutic NAI dosing and remain ill (*C-III*).
 - Patients with severe influenza who do not improve with NAI treatment and have evidence of persistent influenza viral replication (eg, after 7–10 days) (*C-II*).
29. Clinicians should remain informed on current CDC and WHO surveillance data on the frequency and geographic distribution of NAI-resistant influenza viruses during influenza season, and with the latest CDC antiviral treatment recommendations (*A-III*).

Evidence Summary

Influenza virus resistance to NAI drugs is detected infrequently in clinically significant situations [246]. A patient may be infected with NAI-resistant influenza virus circulating in the community, or resistance may develop during therapy. In the first situation, the patient will not respond to appropriate therapy, and in the second, clinical deterioration may occur following an initial response. The emergence of NAI resistance during antiviral chemoprophylaxis or treatment has been reported uncommonly in immunocompetent patients [189, 246, 332–334]. In contrast, NAI resistance has been reported among severely immunocompromised patients more frequently than immunocompetent patients during prolonged influenza viral replication and antiviral treatment, and after postexposure antiviral chemoprophylaxis [289, 335–342]. Patients who received subtherapeutic NAI dosing and who remain ill with laboratory-confirmed influenza might be at increased risk of emergence of NAI-resistant virus, although the risk is likely higher in severely immunocompromised patients. While some studies have suggested that young children with uncomplicated influenza may also be at higher risk for the emergence of drug resistance during or after NAI use based on molecular detection methods, presumably due to longer viral shedding, no effect on illness resolution has been reported [246, 333, 334, 343].

If there is clinical suspicion of antiviral resistance as the cause of failure to improve or clinical deterioration, it is critical to consider a change in NAI treatment and to perform testing to confirm the presence of continued viral replication and to document resistance. NAI resistance can vary among influenza viruses and the specific NAI being used. The most commonly detected molecular marker of resistance is the H275Y substitution in viral neuraminidase in A(H1N1)pdm09 and other N1-containing influenza A viruses, which confers highly reduced susceptibility to oseltamivir and reduced susceptibility to peramivir while maintaining susceptibility to zanamivir [344, 345]. Less common molecular markers of resistance that have been reported include the E119E/V and R292K substitutions in the neuraminidase of A(H3N2) and avian influenza A(H7N9) viruses, which confer highly reduced susceptibility to oseltamivir [250, 346]. R292K confers reduced susceptibility to all licensed NAIs, much greater for oseltamivir than zanamivir, and should prompt consultation with an infectious disease specialist. Currently, only testing for the H275Y marker in A(H1N1)pdm09 viruses is available commercially. Comprehensive testing for molecular markers associated with NAI resistance requires specialized assays that may be available at some public health and academic laboratories.

In general, influenza patients who were treated with oseltamivir and are suspected of developing oseltamivir resistance should be switched to inhaled zanamivir, unless contraindicated. Inhaled zanamivir is FDA approved for children aged ≥ 5 years for chemoprophylaxis and ≥ 7 years for treatment, but there are limited options for treating oseltamivir-resistant virus. Clinicians should evaluate the ability to reliably use inhaled zanamivir in children 5–7 years old. Consultation should be sought with an expert on management of patients with antiviral-resistant influenza virus infection.

There are no randomized trials to inform the optimal management of patients infected with influenza viruses with resistance to NAIs. Two studies conducted during 2008–2009 when H275Y H1N1 virus variants (oseltamivir resistant, but amantadine and zanamivir susceptible) circulated in the community suggested that treatment with zanamivir or a related drug, lani-namivir, had superior clinical outcomes compared to oseltamivir [347, 348]. Most of the available clinical data from patients with resistant virus infections that emerged during treatment are derived from case reports and case series in which patients on oseltamivir treatment were switched to other antivirals often late in the clinical course of their illness [285, 286, 340, 349–353]. The best outcomes appear to be associated with early change in antiviral therapy to an agent with in vitro activity against the oseltamivir-resistant influenza virus. Combination antiviral therapy with 2 or more active agents with different mechanisms of action is an investigational approach that may reduce the development of additional de novo resistance in immunocompromised patients and other patients at higher risk for the emergence of resistant viruses during or after therapy [354, 355]. Use of convalescent plasma or intravenous immunoglobulin (IVIg) that contains neutralizing antibodies [356, 357], as well as other antiviral agents (eg, polymerase inhibitors baloxavir marboxil, pimodivir, favipiravir), are under investigation.

Community Circulation of Antiviral-Resistant Influenza Viruses—Currently, circulation of NAI-resistant influenza viruses is rare, although limited community circulation of oseltamivir-resistant A(H1N1)pdm09 viruses has been reported in several

countries [358–360]. The CDC and WHO perform ongoing assessment of the antiviral susceptibility of circulating influenza viruses [349]; updated summaries of US data are available at <https://www.cdc.gov/flu/weekly/summary.htm>. If circulation of NAI- resistant influenza viruses increases in prevalence, updated guidance will be available from the CDC.

Should Adjunctive Therapy Be Administered to Patients With Suspected or Confirmed Influenza?

Recommendations

30. Clinicians should not administer corticosteroid adjunctive therapy for the treatment of adults or children with suspected or confirmed seasonal influenza, influenza-associated pneumonia, respiratory failure, or ARDS, unless clinically indicated for other reasons (*A-III*).
31. Clinicians should not routinely administer immunomodulation using immunoglobulin preparations such as IVIg for treatment of adults or children with suspected or confirmed seasonal influenza (*A-III*).

Evidence Summary

Corticosteroid Therapy—While current evidence is limited, corticosteroid treatment of influenza patients should be avoided unless clinically indicated for other reasons (eg, exacerbation of asthma, COPD, low-dose hydrocortisone for adrenal insufficiency or refractory septic shock), as the risks of corticosteroid treatment are not balanced by a documented clinical benefit in the treatment of influenza [361]. For those who require corticosteroid therapy, systematically collected data on clinical and virologic response to antiviral therapy from randomized prospective trials are not available; these patients may not respond to antiviral treatment as expected in otherwise healthy populations.

Data from randomized controlled clinical trials of corticosteroid treatment of influenza patients are not available. One RCT of corticosteroid treatment of mechanically ventilated adults with influenza A(H1N1)pdm09 virus infection did not complete enrollment [362]. One RCT of hydrocortisone treatment of mechanically ventilated adults with septic shock of multiple infectious etiologies reported no significant difference in 90-day mortality vs placebo [363]. Two meta-analyses of methodologically weaker observational studies (including concurrent antiviral treatment for most patients) reported that despite the limitations of the included studies, corticosteroid treatment of hospitalized influenza patients appeared to be associated with increased mortality, but firm conclusions were not possible due to lack of information on dosing, or indication for corticosteroid treatment [364, 365]. An additional meta-analysis of published observational studies suggested that not only was mortality increased, but also nosocomial bacterial infection, duration of mechanical ventilation, and ICU stay were greater in corticosteroid-treated patients (patient ages not reported) with suspected or confirmed influenza [366].

Most observational studies of corticosteroid treatment of hospitalized patients have been reported in adults [199, 367, 368]. One observational study reported that early corticosteroid treatment (within 72 hours of illness onset) of patients with influenza A(H1N1)pdm09 virus

infection was associated with increased mortality [369]. In 2 observational studies that utilized propensity scoring to adjust for confounding by treatment assignment, corticosteroid treatment of critically ill adults with influenza A(H1N1)pdm09 virus infection was associated with longer duration of mechanical ventilation and increased mortality [367, 368]. One observational study of critically ill children with influenza A(H1N1)pdm09 virus infection reported that those who received high-dose corticosteroids had an elevated risk of death compared to those not treated with high-dose corticosteroids [308].

One large retrospective observational study not included in any meta-analyses reported data for 607 adults hospitalized with influenza A(H1N1)pdm09 in 51 Canadian ICUs [370]. In-hospital mortality was significantly higher in patients treated with corticosteroids in crude and multivariable analyses; however, further analyses using propensity scoring matching, and adjusting for time-dependent between-group differences during ICU admission, did not demonstrate significant differences in mortality between patients treated with and without corticosteroids, demonstrating the need to control for covariates that may impact survival [370]. Another large observational study, not included in any meta-analyses, of 2141 adolescents and adults hospitalized with influenza A(H1N1)pdm09 viral pneumonia in China used propensity score-matched case-control analysis. Low- to moderate-dose (25–150 mg/day methylprednisolone or equivalent), but not higher-dose, corticosteroid treatment was associated with lower 30-day mortality compared with no treatment (adjusted hazard ratio [aHR], 0.64; 95% CI, .43–.96; $P = .033$) [371]. In patients with mild or worse hypoxemia (partial pressure of arterial oxygen/fraction of inspired oxygen [$\text{PaO}_2/\text{FIO}_2$] <300 mm Hg), low-to moderate-dose, but not high-dose, corticosteroid treatment significantly reduced 30-day and 60-day mortality [371]. However, in patients with mild disease ($\text{PaO}_2/\text{FIO}_2 \geq 300$ mm Hg), corticosteroid treatment was not associated with survival benefit, and was associated with higher 60-day mortality.

A case-control study from China analyzed corticosteroid use in hospitalized adults with avian influenza A(H7N9) virus infection from 84 cities within 16 provinces using propensity score matching with multivariable Cox regression [372]. Mortality at 60 days was higher in patients who received corticosteroids compared with those who did not (aHR, 1.98; 95% CI, 1.03–3.79; $P = .04$). In this study, a subgroup analysis demonstrated that patients who received high doses (>150 mg/ day methylprednisolone or equivalent) had much higher 30-day and 60-day mortality than those who received no steroid therapy ($P = .031$ and $P = .002$, respectively) [372]. There was no significant impact on mortality for patients who received low to moderate doses of corticosteroids compared with matched controls without corticosteroid treatment.

Multiple observational studies have reported that corticosteroid treatment was associated with prolonged influenza viral shedding [373–375], including A(H7N9) viral shedding and emergence of antiviral resistance [346], and secondary bacterial and invasive fungal coinfections [199, 376–378].

Passive Immunotherapy—Immunotherapy with plasma, immune serum globulin, or IVIg can result in immune-modulating as well as virus neutralizing activity. Following infection, influenza virus strain-specific antiviral activity is present in convalescent plasma

of immunocompetent persons. During the 2009 H1N1 pandemic, a prospective cohort study in Hong Kong reported that treatment with convalescent plasma containing virus-specific neutralizing antibodies reduced respiratory tract A(H1N1)pdm09 viral load, serum cytokine response, and mortality compared with untreated patients [379]. In a multicenter, prospective, double-blind, randomized controlled trial of hyperimmune IVIg for severe illness with influenza A(H1N1)pdm09 virus infection (17 received hyperimmune IVIg from persons who recovered from laboratory-confirmed influenza A(H1N1)pdm09 virus infection, 18 received IVIg created from donors prior to the pandemic as a control group), hyperimmune IVIg treatment was associated with significant reduction in respiratory tract viral load and mortality [357]. An open-label multicenter RCT of convalescent or postimmunization plasma (containing variable concentrations of hemagglutinin inhibition antibodies) treatment plus standard care vs standard care alone in hospitalized children and adults with laboratory-confirmed influenza did not find significant clinical benefit or antiviral effects, but convalescent plasma was well-tolerated, and a phase 3 trial is under way [380].

Additional research from randomized controlled trials to confirm these findings and to assess the contributions of immunomodulation vs antiviral activity are needed before recommendations can be made for administration of convalescent plasma, IVIg, or other immunoglobulin preparations to patients with severe influenza.

Other Immunomodulatory Agents—Studies of other drugs with immune-modulating activity, such as the hydroxy-methylglutaryl-coenzyme A reductase inhibitors (statins), have been proposed as adjunctive therapy for influenza, but no prospective data are available on which to make recommendations [381]. An open-label, randomized controlled trial of oseltamivir and azithromycin vs oseltamivir alone for treatment of adults hospitalized with laboratory-confirmed influenza in Hong Kong reported that oseltamivir and azithromycin treatment significantly reduced several proinflammatory cytokines compared with oseltamivir alone [382]. One open-label randomized controlled trial of a combination of clarithromycin, naproxen, and oseltamivir vs oseltamivir alone for early treatment of elderly patients hospitalized with laboratory-confirmed influenza reported that the combination significantly reduced 30-day mortality [383]. Further randomized controlled trials of adjunctive macrolide antibiotic treatment and nonsteroidal anti-inflammatory drugs are needed before recommendations can be made.

ANTIVIRAL CHEMOPROPHYLAXIS IN COMMUNITY SETTINGS

Who Should Be Considered for Antiviral Chemoprophylaxis to Prevent Influenza in the Absence of Exposure or an Institutional Outbreak (Preexposure Chemoprophylaxis)?

Recommendations—Antiviral drugs should not be used for routine or widespread chemoprophylaxis outside of institutional outbreaks; antiviral chemoprophylaxis can be considered in certain situations:

32. Clinicians can consider antiviral chemoprophylaxis for the duration of the influenza season for adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza and for whom influenza

vaccination is contraindicated, unavailable, or expected to have low effectiveness (eg, persons who are significantly immunocompromised) (*C-II*).

33. Clinicians can consider antiviral chemoprophylaxis for the duration of the influenza season for adults and children aged ≥ 3 months who have the highest risk of influenza-associated complications, such as recipients of HSCT in the first 6–12 months posttransplant and lung transplant recipients (*B-II*).
34. Clinicians can consider short-term antiviral chemoprophylaxis in conjunction with prompt administration of inactivated influenza vaccine for unvaccinated adults and children aged ≥ 3 months who are at high risk of developing complications from influenza in whom influenza vaccination is expected to be effective (but not yet administered) when influenza activity has been detected in the community (*C-II*).
35. Clinicians can consider short-term antiviral chemoprophylaxis for unvaccinated adults, including healthcare personnel, and for children aged ≥ 3 months who are in close contact with persons at high risk of developing influenza complications during periods of influenza activity when influenza vaccination is contraindicated or unavailable and these high-risk persons are unable to take antiviral chemoprophylaxis (*C-III*).
36. Clinicians can consider educating patients and parents of patients to arrange for early empiric initiation of antiviral treatment as an alternative to antiviral chemoprophylaxis (*C-III*).

Which Antiviral Drugs Should Be Used for Preexposure Chemoprophylaxis for Influenza?

Recommendation

37. Clinicians should use an NAI (oral oseltamivir or inhaled zanamivir) if preexposure chemoprophylaxis for influenza is administered rather than an adamantane antiviral (*A-II*).

What Is the Duration of Preexposure Antiviral Chemoprophylaxis to Prevent Influenza?

Recommendations

38. Clinicians should administer preexposure antiviral chemoprophylaxis for adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza (eg, severely immunocompromised persons such as HSCT recipients) and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness, as soon as influenza activity is detected in the community and continued for the duration of community influenza activity (*A-II*).
39. Clinicians should test for influenza and switch to antiviral treatment dosing in persons receiving preexposure antiviral chemoprophylaxis who become symptomatic, preferably with an antiviral drug with a different resistance profile if not contraindicated (*A-II*).

Which Asymptomatic Persons Exposed to Influenza Should Be Considered for Postexposure Antiviral Chemoprophylaxis in a Noninstitutional Setting?

Recommendations

40. Clinicians can consider postexposure antiviral chemoprophylaxis for asymptomatic adults and children aged ≥ 3 months who are at very high risk of developing complications from influenza (eg, severely immunocompromised persons) and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness after household exposure to influenza (*C-II*).
41. Clinicians can consider postexposure antiviral chemoprophylaxis (in conjunction with influenza vaccination) for adults and children aged ≥ 3 months who are unvaccinated and are household contacts of a person at very high risk of complications from influenza (eg, severely immunocompromised persons), after household exposure to influenza (*C-II*).
42. Clinicians can consider educating patients and arranging for early empiric initiation of antiviral treatment as an alternative to postexposure antiviral chemoprophylaxis (*C-III*).

When Should Postexposure Antiviral Chemoprophylaxis Be Started?

Recommendations

43. If chemoprophylaxis is given, clinicians should administer postexposure antiviral chemoprophylaxis as soon as possible after exposure, ideally no later than 48 hours after exposure (*A-III*).
44. Clinicians should not administer once-daily postexposure antiviral chemoprophylaxis if >48 hours has elapsed since exposure. Full-dose empiric antiviral treatment should be initiated as soon as symptoms occur, if treatment is indicated (*A-III*).

How Long Should Postexposure Antiviral Chemoprophylaxis Be Given?

Recommendations

45. Clinicians should administer postexposure antiviral chemoprophylaxis in a nonoutbreak setting for 7 days after the most recent exposure to a close contact with influenza (*A-III*).
46. Clinicians should test for influenza and switch to antiviral treatment dosing in persons receiving postexposure antiviral chemoprophylaxis who become symptomatic, preferably with an antiviral drug with a different resistance profile if not contraindicated (*A-III*).

Which Antiviral Drugs Should Be Used for Postexposure Chemoprophylaxis?

Recommendation

47. Clinicians should administer an NAI (inhaled zanamivir or oral oseltamivir) if postexposure chemoprophylaxis for influenza is given, rather than an adamantane antiviral (*A-II*).

Evidence Summary

Nine randomized controlled clinical trials [206, 384–391] and 2 meta-analyses [392, 393] have demonstrated that preexposure or postexposure antiviral chemoprophylaxis with an NAI (oral oseltamivir or inhaled zanamivir) decreases the likelihood of developing symptomatic laboratory-confirmed influenza. Three of these randomized trials evaluated preexposure NAI chemoprophylaxis. In one study, oral oseltamivir was 74% effective (95% CI, 53%–88%; attack rate, 4.8% vs 1.3%) in preventing symptomatic laboratory-confirmed influenza when given to predominantly healthy unvaccinated adults for 42 days [384]. In another, inhaled zanamivir given for 28 days was 84% effective (95% CI, 55%–94%; attack rate, 3.4% vs 0.5%) for symptomatic laboratory-confirmed influenza and 67% effective (95% CI, 39%–83%) against laboratory-confirmed influenza meeting a strict case definition [385]. Among 3363 adults and adolescents at high risk of influenza complications, inhaled zanamivir for 28 days was 83% effective (95% CI, 56%–93%) at preventing symptomatic laboratory-confirmed influenza [391].

A single study evaluated oseltamivir chemoprophylaxis for 12 weeks in solid organ and HSCT recipients. There was no significant difference in the primary endpoint, laboratory-confirmed clinical influenza, in the intent-to-treat population (2.9% vs 2.1%; 95% CI, –2.3 to 4.1; efficacy, 28%); a borderline significant benefit was detected in a secondary analysis using RT-PCR and excluding patients who were RT-PCR positive at study entry (3.0% vs 0.04%; 95% CI, .1–5.7; efficacy, 86%) [394].

Oseltamivir chemoprophylaxis is associated with a modest increase in upper gastrointestinal symptoms; 12% and 15% when used once or twice daily respectively, significantly more frequent than among placebo recipients (5%) [384]. The rate of reported adverse events among patients using inhaled zanamivir for extended chemoprophylaxis was not different than among those using a placebo inhaler [384]. A study of extended (16 weeks) oral oseltamivir or inhaled zanamivir chemoprophylaxis vs placebo among Thai healthcare personnel reported no significant differences in adverse events and no withdrawals by drug recipients [395].

When considering whether to use extended antiviral chemoprophylaxis during seasonal influenza epidemics, it is important to appreciate that absolute risk reductions were modest and the number needed to treat (NNT) in studies conducted to date were high. This varied with influenza vaccine use and severity of seasonal influenza epidemics. Oseltamivir chemoprophylaxis given once or twice daily vs placebo for 6 weeks reduced laboratory-confirmed influenza by 3.5% in an unvaccinated adult population (from 4.8% to 1.3%; NNT to prevent one case of laboratory-confirmed symptomatic influenza, 29) [384]. Zanamivir chemoprophylaxis for 6 weeks vs placebo in unvaccinated adults resulted in a 3% reduction

in laboratory-confirmed influenza with fever (3.4% to 0.5%; NNT, 33) [385], and a 1.2% reduction when used for 28 days vs placebo in high-risk adolescents and adults (1.4% to 0.2%; NNT, 83) [391]. The risk of severe complications and death from influenza varies significantly among groups at high risk for complications, so the expected benefit in preventing severe complications varies. The risk of death from influenza is highest among HSCT and lung transplant patients [396, 397]. Decisions on extended duration of antiviral chemoprophylaxis for severely immunocompromised patients such as HSCT recipients should consider issues such as the potential for emergence of antiviral-resistant influenza viruses as well as tolerability and absorption issues for those with gastrointestinal graft-vs-host disease.

Several studies have evaluated the efficacy of postexposure antiviral chemoprophylaxis for household members after influenza diagnosis in a household member [386–390]. Two trials evaluated oseltamivir; one included adolescents aged ≥ 13 years and adults [388], and the other included children aged >1 year as well as adults [390]. The pooled efficacy against laboratory-confirmed symptomatic influenza was 81% (95% CI, 55%–92%) [398]. A subgroup analysis of the efficacy in children demonstrated 64% efficacy (95% CI, 16%–85%) [390]. Three trials evaluated postexposure antiviral chemoprophylaxis with inhaled zanamivir; 2 included children older than 5 years and adults [387, 389], and one trial was restricted to persons aged 13–65 years [386]. All showed statistically significant protection; the pooled estimate of efficacy against laboratory-confirmed symptomatic influenza for the 3 trials was 79% (95% CI, 67%–87%) [398]. Absolute risk reductions were modest. Data on the ability of postexposure antiviral chemoprophylaxis to prevent serious complications of influenza are not available, although reductions in symptomatic influenza cases would be expected to also reduce the risk of complications. To reduce the risk of subtherapeutic dosing if influenza virus infection has occurred following exposure, antiviral treatment (twice-daily dosing) rather than once-daily chemoprophylaxis dosing has been recommended by some experts, particularly in immunocompromised patients, when postexposure antiviral chemoprophylaxis is indicated. This may also be appropriate if >48 hours has elapsed since exposure, as the patient may already have infection established, warranting full-dose therapy. No studies have adequately evaluated this strategy. Decisions on whether to administer postexposure antiviral chemoprophylaxis should consider the nature of the exposure, the exposed person's risk of developing complications from influenza, the ability to promptly administer antiviral therapy if symptoms develop, advice from public health authorities, and clinical judgment.

Although older studies demonstrated efficacy of adamantanes (amantadine and rimantadine) for chemoprophylaxis, the use of adamantanes is not recommended because of widespread adamantane resistance among circulating influenza A viruses [249, 399, 400], the inherent resistance of influenza B viruses to adamantanes, and the rapid emergence and transmission of adamantane-resistant influenza A viruses during adamantane treatment. NAI resistance remains relatively uncommon in currently circulating influenza virus strains. However, during the 2008–2009 season, an oseltamivir-resistant H1N1 virus strain (susceptible to both adamantane and zanamivir) became the predominant circulating strain worldwide [401, 402]. Since then, sporadic cases and clusters of oseltamivir-resistant influenza A(H1N1)pdm09 virus infection have been detected annually [399, 403–405]. The

development of oseltamivir resistance during chemoprophylaxis has been reported, usually with the H275Y mutation, with limited ongoing transmission of resistant virus [96, 336, 358, 406]. Thus, if a patient develops influenza during oseltamivir chemoprophylaxis, inhaled zanamivir can be considered for treatment if there are no contraindications.

The decision to use antiviral chemoprophylaxis must balance the knowledge of the prevalence of antiviral resistance among circulating influenza viruses (see <http://www.cdc.gov/flu/professionals/index.htm>), risk of emergence of resistance, risk of severe complications of influenza, the potential for side effects, and the ability to initiate early therapy for influenza. Influenza vaccination is the primary tool to prevent influenza. Antiviral chemoprophylaxis is not a substitute for influenza vaccination. Educating patients and arranging for early empiric initiation of antiviral therapy if influenza symptoms develop may be an effective alternative to postexposure antiviral chemoprophylaxis, but studies comparing these 2 approaches have not been conducted.

INSTITUTIONAL OUTBREAK CONTROL

When Is There Sufficient Evidence of an Influenza Outbreak in a Long-term Care Facility or Hospital to Trigger Implementation of Control Measures Among Exposed Residents or Patients and Healthcare Personnel to Prevent Additional Cases of Influenza?

Recommendations

48. Active surveillance for additional cases should be implemented as soon as possible when one healthcare-associated laboratory-confirmed influenza case is identified in a hospital or one case of laboratory-confirmed influenza is identified in a long-term care facility (*A-III*).
49. Outbreak control measures should be implemented as soon as possible, including antiviral chemoprophylaxis of residents/patients, and active surveillance for new cases, when 2 cases of healthcare-associated laboratory-confirmed influenza are identified within 72 hours of each other in residents or patients of the same ward or unit (*A-III*).
50. Implementation of outbreak control measures can be considered as soon as possible if one or more residents or patients has suspected healthcare-associated influenza and results of influenza molecular testing are not available on the day of specimen collection (*B-III*).

Evidence Summary

Data are limited to inform recommendations regarding when an influenza outbreak should be declared in a long-term care facility or hospital, and on the effectiveness of interventions to prevent or control institutional influenza outbreaks. Observational studies have used different definitions for declaring an influenza outbreak on a single ward, including (*i*) 2 cases of ILI with one laboratory-confirmed influenza case, over a 3-day period, or 3 ILI cases with one laboratory-confirmed influenza case, over a 7-day period; (*ii*) 2 cases of acute respiratory illness occurring in 48 hours; (*iii*) 10% of residents on a nursing unit with acute respiratory illness in a 7-day period with influenza virus isolated from a resident in the

facility; and (iv) 2 cases of laboratory-confirmed influenza occurring in a 5-day period [407–413].

Early detection of influenza outbreaks in long-term care facilities and hospitals is important because influenza virus transmission can occur rapidly, with high attack rates [412–418], and because the risk of complications and mortality from influenza is higher than in other high-risk groups for frail older adults, severely disabled persons of any age, and immunocompromised patients [79, 419–423]. However, early detection of influenza is often difficult because severely handicapped persons and frail older adults may not present with typical influenza signs and symptoms [90] and because many residents with neurocognitive impairment or dementia may not be able to describe or complain of symptoms. The difficulty of identifying influenza in residents of long-term care facilities means that undetected cases may be present coincident with the detection of the first confirmed influenza case.

Although laboratory testing of additional suspected cases is the most definitive means to confirm an outbreak, waiting for laboratory testing results may delay outbreak control measures. A negative result of an influenza test with low to moderate sensitivity may be falsely negative and does not exclude a diagnosis of influenza; therefore, use of highly sensitive molecular assays is recommended for influenza testing. When the results of influenza molecular testing will not be available until the next day, outbreak control measures should be instituted when a single laboratory-confirmed case of influenza is accompanied by influenza activity in the community and by 2 or more other residents with symptoms compatible with influenza.

There are no data available that provide an estimate of how often a single identified laboratory-confirmed influenza case represents the start of an influenza outbreak. Evidence from several observational studies demonstrates that higher influenza vaccination coverage is associated with a lower risk of influenza outbreaks [424–429]. Although no other factors have been demonstrated to be associated with the risk of outbreaks, biological plausibility and expert opinion suggest that volume and patterns of air flow, degree of crowding in rooms or public areas, the effectiveness of policies excluding ill visitors and ill staff, and the ability to reduce interresident and staff contact in response to a single identified influenza case may all influence whether introduction of a single case of influenza will result in an outbreak [430]. These factors should be considered when judging whether a single confirmed influenza case represents the beginning of an outbreak. The ability to rapidly identify other cases—the combination of a sensitive surveillance case definition and use of RT-PCR testing of upper respiratory tract specimens for laboratory diagnosis—can reduce the risk that additional, undetected influenza cases are present at the time the first case is diagnosed and help to ensure early detection of influenza virus transmission if an outbreak has started [431].

The identification of one healthcare-associated laboratory-confirmed influenza virus infection in a long-term care resident should prompt a careful review to identify other undiagnosed cases, as well as an assessment of the likelihood of influenza virus transmission and the need to institute outbreak control measures. Staff at facilities with low influenza

vaccination coverage among staff and/or residents, lack of surveillance for acute respiratory illness in residents, <6 air changes per hour, many multibed shared rooms, crowded dining and activity rooms, and multiple frequent visitors who are not adequately screened for illness symptoms should consider early and rapid implementation of outbreak control measures after a single laboratory-confirmed influenza case.

Hospital units with longer length-of-stay patients (eg, rehabilitation units, transplant units) and skilled nursing facilities are relatively closed environments with high-risk patient populations and are similar to long-term care facilities for the elderly [417, 432, 433]. The threshold for declaring an outbreak in hospital units with longer-stay patients should be the same as that in long-term care facilities for the elderly. One pertinent difference to note is the challenge associated with identifying whether cases of influenza with onset within 72–96 hours of hospital admission are acquired in the hospital vs community acquired with onset after admission, because the incubation period for influenza ranges from 1 to 4 days.

Which Residents/Patients Should Be Considered to Have Influenza and Be Treated With Antivirals During an Influenza Outbreak in a Long-term Care Facility or Hospital?

Recommendations

51. When an influenza outbreak has been identified in a long-term care facility or hospital, influenza testing should be done for any resident/patient with one or more acute respiratory symptoms, with or without fever, or any of the following without respiratory symptoms: temperature elevation or reduction, or behavioral change (*A-III*).
52. Empiric antiviral treatment should be administered as soon as possible to any resident or patient with suspected influenza during an influenza outbreak, without waiting for the results of influenza diagnostic testing (*A-III*).

Evidence Summary

Ascertainment of influenza symptoms may be challenging in residents or patients with developmental disabilities, with severe neurologic impairment or dementia, or who are nonverbal. Older adults may not always mount a fever with influenza, and behavioral change may be the only sign of influenza virus infection in some frail elderly persons [76]. Hospitalized children and adults with chronic illness who develop nosocomial influenza may not initially manifest typical influenza signs and symptoms [434, 435]. Therefore, during an institutional influenza outbreak, there should be a low threshold for suspecting influenza and initiating antiviral treatment without waiting for the results of influenza molecular testing. Although early antiviral treatment of persons with influenza may reduce the risk of influenza virus transmission to exposed close contacts, the magnitude of this effect is unknown, and therefore other control measures also should be implemented as soon as possible (Table 10). Since not all persons who receive a 5-day antiviral treatment course without laboratory confirmation of influenza actually had influenza virus infection or can mount an immune response, antiviral chemoprophylaxis should be resumed after treatment is completed if chemoprophylaxis is continued for ongoing influenza exposures of other residents on their unit/ward.

When an institutional influenza outbreak is recognized, it is very likely that some exposed residents or patients are already incubating influenza virus infection coincident with the initiation of antiviral chemoprophylaxis. Additionally, antiviral chemoprophylaxis is not completely effective in preventing influenza, and some persons receiving antiviral chemoprophylaxis can develop influenza [393, 435]. Persons receiving antiviral chemoprophylaxis who develop any signs or symptoms of influenza should be switched to receive antiviral treatment dosing.

Antiviral chemoprophylaxis (once daily) rather than treatment dosing (twice daily) given to persons with asymptomatic influenza virus infection might theoretically increase the risk of selection for antiviral-resistant influenza viruses. However, the risk for developing NAI antiviral resistance is low except in severely immunocompromised persons, who can have prolonged and asymptomatic influenza virus replication [134]. Because some exposed persons can have asymptomatic or sub-clinical influenza virus infection, consideration can be given to using antivirals for chemoprophylaxis at the daily treatment dosing (twice daily with renal dose adjustment if indicated) to exposed residents or patients instead of antiviral chemoprophylaxis dosing (once daily) during outbreaks of influenza in long-term care facilities or healthcare facilities, including in immunosuppressed exposed patients [437, 438]. In this situation, antiviral treatment dosing should be continued for a full treatment course (twice daily) for 5 days before reducing to the recommended chemoprophylaxis dosing (once daily) until the outbreak is declared over.

To Control an Influenza Outbreak in a Long-term Care Facility or Hospital, Should Antiviral Chemoprophylaxis Be Administered to Exposed Residents/Patients?

Recommendation

53. Antiviral chemoprophylaxis should be administered as soon as possible to all exposed residents or patients who do not have suspected or laboratory-confirmed influenza regardless of influenza vaccination history, in addition to implementation of all other recommended influenza out-break control measures, when an influenza outbreak has been identified in a long-term care facility or hospital (*A-III*).

During an Influenza Outbreak at a Long-term Care Facility, Should Antiviral Chemoprophylaxis Be Administered to Residents Only on Affected Units or to All Residents in the Facility?

Recommendation

54. Antiviral chemoprophylaxis should be administered to residents on outbreak-affected units, in addition to implementing active daily surveillance for new influenza cases throughout the facility (*A-II*).

Evidence Summary

Residents of long-term care facilities and hospitalized patients are at high risk for complications of influenza, even if vaccinated, because influenza vaccine effectiveness may be low, particularly in elderly persons. Influenza vaccine should be administered to all

healthcare personnel each season, as vaccine is more likely to be immunogenic in healthcare personnel compared with residents. Several RCTs of antiviral chemoprophylaxis have been conducted among long-term care residents. Two RCTs of inhaled zanamivir for postexposure chemoprophylaxis have reported efficacy in reducing laboratory-confirmed influenza in elderly long-term care residents with high influenza vaccine coverage in the United States [409] and in an unvaccinated population in Lithuania [439]. One RCT of oseltamivir chemoprophylaxis for 10 days vs placebo in frail elderly patients in long-term care facility units after a single laboratory-confirmed case of influenza over 4 seasons in the Netherlands did not find a significant benefit; however, this study was underpowered due to fewer influenza outbreaks than expected [440]. In a cluster randomized trial over 3 seasons in Australia comparing oseltamivir treatment of symptomatic persons and provision of oseltamivir chemoprophylaxis for elderly long-term care residents and staff, researchers found that chemoprophylaxis reduced the influenza attack rate among residents compared with treatment of symptomatic persons [407]. One multicountry RCT of oseltamivir chemoprophylaxis vs placebo for 6 weeks in vaccinated residents reported high efficacy in preventing influenza outbreaks in nursing homes [441].

Multiple observational studies have reported effectiveness of oseltamivir chemoprophylaxis in controlling influenza out-breaks in long-term care facilities [410, 442–444]. One retrospective analysis of surveillance and administrative data on influenza outbreaks in long-term care facilities over 2 seasons in Alberta, Canada, reported that a 1-day delay in administering oseltamivir chemoprophylaxis among residents was associated with an increase of 2.2 days (95% CI, 1.37–3.06) in outbreak duration after the intervention [443].

However, a retrospective observational study of routinely collected influenza outbreak data in aged care facilities in 3 local health districts in Australia reported no difference in outbreak duration, attack rates, hospitalization, or case fatality between residents of facilities where antiviral chemoprophylaxis (oral oseltamivir) was routinely recommended compared with facilities where antiviral treatment, but not routine antiviral chemoprophylaxis, was recommended [444].

Data on the effectiveness of antiviral chemoprophylaxis for controlling influenza outbreaks in hospitals are limited. The use of oseltamivir or zanamivir chemoprophylaxis of exposed patients has been described in neonates, older children, and adults in conjunction with other interventions to control nosocomial influenza outbreaks [445–448]. Decisions about antiviral chemoprophylaxis should consider the anticipated severity of illness, risk of complications, and mortality associated with influenza in the population at risk, and on the ability to implement control measures, including isolation and spatial separation of susceptible individuals from each other. Decisions about the choice of antivirals and whether to utilize chemoprophylaxis vs treatment dosing should be carefully considered for control of influenza outbreaks in units with immunocompromised and immunosuppressed patients because such patients can have prolonged influenza viral replication with emergence and nosocomial transmission of antiviral-resistant influenza virus strains [352, 449].

There are very limited data to inform the use of antiviral chemoprophylaxis beyond affected units during influenza out-breaks in long-term care facilities. One observational study

reported that outbreak duration was the shortest when oseltamivir chemoprophylaxis was administered to all residents of one nursing home vs only for exposed residents at another nursing home or not used at a third nursing home [410]. There are no published data to quantify the risk of influenza virus transmission among different wards of a long-term care facility. Some factors that can facilitate influenza virus transmission among different units and buildings include the amount of mixing by shared staff, sharing circulating air or patient care equipment, and the duration of resident interaction such as in common rooms for shared meals or other group activities. The risk of wider influenza virus transmission likely increases as the number of influenza cases increases and as the time extends between onset of the first cases, recognition of the outbreak, and implementation of interventions.

Decisions on whether to widen antiviral chemoprophylaxis should consider the potential for influenza virus transmission between different wards and buildings of the facility and balance the risk of complications associated with additional cases of influenza in residents against the cost and adverse consequences of antiviral chemoprophylaxis. Use of antiviral chemoprophylaxis limited to an individual affected ward is reasonable if the number of influenza cases is small when the outbreak is declared, and if the affected ward's residents and staff had limited contact with those of other wards before the outbreak was declared. This approach is also reasonable if residents and staff can be effectively separated from other wards or buildings after the outbreak is declared. Active daily surveillance for new influenza cases, with influenza testing for suspected cases, should be enhanced throughout the entire facility as soon as an outbreak is declared on any one ward. Finding influenza virus transmission on a second ward should prompt consideration of facility-wide antiviral chemoprophylaxis, as considerable experience by subject matter experts in this scenario has demonstrated eventual emergence of further influenza virus transmission to multiple units within the facility when implementation of facility-wide antiviral chemoprophylaxis is not implemented.

Use of antiviral chemoprophylaxis might be considered along with other control measures for influenza outbreaks in other institutional settings among persons generally not at high risk for complications from influenza, such as in dormitories at boarding schools, universities, and summer camps. However, in populations with lower risk of influenza complications, the benefits of prevention with antivirals may be marginal. As such, considerable uncertainty remains about how, when, and for whom antiviral chemoprophylaxis should be used for these other institutional settings.

Which Healthcare Personnel Should Receive Antiviral Chemoprophylaxis During an Institutional Outbreak?

Recommendations

55. Clinicians can consider antiviral chemoprophylaxis for unvaccinated staff, including those for whom chemoprophylaxis may be indicated based upon underlying conditions of the staff or their household members (see recommendations 41–43) for the duration of the outbreak (*C-III*).

56. Clinicians can consider antiviral chemoprophylaxis for staff who receive inactivated influenza vaccine during an institutional influenza outbreak for 14 days postvaccination (*C-III*).
57. Clinicians can consider antiviral chemoprophylaxis for staff regardless of influenza vaccination status to reduce the risk of short staffing in facilities and wards where clinical staff are limited and to reduce staff reluctance to care for patients with suspected influenza (*C-III*).

Evidence Summary

There are no data available to address the effectiveness of antiviral chemoprophylaxis of staff to control institutional influenza outbreaks in residents or patients, or to guide whether, when, and which staff should be considered for antiviral chemoprophylaxis. Observational studies have described the use of antiviral chemoprophylaxis of staff in addition to exposed residents [450–452], and some randomized controlled trials for antiviral chemoprophylaxis of residents also offered chemoprophylaxis to staff [409, 430].

Factors to consider when deciding whether to offer antiviral chemoprophylaxis include: (i) staff can serve as sources of influenza virus transmission to residents; (ii) staff absenteeism for respiratory illness will impact workforce available for care of facility residents; and (iii) staff could be infected with influenza viruses from ill residents or patients. Antiviral chemoprophylaxis in vaccinated staff may be less beneficial to institutional outbreak control than use in unvaccinated staff if vaccine is not available. Many facilities cannot afford to have several ill staff absent from work, and increased staff demands at the time of outbreak declaration may make it challenging for referral to a primary care provider to prescribe antiviral chemoprophylaxis. Therefore, facility medical directors should plan for prescribing antivirals (including renal dosing adjustments if needed) by facility physicians vs referral to external providers.

All healthcare personnel should receive annual influenza vaccination [453]. During influenza outbreaks, influenza vaccine should be offered to unvaccinated staff throughout the facility, and antiviral chemoprophylaxis can be offered for 14 days postvaccination (until protective antibodies have developed). If influenza vaccine is not available, antiviral chemoprophylaxis can be offered to all unvaccinated staff. Antiviral chemoprophylaxis can also be offered to unvaccinated staff with vaccine contraindications and to immunocompromised staff (who are expected to have poor immune response to vaccination) for the duration of an institutional outbreak.

The importance of limiting staff absenteeism for outbreak control and maintaining quality of patient and resident care during the outbreak should be assessed and incorporated into decisions about antiviral chemoprophylaxis of staff. Especially during seasons in which influenza vaccine effectiveness is low, consideration can be given to administration of antiviral chemoprophylaxis to vaccinated staff for the duration of an outbreak.

Effective isolation and control of outbreaks can be challenging and may require different strategies. Facility medical directors should consider consultation from public health experts.

How Long Should Antiviral Chemoprophylaxis Be Given to Residents During an Influenza Outbreak in a Long-term Care Facility?

Recommendation

58. Clinicians should administer antiviral chemoprophylaxis for 14 days and continue for at least 7 days after the onset of symptoms in the last case identified during an institutional influenza outbreak (*A-III*).

Evidence Summary

One older randomized trial conducted during 1991–1995 reported that antiviral chemoprophylaxis with amantadine or rimantadine for 14 days (and for 7 days after the last confirmed influenza case) was sufficient to control influenza A outbreaks compared to 21 days (and for 7 days after the last confirmed influenza case) [454]. No randomized trials have been conducted to assess the duration of NAI chemoprophylaxis to control influenza outbreaks in long-term care facilities. One observational study described successful use of oseltamivir chemoprophylaxis to control 5 influenza outbreaks in long-term care residents after use of amantadine failed to contain the outbreaks [442]. Other studies have described the use of oseltamivir or zanamivir chemoprophylaxis for 7–14 days [407–410, 439, 440, 451, 454].

The incubation period for influenza is believed to be typically 1–3 days, up to 4 days, with a mean serial interval (time from illness onset of the index case to illness onset of a secondary case, such as in household transmission studies) of approximately 2–3 days in most persons [455]. Influenza A(H1N1)pdm09 viral RNA can be detected for approximately 4–7 days after onset of symptoms in most persons (although influenza virus is recoverable in viral culture for shorter periods), and immunosuppressed, hospitalized and critically ill patients can have prolonged influenza viral shedding [455]. Two recent household studies suggested that influenza A(H1N1)pdm09 virus transmission was substantially reduced >3 days after onset of symptoms [456], but another study reported that more than one-third of patients had A(H1N1)pdm09 viral RNA detected at 7 days after illness onset [457]. While data are limited on the optimal duration of antiviral chemoprophylaxis to control institutional influenza outbreaks, the CDC recommends that antiviral chemoprophylaxis should be administered initially for 14 days, and if surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until 7 days after the last case has been identified [458].

Research Gaps

Following global consultations with multiple stakeholders, the WHO posted a comprehensive influenza research agenda in 2009 that addressed research gaps including surveillance, the animal-human interface, novel influenza A virus infections, transmission, vaccines and other prevention strategies, diagnostics, disease pathogenesis, antivirals, and clinical management. During 2016–2017, some IDSA panelists worked with international experts on reviewing advances in the field and updating this research agenda. Specific issues of interest to IDSA are included in the WHO Research Agenda, Stream 4: optimizing the

treatment of patients (available at http://www.who.int/influenza/resources/research/Stream_4_BD_final_GIP.pdf?ua=1).

New Developments After Guideline Finalization

Baloxavir marboxil is a cap-dependent endonuclease inhibitor that was approved by the FDA for treatment of acute uncomplicated influenza in patients aged ≥ 12 years who have been symptomatic for no more than 48 hours. As FDA approval occurred after finalization of these guidelines, the panel was unable to make recommendations on use of baloxavir. In a phase 3 randomized controlled trial of baloxavir, oseltamivir, and placebo in 1066 otherwise healthy patients aged 12–64 years with uncomplicated influenza for no more than 48 hours, a single dose of baloxavir significantly shortened the median time to alleviation of symptoms by 26.5 hours compared with placebo ($P < .001$) [459]. There was no difference in clinical benefit for a single dose of baloxavir compared with 5 days of twice-daily oseltamivir [459]. Baloxavir was well tolerated, with no difference in adverse events compared with oseltamivir or placebo. The median duration of infectious virus detection in upper respiratory tract specimens was significantly shorter for baloxavir compared with oseltamivir (24 vs 72 hours, respectively; $P < .001$) [459]. However, 10% of the baloxavir recipients with paired sequenced samples had emergence of viral escape mutants with reduced drug susceptibility, and most of these patients had infectious virus detected 5 days after treatment and longer duration of symptoms than in baloxavir recipients without these mutations [459].

The results of a phase 3, randomized controlled trial of baloxavir, oseltamivir, and placebo in 1163 patients aged ≥ 12 years, with at least one high-risk medical condition and uncomplicated influenza for no more than 48 hours were presented after finalization of these guidelines. In this study, a single dose of baloxavir reduced the median time to improvement of symptoms by 29.1 hours compared with placebo ($P < .0001$), but was not significantly different than 5 days of twice-daily oseltamivir [460]. In patients with influenza B, baloxavir significantly reduced the median time to improvement of symptoms by 26 hours compared with placebo ($P < .0138$) and 27 hours compared with oseltamivir ($P < .0251$) [460]. Baloxavir significantly reduced systemic antibiotic use and influenza-related complications compared with placebo [460].

Multiple influenza diagnostics and therapeutics are in advanced development, and new influenza tests, antiviral medications, and other therapeutics might be approved by the FDA after publication of these guidelines. Clinicians should consult the CDC webpages for the latest information on approved influenza tests (<https://www.cdc.gov/flu/professionals/diagnosis/index.htm>) and approved antivirals (<https://www.cdc.gov/flu/professionals/antivirals/index.htm>).

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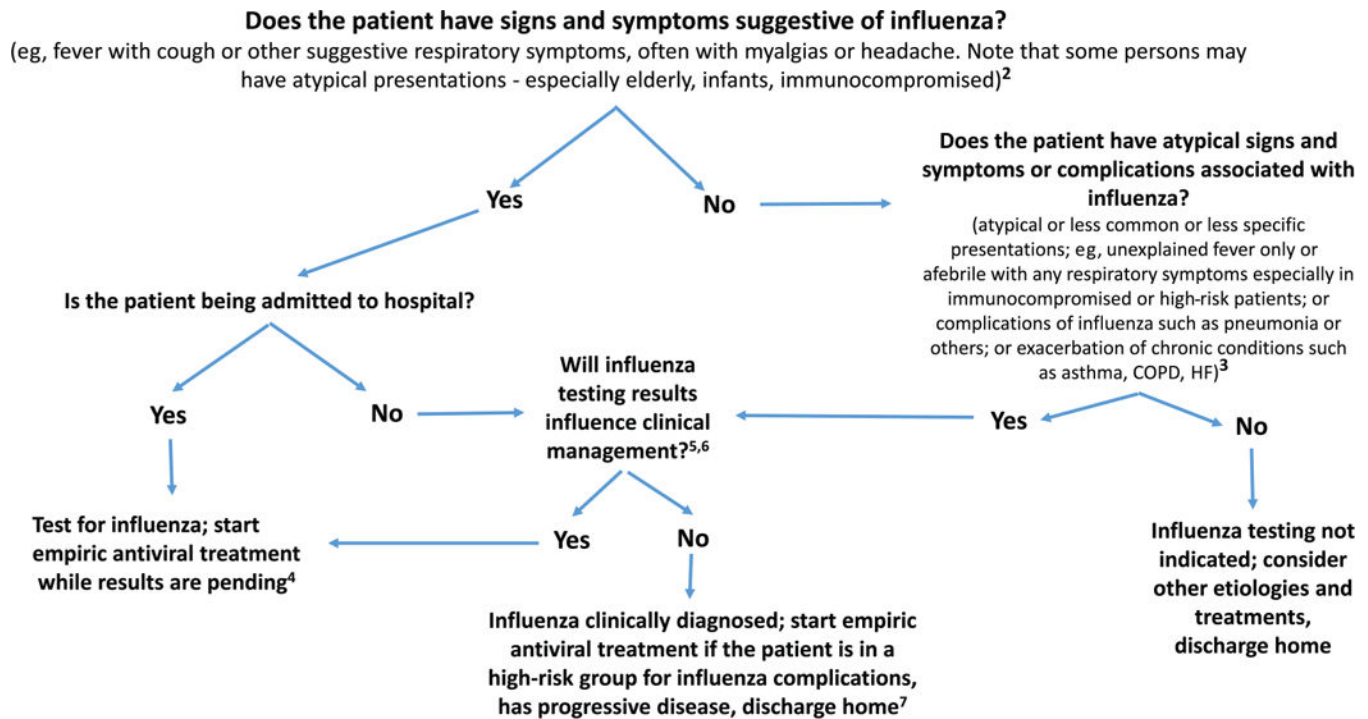


Figure 1.

Guide for considering influenza testing when influenza viruses are circulating in the community (regardless of influenza vaccination history). ¹Confirmation of influenza virus infection by diagnostic testing is not required for decisions to prescribe antiviral medication. Decision making should be based upon signs and symptoms consistent with influenza illness and epidemiologic factors. Initiation of empiric antiviral treatment should not be delayed while influenza testing results are pending. Antiviral treatment is clinically most beneficial when started as close to illness onset as possible. ²Signs and symptoms of uncomplicated influenza (see Table 2). ³Clinical manifestations and complications associated with influenza (see Table 3) and persons who are at high risk of complications from influenza (Table 4). ⁴All hospitalized patients with suspected influenza should be tested, as detection of influenza virus infection and prompt initiation of antiviral therapy are most clinically beneficial, and implementation of infection prevention and control measures is essential for prevention of nosocomial influenza outbreaks. ⁵Influenza testing may be used to inform decisions on use of antibiotics or continuation of antiviral medication, on need for further diagnostic tests, on consideration for home care, or on recommendations for ill persons living with others who are at high risk for influenza complications (see Table 4). ⁶Influenza testing may be required to inform decisions on infection control practices. ⁷Antiviral treatment is recommended for outpatients with suspected influenza who are at high risk for complications from influenza, or those with progressive disease not requiring hospital admission. Antiviral treatment of outpatients who are not at high risk for influenza complications (see Table 4) can be considered based upon clinical judgment if presenting within 2 days of illness onset. Abbreviations: HF, heart failure; COPD, chronic obstructive pulmonary disease.

Table 1.

Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines

Category and Grade		Definition
Strength of recommendation		
A		Good evidence to support a recommendation for or against use
B		Moderate evidence to support a recommendation for or against use
C		Poor evidence to support a recommendation
Quality of evidence		
I		Evidence from 1 or more properly randomized controlled trials
II		Evidence from 1 or more well-designed clinical trials, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III		Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Adapted from the Canadian Task Force on the Periodic Health Examination [6].

Table 2.

Signs and Symptoms of Uncomplicated Influenza^a

General	Head, Eyes, Ears, Nose, Throat	Neuromuscular	Gastrointestinal ^b	Pulmonary
Fever ^{c, d}	Headache	Myalgia, arthralgia	Abdominal pain	Nonproductive cough
Chills	Nasal congestion ^d	Weakness	Vomiting	Pleuritic chest pain
Malaise	Rhinorrhea ^d	Chest pain	Diarrhea ^d	
Fatigue	Sore throat/hoarseness			

Adapted from Jani AA, Uyeki TM. Chapter 46. Influenza. In: Emergency management of infectious diseases. 2nd ed. Chin RL, ed. Cambridge, UK: Cambridge University Press, 2018.

^a Abrupt onset of respiratory and systematic signs and symptoms, with or without fever.

^b Gastrointestinal symptoms vary with age: Diarrhea is more common among infants, young children, and school-aged children; abdominal pain may be present among school-aged children; vomiting may be present among adults.

^c Fever can be age-specific: High fever or fever alone may be the only sign in infants and young children; fever may be absent or low grade in infants and the elderly.

^d Fever, nasal congestion, rhinorrhea, and diarrhea may be present among infants and young children.

Table 3.**Clinical Manifestations and Complications Associated With Influenza**

Population	Clinical Manifestation/Complication
Infants and preschool children	Fever without respiratory complications, “sepsis-like syndrome” Otitis media Parotitis Bronchiolitis Croup Reactive airway disease Pneumonia Myocarditis, pericarditis Rhabdomyolysis Febrile seizures Encephalopathy and encephalitis Invasive bacterial coinfection Reye syndrome (with aspirin exposure) Sudden death Exacerbation of chronic disease
School-aged children	Otitis media Parotitis Bronchitis Sinusitis Reactive airway disease Pneumonia Myocarditis, pericarditis Myositis (bilateral gastrocnemius, soleus) Rhabdomyolysis Encephalopathy and encephalitis Invasive bacterial coinfection Reye syndrome (with aspirin use) Toxic shock syndrome Sudden death Exacerbation of chronic disease
Adults	Parotitis Bronchitis Sinusitis Reactive airway disease Pneumonia Myocarditis, pericarditis Myositis Rhabdomyolysis Invasive bacterial coinfection Invasive fungal coinfection (rare) Toxic shock syndrome due to <i>Staphylococcus aureus</i> or <i>Streptococcus pyogenes</i> Precipitation of acute cardiovascular events (eg, cardiac failure, myocardial infarction, heart failure, cerebrovascular accident) Acute kidney injury and acute renal failure (with rhabdomyolysis or multiorgan failure) Encephalopathy and encephalitis Exacerbation of chronic disease
Elderly patients	Pneumonia Invasive bacterial coinfection Myositis Exacerbation of chronic disease
Special groups: pregnant and postpartum women	Dehydration Pneumonia Cardiopulmonary disease Premature labor Fetal loss
Special groups: immunocompromised, immunosuppressed	Complications similar to immunocompetent patients, but severe pneumonia and acute respiratory distress syndrome may be more common.
All ages	Respiratory failure Acute respiratory distress syndrome Multiorgan failure Sepsis Liver inflammation

Adapted from Jani AA, Uyeki TM. Chapter 46. Influenza. In: Emergency management of infectious diseases. 2nd ed. Chin RL, ed. Cambridge, UK: Cambridge University Press, 2018.

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Table 4.**Persons Who Are at High Risk of Complications From Influenza**

Persons at High Risk of Complications
Children aged <5 years, and especially aged <2 years
Adults aged >65 years
Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), or metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
Persons with immunosuppression, including that caused by medications or by HIV infection ^a
Women who are pregnant or postpartum (within 2 weeks after delivery)
Children and adolescents through 18 years who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection
American Indian/Alaska Native people ^b
Persons with extreme obesity (ie, body mass index ≥ 40 kg/m ²)
Residents of nursing homes and other chronic care facilities

Adapted from Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2017–18 influenza season. *MMWR Recomm Rep* 2017; 66:1–20.

Abbreviation: HIV, human immunodeficiency virus.

^aPersons with the highest risk for complications are those who are severely immunocompromised (eg, hematopoietic stem cell transplant recipients).

^bAmerican Indian/Alaska Native persons are included because of their documented higher rates of influenza-related mortality. Also, 30% of fatal American Indian/Alaska Native influenza cases would not have been classified as high risk during the 2009 H1N1 pandemic using other criteria. *MMWR* 2009; 58:1341–44.

Table 5.**Groups in Whom to Consider a Diagnosis Of Influenza^a**

When to Consider a Diagnosis of Influenza	Symptom and Group
During influenza activity	Acute onset of respiratory symptoms, with or without fever (all ages) • Pneumonia (all ages) • Acute exacerbation of underlying chronic lung disease (eg, chronic obstructive pulmonary disease, asthma), with or without fever (all ages) • Fever without an obvious source (infants, young children) • New-onset neurologic signs and symptoms (eg, seizures, altered mental status), with or without fever (infants, young children) • Exacerbation or new onset of cardiovascular events (eg, heart failure, myocardial infarction or ischemia, cerebrovascular accident in adults) or altered mental status, with or without fever (all ages) • Severe, complicated, or progressive (worsening) acute respiratory illness, without an alternative diagnosis (all ages) • Hospitalized patients who develop new onset of acute respiratory symptoms, with or without fever (all ages)
Year-round	Acute onset of respiratory symptoms, with or without fever, especially those at high risk for influenza complications who are epidemiologically linked to recent influenza cases or outbreaks (all ages) • Healthcare personnel caring for influenza patients • Healthcare personnel, residents, or visitors to an institution experiencing an influenza outbreak • Close contacts of persons with suspected influenza (household or a congregate setting, such as daycare, school, or healthcare facility) • Travelers who returned recently from areas where influenza viruses may be circulating • Organized tour group participants • Participants in international mass gatherings • Summer camp attendees • Cruise or military ship passengers

^a A diagnosis of influenza should be considered regardless of current season influenza vaccination because influenza vaccine effectiveness is variable.

Table 6.

Influenza Diagnostic Tests for Respiratory Specimens

Testing Category	Method	Influenza Viruses Detected	Distinguishes Influenza A Virus Subtypes	Time to Results	Performance
Rapid molecular assay	Nucleic acid amplification	Influenza A or B viral RNA	No	15–30 minutes	High sensitivity; high specificity
Rapid influenza diagnostic test	Antigen detection	Influenza A or B virus antigens	No	10–15 minutes	Low to moderate sensitivity (higher with analyzer device); high specificity;
Direct and indirect immunofluorescence assays	Antigen detection	Influenza A or B virus antigens	No	1–4 hours	Moderate sensitivity; high specificity
Molecular assays (including RT-PCR)	Nucleic acid amplification	Influenza A or B viral RNA	Yes, if subtype primers are used	1–8 hours	High sensitivity; high specificity
Multiplex molecular assays	Nucleic acid amplification	Influenza A or B viral RNA, other viral or bacterial targets (RNA or DNA)	Yes, if subtype primers are used	1–2 hours	High sensitivity; high specificity
Rapid cell culture (shell vial and cell mixtures)	Virus isolation	Influenza A or B virus	Yes	1–3 days	High sensitivity; high specificity
Viral culture (tissue cell culture)	Virus isolation	Influenza A or B virus	Yes	3–10 days	High sensitivity; high specificity

Negative results may not rule out influenza. Respiratory tract specimens should be collected as close to illness onset as possible for testing. Clinicians should consult the manufacturer's package insert for the specific test for the approved respiratory specimen(s). Most US Food and Drug Administration (FDA)-cleared influenza diagnostic tests are approved for upper respiratory tract specimens but not for sputum or lower respiratory tract specimens. Specificities are generally high (>90%) for all tests compared to RT-PCR. FDA-cleared rapid influenza diagnostic tests are Clinical Laboratory Improvement Amendments (CLIA)-waived; most FDA-cleared rapid influenza molecular assays are CLIA-waived, depending on the specimen.

Abbreviation: RT-PCR, reverse-transcription polymerase chain reaction.

Table 7.

Interpretation of Influenza Testing Results on Respiratory Specimens

Test and Characteristics	Low Influenza Activity ^a		High Influenza Activity ^b	
Rapid influenza diagnostic test (antigen detection: immunoassay or immunofluorescence assay) • Low to moderate sensitivity • High specificity ➤ Should not be used for testing of patients with progressive illness and hospitalized patients	Negative result NPV is high: ➤ Likely to be a true-negative result if an upper respiratory tract specimen was collected <4 days after illness onset ➤ If epidemiologically linked to an influenza outbreak, consider confirming with molecular assay	Positive result PPV is low: ➤ Likely to be a false-positive result ➤ Confirm with molecular assay	Negative result NPV is low: ➤ May be a false-negative result, especially if upper respiratory tract specimen was collected >4 days after illness onset, cannot exclude influenza virus infection ➤ Do not withhold antiviral treatment if clinically indicated ➤ Confirm with molecular assay	Positive result PPV is high: ➤ Likely to be a true-positive result
	Negative result NPV is high: ➤ Very likely to be a true-negative result, especially if an upper respiratory tract specimen was collected <4 days after illness onset	Positive result PPV is low: ➤ False-positive result is possible	Negative result NPV is low: ➤ May be a true-negative result in a patient without lower respiratory tract disease ➤ Consider potential for a false-negative result, especially if an upper respiratory tract specimen was collected in a hospitalized patient ➤ For hospitalized patients on mechanical ventilation who tested negative on upper respiratory tract specimens, collect lower respiratory tract specimens (endotracheal aspirate, BAL fluid) for testing	Positive result PPV is high: ➤ Likely to be a true-positive result

Abbreviations: BAL, bronchoalveolar lavage; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; RT-PCR, reverse-transcription polymerase chain reaction.

^aLow influenza activity refers to periods when influenza viruses are not known to be circulating or are only sporadically detected among the patient population being tested, such as during the summer months in the United States.

^bHigh influenza activity refers to periods when influenza viruses are known to be circulating among the patient population being tested, such as during the winter months in the United States.

^cRapid molecular assays may have lower sensitivity and specificity compared to other molecular assays (eg, RT-PCR).

Table 8.
Antiviral Agents and Dosing Recommendations for Treatment and Chemoprophylaxis of Influenza

Antiviral Agents and Age Group	Treatment Dosing	Chemoprophylaxis Dosing
Oseltamivir		
Adults	75 mg twice daily	75 mg once daily
Pregnancy (any trimester) ^a	75 mg twice daily ^b	75 mg once daily ^b
Children (1 year or older) ≤15 kg	30 mg twice daily	30 mg once daily
Children >15–23 kg	45 mg twice daily	45 mg once daily
Children >23–40 kg	60 mg twice daily	60 mg once daily
Children >40 kg	75 mg twice daily	75 mg once daily
Infants 9–11 months	3.5 mg/kg per dose twice daily ^c	3.5 mg/kg per dose once daily ^c
Term infants 0–8 months	3 mg/kg per dose twice daily ^c 3 mg/kg per dose twice daily	3 mg/kg per dose once daily ^c 3 mg/kg per dose once daily if ≥3 months; not recommended for infants <3 months unless the situation is judged critical due to lack of safety and efficacy data
Preterm infants	See details in footnote ^a	No data
Zanamivir		
Adults	10 mg (two 5-mg inhalations), twice daily	10 mg (two 5-mg inhalations), once daily
Children (≥7 years)	10 mg (two 5-mg inhalations), twice daily	10 mg (two 5-mg inhalations), once daily
Peramivir^d		
Adults	600 mg intravenous infusion once, given over 15–30 minutes	NA
Children (2–12 years)	One 12 mg/kg dose, up to 600 mg maximum, intravenous, given over 15–30 minutes	NA
Children (13–17 years)	600 mg intravenous infusion once, given over 15–30 minutes	NA

Antiviral resistance information is available in the weekly Centers for Disease Control and Prevention (CDC) influenza surveillance report: <https://www.cdc.gov/flu/weekly/index.htm>. Abbreviation: NA, not applicable.

^aThe weight-based dosing recommendation for preterm infants is lower than for term infants. Preterm infants may have lower clearance of oseltamivir because of immature renal function, and doses recommended for full-term infants may lead to very high drug concentrations in this age group. Limited data from the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group provide the basis for dosing preterm infants using their postmenstrual age (ie, gestational age + chronological age): 1.0 mg/kg per dose, orally, twice daily, for those <38 weeks postmenstrual age; 1.5 mg/kg per dose, orally, twice daily, for those 38–40 weeks postmenstrual age; 3.0 mg/kg per dose, orally, twice daily, for those >40 weeks postmenstrual age. For extremely premature infants (<28 weeks), please consult a pediatric infectious diseases physician (Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2017–2018. *Pediatrics* 2018; 141: pii:e20173535).

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Based on pharmacokinetic data in pregnancy, regardless of trimester, a dose of 105 mg twice daily was predicted to provide the effective exposure provided to nonpregnant adults. Some experts recommend 150 mg twice daily for severe illness in pregnant women. Optimal dosing for prophylaxis in pregnant women is unknown.

^cThe American Academy of Pediatrics recommends 3.5 mg/kg per dose twice daily; CDC and US Food and Drug Administration (FDA)-approved dosing is 3 mg/kg per dose twice daily for children aged 9–11 months.

^dApproved for early treatment of uncomplicated influenza in outpatients. If used off-label for treatment of hospitalized patients, repeated once-daily dosing can be considered, although data are very limited.

Table 9.

List of Differential Diagnoses to Consider for Patients With Influenza Who Do Not Improve or Have Clinical Deterioration With Antiviral Treatment^a

Differential Diagnoses	Supportive Tests and Clinical Clues
Inadequate NAI exposure	Inadequate antiviral dosing (oral, IV, inhaled) Inadequate bioavailability: • For oral administration (vomiting, poor compliance, esterase deficiency in converting oseltamivir phosphate to oseltamivir carboxylate) • For inhaled administration (inadequate delivery to sites of infection, poorly tolerated or poor compliance) Late initiation of NAI treatment relative to illness onset or after severe illness has occurred, with ongoing viral replication, including in the lower respiratory tract No other etiology identified to explain findings associated with current influenza virus infection of the upper or lower respiratory tract
Extrapulmonary complications of influenza virus infection of the respiratory tract: • Encephalopathy or encephalitis • Myocarditis, pericarditis • Myositis, rhabdomyolysis Postinfluenza immune-mediated neurologic complications • Encephalitis or ADEM • Guillain-Barré syndrome Community-acquired bacterial coinfection with influenza (eg, pneumonia, otitis media, sinusitis, tracheitis, meningitis, toxic shock syndrome)	No other etiology identified to explain neurologic findings associated with recent influenza virus infection of the upper or lower respiratory tract Clinical indicators, imaging studies, laboratory markers (eg, CRP, procalcitonin), bacterial cultures or specific tests from sterile sites and upper/lower respiratory tract, current and prior antibiotic exposure history. Bacterial meningitis can occur during influenza virus infection or after influenza has resolved.
Community-acquired viral coinfection with influenza (eg, RSV, HMPV, adenovirus)	Multiple viruses can be detected by multiplex respiratory viral PCR testing.
Hospital-acquired infection ^b (bacterial, viral, fungal), DIC, septic shock	• Ventilator-associated pneumonia • Healthcare-associated pneumonia • Catheter-related bloodstream infection • Catheter-associated UTI
NAI-resistant influenza virus infection	Persistent virus detection during or after NAI therapy ^c ; detection of molecular marker(s) associated with NAI resistance; or notification of community circulation of NAI-resistant viruses (testing per guidance)
Respiratory failure, ARDS with influenza	Lower respiratory tract complications can occur without bacterial coinfection. Respiratory failure and ARDS can occur with or without bacterial coinfection of the lower respiratory tract Clinical indicators, imaging studies, laboratory markers (eg, CRP)
Multorgan dysfunction or failure (respiratory failure, acute kidney injury, or renal failure), DIC, septic shock	Clinical indicators, imaging studies, laboratory markers
Cardiovascular event: MI, angina, arrhythmias	Clinical indicators, imaging studies
Pulmonary event: poor control of underlying comorbid condition (eg, COPD, heart failure), pulmonary embolism	Imaging studies, neurological assessment
Cerebrovascular events: CVA	Clinical history and appropriate laboratory tests
Immune deficiency with inadequate antiviral response (eg, chemotherapy or other immunosuppression, pregnancy)	Hyperammonemia, hypoglycemia, fatty liver, altered mental status (especially if the patient received salicylates or was on long-term aspirin therapy)
Reye syndrome	Rejection, hemolytic uremic syndrome, sirolimus pneumonitis/serositis
Immunocompromised host-specific syndromes	

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Abbreviations: ADEM, acute disseminated encephalomyelitis; ARDS, acute respiratory distress syndrome; CRP C-reactive protein; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; HMPV, human metapneumovirus; IV, intravenous; MI, myocardial infarction; NAI, neuraminidase inhibitor; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; UTI, urinary tract infection.

^aIf an obvious alternative source is not identified, consider other sites of infection (eg, aspiration in neurologically impaired, endocarditis, *Clostridium difficile* colitis)

^bNosocomial influenza virus infection can complicate other conditions requiring hospitalization.

^cPersistent detection of influenza viral RNA after antiviral treatment does not necessarily indicate that antiviral-resistant virus infection is present.

Table 10.

Control Measures for Managing Institutional Influenza Outbreaks

Level	Control Measures
Resident level	• Identify and isolate all ill residents or patients with suspected or laboratory-confirmed influenza; encourage ill residents to stay in their rooms as much as possible • Ask ill residents or patients with suspected or laboratory-confirmed influenza to wear facemasks when out of their rooms • Promptly identify influenza virus infection in residents and initiate antiviral treatment in suspected or confirmed influenza cases as soon as possible • Encourage and facilitate frequent hand washing • Educate residents or patients and their families on respiratory etiquette • Arrange beds in rooms housing > 1 resident to maximize distance between the heads of beds to at least 2 meters or approximately 6 feet • Once an influenza outbreak is declared (when 2 cases of laboratory-confirmed influenza are identified within 72 hours of each other in residents or patients of the same ward or unit), start empiric antiviral treatment of newly symptomatic residents with a neuraminidase inhibitor as soon as possible
Ward/unit level	• Implement droplet precautions when providing care for ill residents or patients, in addition to standard precautions already in place regardless of symptoms. • Cohort ill residents by rooming together, or in group activities such as dining or recreation • Post signs diverting nonessential visits • Minimize or restrict staff working on affected wards from working on nonaffected wards • Post signs to remind staff and visitors to wash hands, wear facemasks, and to adhere to standard, contact, and droplet precautions when entering rooms of ill residents or patients • Add distance between individuals during mealtimes and activities, eg, eating just outside of or in their rooms rather than a common dining area • Keep residents on their wards; prohibit or, as feasible, limit and do not overlap movement of residents of affected wards to nonaffected wards or common areas • Once an outbreak is declared, administer empiric antiviral chemoprophylaxis with a neuraminidase inhibitor as soon as possible to asymptomatic exposed residents on the affected ward or unit • Close affected wards to new admissions • Once an influenza outbreak is declared, consider whether to offer empiric antiviral chemoprophylaxis with a neuraminidase inhibitor to unvaccinated staff on the affected ward/unit, including staff with influenza vaccine contraindications or immunocompromised staff (who are expected to have poor immune response to vaccination) for the duration of the outbreak • If there is substantial antigenic drift between circulating influenza viruses and influenza vaccine virus strains, consider whether to extend empiric antiviral chemoprophylaxis with a neuraminidase inhibitor to all staff on the affected ward/unit with an influenza outbreak, regardless of influenza vaccination status
Building level	• Cohorting of ill persons if isolation or nursing unit-level cohorting is not possible at the building level in multibuilding facilities • Once an influenza outbreak is declared, consider whether to offer empiric neuraminidase inhibitor chemoprophylaxis and treatment to all staff working in buildings with residents having new respiratory illness, not just on the affected unit(s)/ward(s)
Institution level	• Have annual influenza vaccination programs in place for residents or patients and healthcare personnel • Have policies and procedures for identification and management of an influenza outbreak, including occupational health aspects (eg, which staff should receive antiviral treatment or chemoprophylaxis, be referred for influenza testing and antiviral treatment; policies for sick leave and return to work) • Have mechanisms in place for rapid collection and handling of respiratory specimens from ill residents or patients and healthcare personnel for influenza testing, preferably by molecular assays. If influenza molecular assays are negative, test specimens for other respiratory pathogens, since noninfluenza respiratory viruses and bacteria infections have also been associated with respiratory disease outbreaks in healthcare and long-term care facilities; the nonpharmaceutical control measures apply to these as well • Implement active daily surveillance for any new respiratory illness (eg, fever, increased work of breathing, coughing, or sneezing) among residents or patients and staff. Respiratory symptoms, even without fever, should trigger suspicion for influenza, especially in elderly individuals. Nonrespiratory manifestations, such as altered mental status, may also be a sign of influenza virus infection in elderly patients • Collect respiratory specimens for influenza testing (preferably by molecular assay such as RT-PCR, if available) from all new symptomatic residents or patients to facilitate identification of the end of the outbreak and inform the extent (units or wards affected) and duration of outbreak control interventions. • Any ill staff who develop respiratory symptoms should don a facemask and promptly be excluded from the facility and, if indicated, be offered or referred for empiric antiviral treatment or have influenza testing performed. Institute a policy where ill staff do not return to work until afebrile >24 hours without antipyretic treatment and with improvement in respiratory symptoms or no earlier than 5 days after illness onset, because lack of fever does not necessarily mean lack of infectiousness • Post and display information about influenza illness signs and symptoms, facility policies related to influenza prevention and control, influenza vaccine recommendations, outbreak activity, and precautions for visitors and staff • Have procedures in place to actively screen all visitors for any illness signs and symptoms, and prohibit anyone with any illness from visiting • Offer influenza vaccination to unvaccinated staff members and residents or patients, and oseltamivir chemoprophylaxis to staff for 14 days after influenza vaccination. If influenza vaccine is not available, antiviral chemoprophylaxis can be offered to all unvaccinated staff for the duration of an institutional outbreak • Notify local public health authorities as soon as possible of a suspected or confirmed influenza outbreak