Neuraminidase inhibitors for preventing and treating influenza in healthy adults (Review)

Jefferson T, Jones MA, Doshi P, Del Mar CB, Dooley L, Hama R, Heneghan CJ

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[Intervention Review]

Neuraminidase inhibitors for preventing and treating influenza in healthy adults

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: Edited (no change to conclusions), published in Issue 11, 2010.
Review content assessed as up-to-date: 6 August 2009.

Citation: Jefferson T, Jones MA, Doshi P, Del Mar CB, Dooley L, Hama R, Heneghan CJ. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD001265. DOI: 10.1002/14651858.CD001265.pub2.

ABSTRACT

Background

Neuraminidase inhibitors (NI) are recommended for use against influenza and its complications in inter-pandemic years and during pandemics.

Objectives

To assess the effects of NIs in preventing and treating influenza, its transmission, and its complications in otherwise healthy adults, and to estimate the frequency of adverse effects.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 3) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to August 2009) and EMBASE (1980 to August 2009).

Selection criteria

Randomised controlled trials (RCTs) or quasi-randomised placebo-controlled trials of NIs in healthy adults exposed to naturally occurring influenza.

Data collection and analysis

Two review authors independently applied inclusion criteria, assessed trial quality, and extracted data. We structured the comparisons into prophylaxis, treatment, and adverse events, with further subdivision by outcome and dose.

Main results

We identified four prophylaxis, 12 treatment and four post-exposure prophylaxis trials. In prophylaxis compared to placebo, NIs had no effect against influenza-like illnesses (ILI) (risk ratio (RR) ranging from 1.28 for oral oseltamivir 75 mg daily to 0.76 for inhaled zanamivir 10 mg daily). The efficacy of oral oseltamivir against symptomatic influenza was 76% (at 75 mg daily), and 73% (at 150 mg daily). Inhaled zanamivir 10 mg daily performed similarly. Neither NI had a significant effect on asymptomatic influenza. Oseltamivir induced nausea (odds ratio (OR) 1.79, 95% CI 1.10 to 2.93). Oseltamivir for post-exposure prophylaxis had an efficacy of 58% and 84% in two trials for households. Zanamivir performed similarly. The hazard ratios for time to alleviation of symptoms were in favour of the treated group 1.20 (1.06 to 1.35) for oseltamivir and 1.24 (1.13 to 1.36) for zanamivir. Because of the exclusion of a review of mainly unpublished trials of oseltamivir, insufficient evidence remained to reach a conclusion on the prevention of complications requiring antibiotics in influenza cases (RR 0.57, 95% CI 0.23 to 1.37). Analysis of the US FDA and Japan's PMDA regulators' pharmacovigilance dataset, revealed incomplete reporting and description of harms preventing us from reaching firm conclusions on the central nervous system toxicity of neuraminidase inhibitors.

Authors' conclusions

Numerous inconsistencies detected in the available evidence, followed by an inability to adequately access the data, has undermined confidence in our previous conclusions for oseltamivir. Independent RCTs to resolve these uncertainties are needed.

PLAIN LANGUAGE SUMMARY

Influenza is an acute infection of the airways and the whole body, caused by a virus

Influenza symptoms include fever, headache and cough. Serious complications such as pneumonia can also occur. This review of trials found that neuraminidase inhibitors (Nls) such as zanamivir (*Relenza*) and oseltamivir (*Tamiflu*) are effective in preventing ('prophylaxis') and treating the symptoms of influenza. They do not prevent infection or stop influenza viruses leaving the nose. Because the review authors could not verify the content of a Roche-sponsored review of 10 randomised trials (eight of which were unpublished), it was excluded. This changes the conclusions as there now is insufficient evidence to say whether NIs prevent complications such as pneumonia. Oseltamivir causes nausea, vomiting and retching while zanamivir causes diarrhoea but the full picture on the drugs' toxicity cannot be reconstructed as the regulators' data are incomplete and too generic. There is no randomised controlled trial evidence to tell us whether NIs are or are not effective against pandemic influenza. Trials are urgently needed to test whether NIs are more effective than symptomatic treatment and hygiene and barrier measures to interrupt influenza transmission in healthy adults.

BACKGROUND

Description of the condition

Influenza is an acute, usually benign and self-limiting infection of the upper airways and at times affects the whole body.

Description of the intervention

In recent years a new generation of antiviral compounds has been developed. These compounds, known collectively as neuraminidase inhibitors (NIs) are nebulised zanamivir (*Relenza,* (formerly known as GG167) developed by Glaxo Wellcome PLC (UK) and oral oseltamivir (*Tamiflu,* formerly known as RO 64-0796 or GS 4104) co-developed by Gilead Sciences Inc (Foster City, CA, USA) and Hoffman La Roche Ltd (Basel, Switzerland). Other NIs are still under development for parenteral or long acting use (Hayden 2009).

How the intervention might work

NIs act by inhibiting the release of virions from the infected cell, neuraminidase being essential for both viral entry and exit from the target cell. The World Health Organization (WHO) encouraged member countries to use antivirals in influenza "inter-pandemic periods". The rationale given is as follows: "wide scale use of antivirals and vaccines during a pandemic will depend on famil-

iarity with their effective application during the inter-pandemic period. The increasing use of these modalities will expand capacity and mitigate the morbidity and mortality of annual influenza epidemics. Studies conducted during the inter-pandemic period can refine the strategies for use during a pandemic" (WHO 2005). The European Medicines Agency (EMEA) took a different line, identifying NIs (especially oseltamivir) as compounds with a complementary effect to vaccines to be used in an influenza pandemic (EMEA 2005) for treatment of index cases and influenza prophylaxis in key personnel (police, fire brigade, healthcare workers).

Why it is important to do this review

The use of NIs has increased dramatically with the spread of the A/H1N1 pandemic beginning in April 2009, a novel and potentially serious infection. Partly because of the rise in amantadine/rimantadine resistance coupled with the lack of an effective vaccine, NIs became a widespread public health intervention. Their use for early containment and interruption was also recommended in many pandemic plans, and the WHO had previously encouraged member countries to gain experience with them.

Although several systematic reviews of the effects of NIs are available, none are up-to-date or evaluate the potential role of NIs in an influenza pandemic, where high viral load and high transmission appear to be the norm; nor do they systematically investigate the potential harms of NIs (Burch 2009; Burls 2002; Cooper 2003; Jefferson 2000; Tappenden 2009; Turner 2003). In this context, trade-off between dosage and adverse event profile in prophylaxis, activity against influenza infection regardless of symptoms (symptomatic and asymptomatic influenza) and viral excretion through body fluids become important (Ward 2005).

In addition, our previous Cochrane review updates (Jefferson 2006; Jefferson 2009c) summary of the evidence on the effects of oseltamivir on lower respiratory tract complications was challenged by Hayashi through the public Cochrane reviews feedback mechanism (Feedback 1). In updating our review, we addressed these additional issues.

OBJECTIVES

1. To assess the efficacy and effectiveness of NIs in preventing cases and complications of influenza (prophylaxis) in healthy adults.

2. To assess the efficacy and effectiveness of NIs in shortening or reducing the impact and complications of influenza (treatment) in healthy adults.

3. To assess the effectiveness of NIs in interrupting the spread of influenza virus.

4. To estimate the frequency of adverse effects associated with NI administration in healthy adults.

METHODS

Criteria for considering studies for this review

Types of studies

Any RCT or quasi-RCT comparing oral oseltamivir and/or zanamivir in humans with placebo, control antivirals or no intervention or comparing doses or schedules of oseltamivir and/or zanamivir. Studies assessing prophylaxis or treatment from exposure to naturally occurring influenza only were considered.

Types of participants

Individuals with no known pre-existing chronic pathology known to aggravate the course of influenza. In keeping with our objective of reviewing evidence on healthy adults, we only considered studies in which no less than 75% of the subjects were aged 14 to 60 to exclude older subjects who are at higher risk of complications.

Types of interventions

Oseltamivir and/or zanamivir as prophylaxis and/or treatment for influenza (efficacy) or for influenza-like illness (ILI/effectiveness).

Types of outcome measures

Primary outcomes

1. Mortality.
2. Hospitalisation and complications.
3. Harms.
4. Drug resistance.

Secondary outcomes

1. Symptom relief.
2. Viral excretion.
3. Interruption of transmission.

Search methods for identification of studies

Electronic searches

For this 2009 update we ran update searches for effectiveness studies and conducted a separate search for adverse effects studies. In previous versions of this review no specific searches for adverse effects were undertaken. We relied instead on information gathered from the RCTs and quasi-RCTs identified in the effectiveness searches. Growing concerns about harms caused us to broaden our approach for this update. We conducted separate, specific adverse effects searches based on the work of Cochrane Adverse Effects Methods Group. As these searches had not been carried out previously they were run over all years.

To identify **effectiveness studies** we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 3) which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (2008 to July 2009); and EMBASE (2008 to July 2009). See Appendix 3 for dates of previous effectiveness searches. We also searched for post-marketing pharmacovigilance data and comparative safety cohorts. The following search strategy was used in MEDLINE in conjunction with the Cochrane highly sensitive search strategy for identifying RCTs (Lefebvre 2008). The same strategy was used to search CENTRAL and the terms were adapted to search EMBASE. See Appendix 1 for the EMBASE search strategy.

MEDLINE (OVID)

1 exp INFLUENZA/
2 influenza$.mp.
3 or/1-2
4 neuraminidase inhibitor$.mp.
5 oseltamivir.mp.
6 zanamivir.mp.
7 GS4071.mp.
8 or/4-7
9 3 and 8

To identify **adverse effects** studies we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 3), MEDLINE (Ovid) (1950 to July Week 5 2009) and EMBASE (Ovid) (1980 to 2009 Week 31).

The following search strategy (based on the work of Golder 2006) was used in MEDLINE. The search strategy was adapted for CENTRAL and EMBASE (Appendix 4).

MEDLINE (Ovid)

1 exp Oseltamivir/
2 exp Zanamivir/
3 (oseltamivir or zanamivir or GS4071 or tamiflu or relenza).tw.
4 neuraminidase inhibitor*.tw.
5 1 or 2 or 3 or 4
6 (ae or to or po or co).fs.
7 (safe or safety).tw.
8 side effect*.tw.
9 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).tw.
10 exp Product Surveillance, Postmarketing/
11 exp Adverse Drug Reaction Reporting Systems/
12 exp Clinical Trials, Phase IV as Topic/
13 exp Poisoning/
14 exp Substance-Related Disorders/
15 exp Drug Toxicity/
16 exp Abnormalities, Drug-Induced/
17 exp Drug Monitoring/
18 exp Drug Hypersensitivity/
19 (toxicity or complication* or noxious or tolerability).tw.
20 exp Case-Control Studies/
21 exp Cohort Studies/
22 or/6-21
23 5 and 22

Searching other resources

We also checked the bibliographies of other systematic reviews of the topic (Burch 2009; Burls 2002; Cooper 2003; Tappenden 2009; Turner 2003). No language or publication restrictions were applied. Please refer to Appendix 2 for a glossary of terms.

Data collection and analysis

Selection of studies

For this 2009 update, two review authors (ED, TOJ) independently read all titles and studies retrieved in the search and applied inclusion criteria. Disagreements were resolved by discussion with a third review author (CDM).

Data extraction and management

The following data were extracted onto standard forms, checked and recorded:

Characteristics of participants

1. Number of participants.
2. Age, gender, ethnic group, risk category.

Characteristics of interventions

1. Type of NI, type of placebo, dose, treatment or prophylaxis schedule, length of follow up (in days).

Characteristics of outcome measures

1. Number and severity of influenza cases in NI and placebo groups.
2. Concentration of influenza viruses excreted by nasal mucous.
3. Adverse effects: presence and type.
4. Date of trial.
5. Location of trial.
6. Funder of trial (specified, known or unknown).
7. Publication status.

No new data were extracted for this 2009 update. Twenty-eight studies were retrieved and 29 studied were excluded.

Assessment of risk of bias in included studies

In the previous publication of this review (Jefferson 2009c) assessment of methodological quality for RCTs was carried out using the risk of bias tool, as recommended in the *Cochrane Handbook of Reviews of Interventions* (Higgins 2008a). We assessed studies according to adequacy of methods of generation of the allocation sequence, allocation concealment and blinding and dealing with losses to follow up. When there was disagreement among the review authors (TOJ, DR) on the quality of a trial, a third review author (VD) arbitrated. No new studies were included in this updated review.

In this update, there were no new trials to assess. One study (Kaiser 2003), a review of 10 other trials, was re-assessed, and found to be ineligible. A full discussion can be found in Appendix 5 (Doshi 2009).

Measures of treatment effect

We used random-effects methods to compare dichotomous outcomes (RR for efficacy and OR for safety), therefore estimates meta-analysed over multiple trials are average treatment effects. Where hazard ratios were not provided, we converted the ratio of medians of treatment groups into (log) hazard ratios (estimating the variance of these) (Parmar 1998) to enable meta-analysis of time to event outcomes.

Assessment of heterogeneity

We assessed heterogeneity used the I^2 statistic and Chi^2 test. Due to the low power of the Chi^2 test we assumed $P < 0.1$ to indicate evidence of heterogeneity.

Assessment of reporting biases

See Appendix 5.

Data synthesis

We structured the comparisons into prophylaxis, treatment and adverse events and further subdivided them by outcome and dose. The RRs of events comparing prophylaxis and placebo groups from the individual trials were combined using random-effects models to include between-trial variability.

Subgroup analysis and investigation of heterogeneity

We planned to investigate possible reasons for heterogeneity using variables such as trial quality and trial sponsorship (industry versus other).

Sensitivity analysis

We carried out a sensitivity analysis of methods used comparing our results obtained using the fixed-effect and random-effects models. In the prophylaxis trials efficacy was derived as 1-RR (risk ratio) x 100 or the RR when not significant. Odds ratios (OR) were used to estimate association of adverse effects with exposure to antivirals. In the treatment trials, analysis of "time to alleviation of symptoms" and "time to return to normal activity" outcomes provided some difficulty due to inconsistent and non-standard reporting in the majority of the trial reports. Most reports described these outcomes in terms of medians for each treatment group. However, standard reporting in a meta-analysis requires these outcomes to be expressed as (log) hazard ratios. If it is assumed that the treatment effect is constant over time (as seems reasonable) then the ratio of the medians can be used to estimate the hazard ratio. To estimate the variance of the log hazard ratio, the method given by Parmar et al was used (Parmar 1998). The number of events was estimated from survival curves when these were available or, when they were not available, assumed to be all patients completing the trial providing follow up was sufficiently long enough for this to be a reasonable assumption.

In one study (Boivin 2000) follow up was possibly not long enough for this to be a reasonable assumption, however this was a small trial (27 participants in total) and follow up was sufficiently long enough for more than 90% of the patients to be expected to reach the endpoint. The impact of including this trial in the overall analysis is likely to be negligible. As a check to see if the estimation methods used are accurate, one study (Makela 2000) provided both hazard ratios and medians. The two methods provided identical results for the intention-to-treat (ITT) population and similar results for the influenza-positive population. The random-effects inverse variance method was used for the meta-analysis of the log hazard ratio. Two studies presented nasal viral titre data as medians and ranges (Nicholson 2000; Treanor 2000). The data were converted into means and standard deviations (SDs) to be consistent with other studies and allow meta-analysis. Means were converted directly from the medians as both are measures of central tendency and should be similar for approximately symmetrical

data. The range was converted to a SD using the method described by Hurlburt 1994. The inter-quartile range (IQR) was converted to SD by multiplying by 68/50 (as 50% of the data is contained within the IQR while +/- 1 SD contains 68% of the data providing it is approximately normally distributed) then dividing by 2 (to estimate 1 SD).

We also searched for evidence of harms more widely, including submitting a Freedom of Information Act request to the US Food and Drug Administration (FDA) for all data on the harms of oseltamivir and zanamivir, and pursuing authors of some papers and manufacturers to obtain raw data (FDA 2009b)

We were unable to meta-analyse the same outcomes reported by Kaiser et al (Kaiser 2003) because the data for those outcomes were not available to us for individual trials. We carried out a sensitivity analysis of complications by excluding the unpublished trials included in the Kaiser review, criticised by Hayashi (Feedback 1).

RESULTS

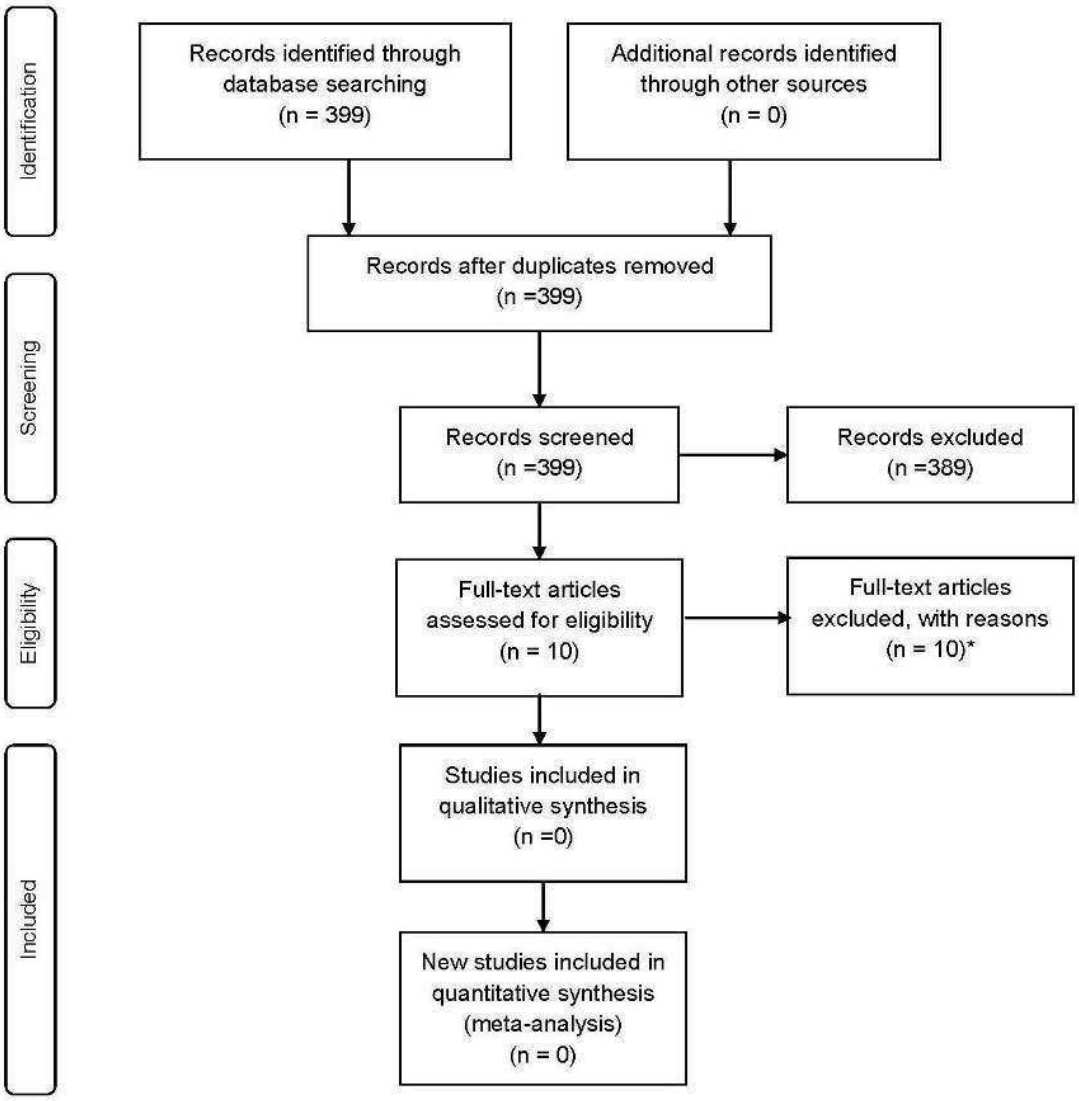
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

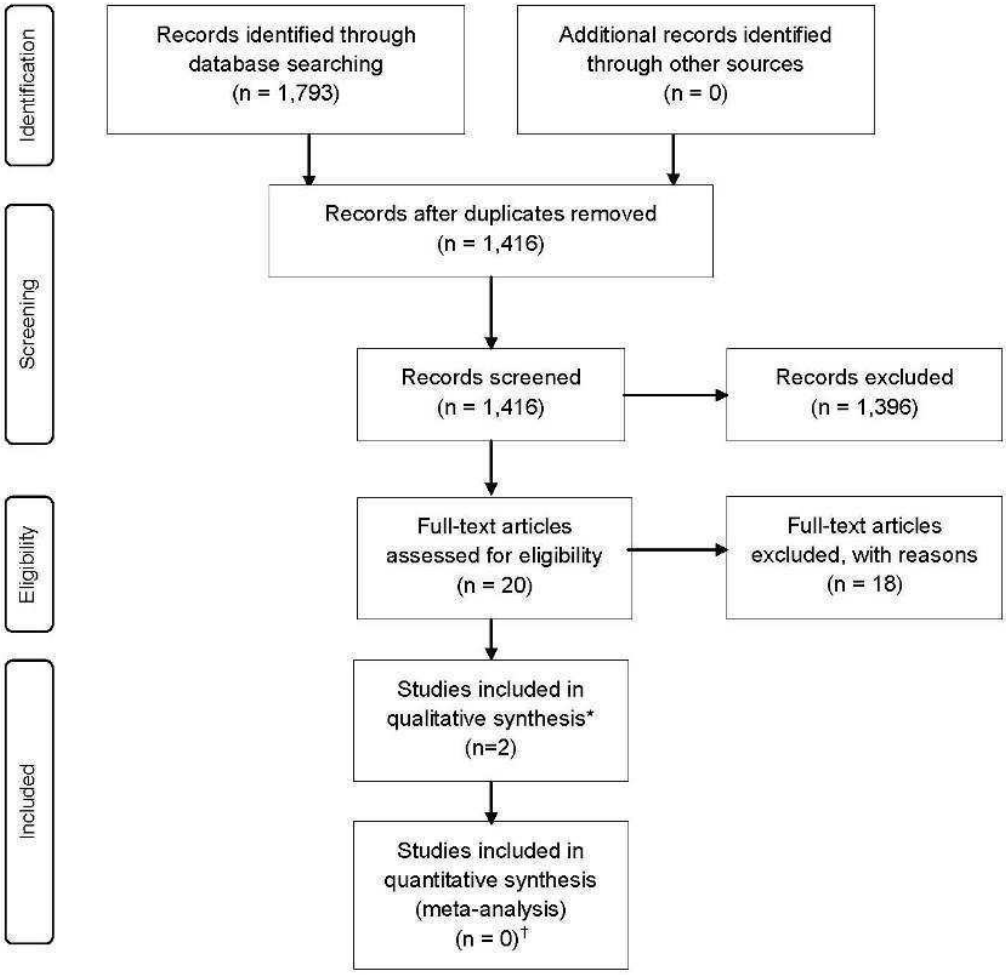
In this updated search we retrieved a total of 399 records in the search for effectiveness studies, and a total of 1793 records in the search for adverse effects studies. We excluded 18 safety and 10 effectiveness studies (six were identified through both search strategies as they assessed both dimensions). We identified four prophylaxis, 12 treatment and four post-exposure prophylaxis (PEP) trials. Twenty-eight studies were retrieved and 29 studied were excluded, Figure 1 and Figure 2. However, two studies provided information on harms of oseltamivir (Blumentals 2007; Toovey 2008). This left 20 included trials in 19 publications (Aoki 2000; Boivin 2000; Hayden 1997; Hayden 1999a; Hayden 2000a; Hayden 2004; Kaiser 2000; Kashiwagi 2000a; Kashiwagi 2000b; Li 2003; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999a; Monto 1999b; Monto 2002; Nicholson 2000; Puhakka 2003; Treanor 2000; Welliver 2001).

Figure 1. Flow of studies identified from randomised controlled trials.



*data from one meta-analysis[1], included in the previous versions of this Cochrane review, was excluded in this review, as described in the text.

Figure 2. Flow of studies identified from the search for evidence from post-marketing studies (excluding AERS)



* studies providing background data on adverse events, but excluded from the effectiveness part of this review:

1. Blumentals WA, Song X. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. *MedGenMed* 2007;9:23
2. Toovey S, Rayner C, Prinssen E, Chu T, Donner B, Thakrar B, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug Saf* 2008;31:1097-114

† in addition, data from the following US and Japanese websites were evaluated:

1. Japan Pharmaceuticals and Medical Devices Agency. New drug approval related information http://www.info.pmda.go.jp/shinyaku/shinyaku_hanbaimei_index.html (accessed 16 Nov 2009)
2. US Food and Drug Administration. The Adverse Event Reporting System (AERS): Older Quarterly Data Files. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm083765.htm (accessed 13 October 2009), 2009
3. US Food and Drug Administration. The Adverse Event Reporting System (AERS): Latest Quarterly Data Files. www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm

Included studies

Prophylaxis trials

We identified four prophylaxis trials, two comparing a total of 697 treated with inhaled zanamivir 10 mg daily versus 602 with placebo (followed for 22 days) (Kaiser 2000; Monto 1999a), and two trials comparing a total of 675 treated with oral oseltamivir 75 mg daily versus 413 placebos (followed for 49 days) (Hayden 1999a; Kashiwagi 2000a). Compared to placebo, NIs had no effect against ILI (RR 1.28, 95% CI 0.45 to 3.66 for oseltamivir 75 mg daily, RR 0.76, 95% CI 0.49 to 1.19 for zanamivir 10 mg daily) (Figure 3). Higher dosages made no difference, although this is based on a single study with only nine events (Hayden 1999a; Hayden 2000a; Kaiser 2000;) Oseltamivir 75 mg daily reduced the chance of symptomatic laboratory-confirmed influenza (RR 0.24, 95% CI 0.12 to 0.48). Zanamivir 10 mg daily was similarly efficacious (RR 0.33, 95% CI 0.18 to 0.59) (Figure 4). Neither protected against asymptomatic influenza (Hayden 1999a; Kashiwagi 2000a; Monto 1999a).

Figure 3. Forest plot of comparison: 1 NI versus placebo for prophylaxis, outcome: 1.1 Influenza-like illness.

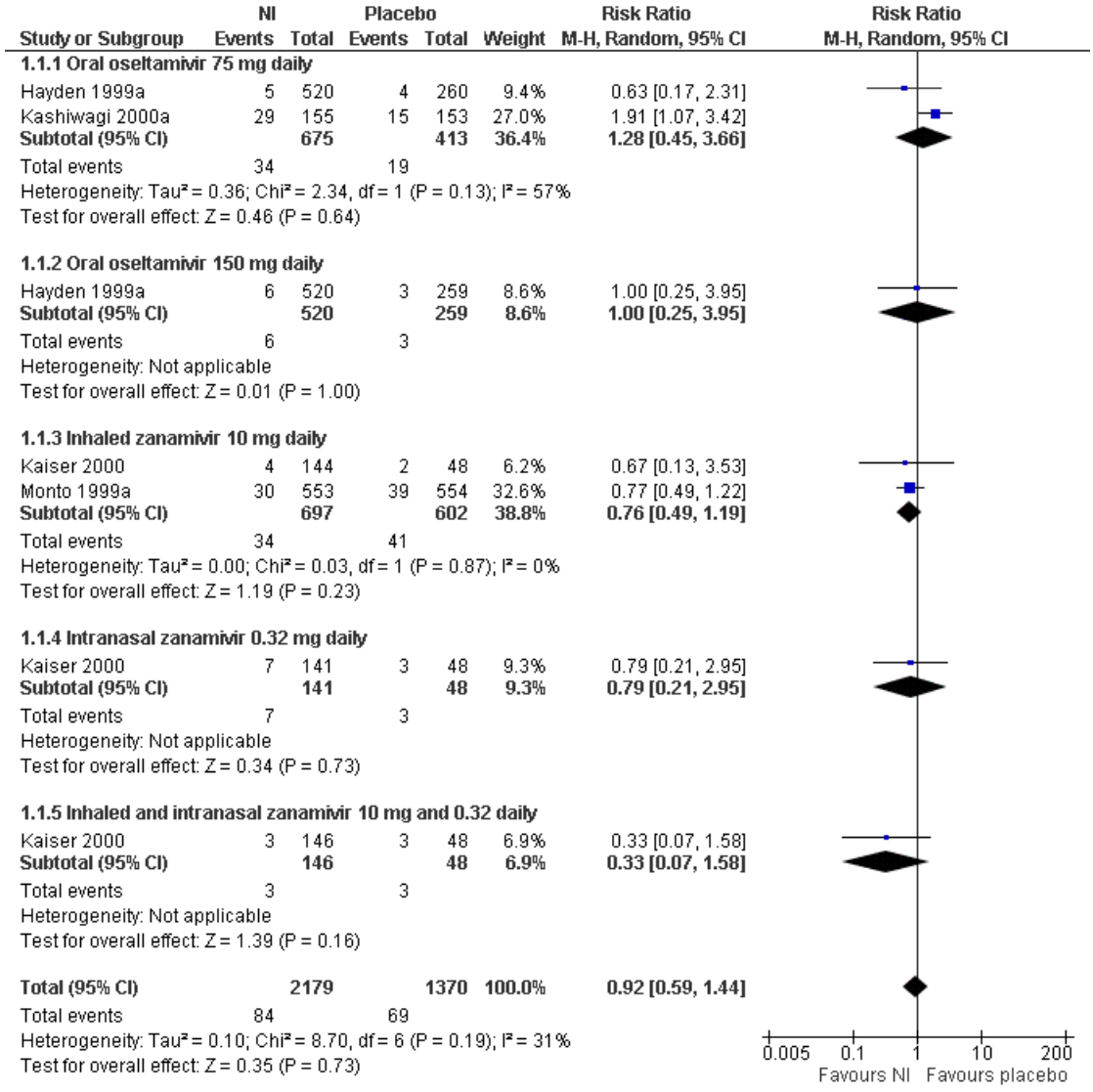
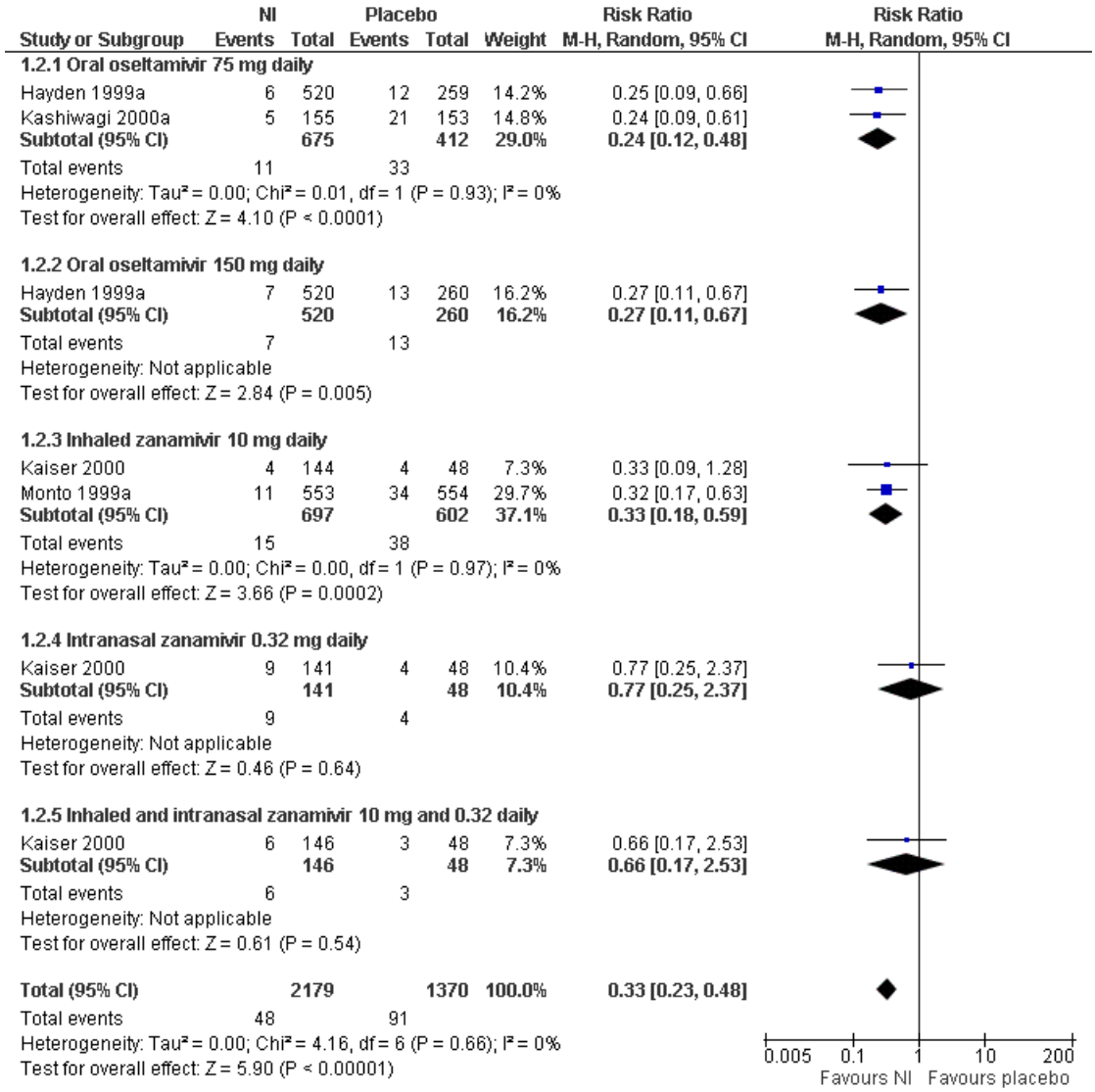


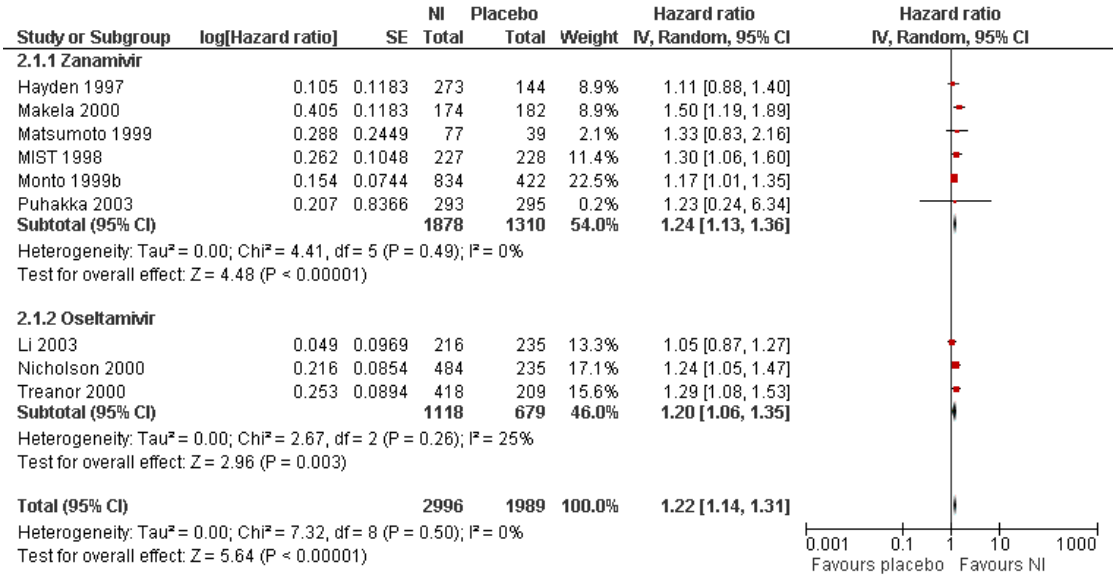
Figure 4. Forest plot of comparison: 1 NI versus placebo for prophylaxis, outcome: 1.2 Influenza (symptomatic).



Treatment trials

We identified eight treatment trials of zanamivir (Aoki 2000; Boivin 2000; Hayden 1997; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Puhakka 2003), of which two (Aoki 2000; Boivin 2000) were linked to others (MIST 1998; Monto 1999b) (a total of 1878 in the treatment arm and 1310 controls, with a mean length of follow up of 26 days). Four of oseltamivir (Kashiwagi 2000b; Li 2001; Nicholson 2000; Treanor 2000), and another trial (Li 2003) was linked to a redundant publication (Li 2001), (totaling 1118 treatment; 679 controls, 21 days follow up). There was evidence of benefit in shortening duration of influenza like-illness for zanamivir (hazard ratio, (HR) 1.24, 95% CI 1.13 to 1.36), and for oseltamivir (HR 1.20, 95% CI 1.06 to 1.35), (Figure 5). This finding is likely to be due to the high percentage of influenza-like illness caused by influenza in some of the included trials (for example, 66%) (Nicholson 2000).

Figure 5. Forest plot of comparison: 2 NI versus placebo for treatment, outcome: 2.1 Time to alleviation of symptoms (ITT).



Post-exposure prophylaxis (PEP) trials

We identified two PEP trials of different design assessing the effects of oseltamivir. Hayden 2004 is a C-RCT comparing the effects on household contacts of expectant treatment with oseltamivir with commencing immediate PEP. Welliver 2001 investigated the effects of oseltamivir on the spread of influenza by randomising household contacts of index cases with influenza to the active principle or placebo. The mean and median oseltamivir arm size was 447 (25th percentile 422 and the 75th% percentile 470).

Two further PEP trials assessed zanamivir (Hayden 2000a; Monto 1999a). In both trials, household contacts of an index case with ILI were randomised to either placebo of zanamivir. The oseltamivir trials reported significant protection for household (RR 0.16 and 0.42) and the zanamivir trials reported similar results (RR 0.19 and 0.21).

See the 'Characteristics of included studies' table for a full description of all included studies.

Excluded studies

For this 2009 update overall, 29 studies made up of 10 effectiveness and 10 safety studies (six were identified by both searches) were excluded. After additional deliberations, another three effectiveness studies were excluded (Blumentals 2007; Kaiser 2003; Toovey 2008). This left 20 included trials in 19 publications. Two

studies that were excluded from the effectiveness screen were included in the safety data sources (Blumentals 2007; Toovey 2008), Figure 1 and Figure 2.

Risk of bias in included studies

One prophylaxis trial had adequate methodological quality (Monto 1999a), one had an unclear measures to protect double blinding (Hayden 1999a) and two (Kaiser 2000; Kashiwagi 2000a) had unclearly described methods. Kaiser 2000 reported no dropouts from the trial. Four treatment studies (Makela 2000; MIST 1998; Nicholson 2000; Treanor 2000) had adequate methodological quality, three trials (Aoki 2000; Boivin 2000; Kashiwagi 2000b) has unclearly described processes, although two (Aoki 2000; Boivin 2000) were linked to larger studies. The remainder had at least one unclearly described item. One trial (Li 2003) did not include withdrawals in the analysis.

Withdrawals were included in all PEP trials but all other items were poorly described. Hayden 2004 was an open-label C-RCT. Allocation concealment was not described in the zanamivir trials.

Allocation

On the basis of the published text only five trials were judged adequate by usual Cochrane Collaboration methods (Higgins 2008b). One trial on prophylaxis (Monto 1999a) and four on treatment (Makela 2000; MIST 1998; Nicholson 2000; Treanor 2000).

Incomplete outcome data

Most of the trials were at risk of bias, arising from poor descriptions of the methods (Aoki 2000; Boivin 2000; Kaiser 2000; Kashiwagi 2000a; Kashiwagi 2000b; Hayden 1999a) such as no description of losses to follow up and blinding (Kaiser 2000). Attempts to deal with these shortcomings were unsuccessful. To address the Hayshi comment (Feedback 1) we wrote to all first or corresponding trial authors of studies on oseltamivir treatment. Although five responded to our contact, none had original data and referred us to the manufacturer (Roche), which was not able to unconditionally provide the information as quickly as we needed it to update this review (Doshi 2009). The Kaiser et al 2003 meta-analysis (Kaiser 2003) was made up of data from 10 studies. We were obliged to exclude the meta-analysis because we were unable to determine the number of healthy adults experiencing complications in each study (some studies contained mixed populations of healthy and comorbid participants), nor the number of patients experiencing one of more of "bronchitis, lower respiratory tract infection, or pneumonia" presenting to each study.

Other potential sources of bias

We are unable to assess the size and direction of the obvious bias in the treatment data set due to the non-publication or partial-publication of eight trials, as the data provided to us by Roche are insufficient to fill the gaps in our understanding of the population, methods and results of the studies.

Effects of interventions

We carried out three main comparisons with placebo: NIs in a pre-exposure, post-exposure prophylaxis (PEP) and treatment roles. We further subdivided each comparison according to outcome case definition. We did not meta-analyse data from the PEP trials, as they had different study designs.

Prophylaxis trials

Compared to placebo, NIs have no effect against ILI (RR 1.28, 95% CI 0.45 to 3.66 for oral oseltamivir 75 mg daily (Figure 3); and RR 0.76, 95% CI 0.49 to 1.19 for inhaled zanamivir 10 mg daily). Higher dosages appear to make no difference, although this observation is based on single studies with very low viral circulation (Hayden 1999a; Kaiser 2000).

The efficacy of oral oseltamivir 75 mg daily against symptomatic influenza is 76% (RR 0.24, 95% CI 0.12 to 0.48), or 73% (RR 0.27, 95% CI 0.11 to 0.67) at 150 mg daily, although this last observation is based on a single study. Inhaled zanamivir 10 mg daily is 67% efficacious (RR 0.33, 95% CI 0.18 to 0.59) (Figure 4). The addition of an intranasal dose does not seem to enhance its prophylactic activity (RR 0.66, 95% CI 0.17 to 2.53), although again this last observation is based on a single study.

Oseltamivir confers 64% protection against symptomatic and asymptomatic influenza (RR 0.46, 95% CI 0.31 to 0.68) at a lower dose of 75 mg daily. An increase to 150 mg daily does not appear to enhance its activity (RR 0.48, 95% CI 0.29 to 0.80) although this observation is based on a single study. Similarly zanamivir has a 43% protective effect (RR 0.67, 95% CI 0.50 to 0.91) and based on a single study the addition of intranasal dose does not appear to enhance its activity (RR 0.77, 95% CI 0.38 to 1.56).

However, when the outcome is asymptomatic influenza no NI has significant effects (oseltamivir 75 mg daily RR 0.73, 95% CI 0.43 to 1.26; oseltamivir 150 mg daily RR 0.67, 95% CI 0.35 to 1.28; zanamivir 10 mg daily 0.98, 95% CI 0.65 to 1.47). These observations are based on three studies (Hayden 1999a; Kashiwagi 2000a; Monto 1999a) with a combined denominator of 2974 in the presence of relatively high viral circulation (5% in the combined placebo arms).

Oseltamivir induces nausea (OR 1.79, 95% CI 1.10 to 2.93), especially at the higher prophylactic dose of 150 mg daily (OR 2.29, 95% CI 1.34 to 3.92).

Post-exposure prophylaxis (PEP) trials

Hayden 2004 reports that PEP provided an efficacy of 58.5% (15.6% to 79.6%) for households and of 68% (34.9% to 84.2%) for individual contacts. Given the high circulation of virus (184 out of 298 index cases had influenza, 66% of which had influenza AH1N1 and remainder influenza B virus) effectiveness was high 62.7% (26% to 81%).

Welliver 2001 reports 89% (67% to 97%) protective efficacy in contacts of index cases with influenza and 84% (45% to 95%) for index cases.

Neither trial reported the onset of viral resistance after five (Hayden 2004) and seven days (Welliver 2001) of prophylaxis at a dose of 75 mg twice daily (Hayden 2004) and once daily (Welliver 2001). Neither the background rate of infection in the community nor the viral strains are reported, although influenza A and B were co-circulating at the time.

Monto 2002 reports a 79% effectiveness and 81% efficacy (64% to 90%) for households and 82% for individuals against symptomatic influenza, 55% to 59% against all asymptomatic and symptomatic influenza. Zanamivir shortened duration of illness by 1.5 days and was well tolerated and no viral resistance was reported.

Hayden 2000a concludes that zanamivir was 79% (57% to 89%) effective and 72% (42% to 87%) effective in preventing contacts from developing symptomatic influenza and 53% (27% to 70%) effective and 48% (15% to 68%) efficacious in preventing symptomatic and asymptomatic influenza. Zanamivir also shortened duration of symptoms by 2.5 days. There was no evidence of the onset of resistance.

Treatment trials

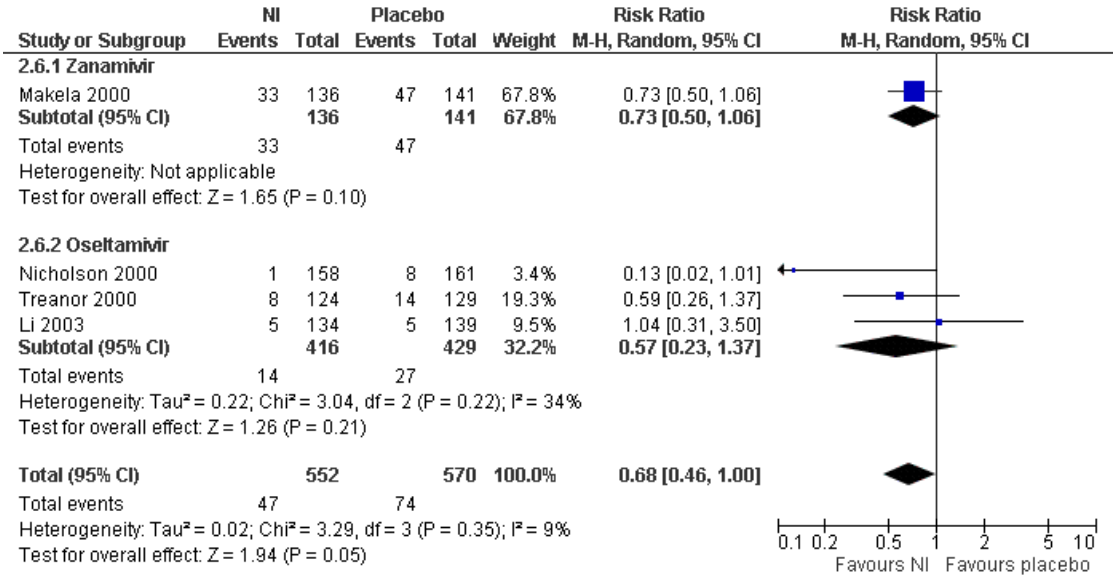
Time to alleviation of symptoms (considering ITT population) was assessed in nine trials (Hayden 1997; Li 2003; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Nicholson 2000; Puhakka 2003; Treanor 2000). The estimated hazard ratios for zanamivir were greater than one, hence in favour of the treated group and there was no evidence of heterogeneity (I^2 statistic = 0%). The pooled hazard ratio is 1.24 (95% CI 1.13 to 1.36) indicating that the treated group are 24% more likely to have their symptoms alleviated than the placebo group by a given time-point. We obtained a similar result for oseltamivir (hazard ratio 1.20, 95% CI 1.06 to 1.35) (Figure 5). For time to alleviation of symptoms in influenza-positive participants, the hazard ratios were significantly in favour of the treated group 1.33 (95% CI 1.29 to 1.37) for zanamivir and 1.30 (95% CI 1.13 to 1.50) for oseltamivir. There was no evidence of heterogeneity for the zanamivir data meta-analysis, but I^2 statistic was 37.5% for oseltamivir. Application of the fixed-effect model did not materially alter the hazard ratio (Boivin 2000; Hayden 1997; Kashiwagi 2000b; Li 2003; Makela 2000; Matsumoto 1999; MIST 1998; Monto 1999b; Nicholson 2000; Puhakka 2003; Treanor 2000).

Time to return to normal activities (considering ITT population) was assessed by four studies (Matsumoto 1999; MIST 1998; Monto 1999b; Treanor 2000). The pooled estimated hazard ratios for zanamivir was 1.28 (95% CI 1.13 to 1.45), while the single study assessing oseltamivir (Treanor 2000) had a non-significant hazard ratio (1.23, 95% CI 1.02 to 1.48). There was no heterogeneity (I^2 statistic = 0). In influenza-positive participants the pooled hazard ratio was just below significance 1.17 (95% CI 1.00 to 1.37, P value 0.06) for zanamivir (Makela 2000; MIST 1998; Hayden 1997) and significant for oseltamivir 1.34 (95% CI 1.07 to 1.67) although this observation is based on a single study (Treanor 2000). There was no evidence of heterogeneity (I^2 statistic = 0%).

Five studies reported assessing the effect of NI administration on viral load (as estimated by mean nasal titres of excreted viruses at 24 and 48 hours since randomisation) (Boivin 2000; Kashiwagi 2000b; Nicholson 2000; Puhakka 2003; Treanor 2000). Titres were significantly diminished by both zanamivir and oseltamivir (WMD -0.62, 95% CI -0.82 to -0.41). The effect is more marked the longer the time since randomisation (and commencement of treatment). Exclusion of data from the Treanor 2000 and Nicholson 2000 studies does not affect our conclusions. There was evidence of heterogeneity (I^2 statistic = 34.6%) but analysis using a fixed-effect model did not materially affect our findings, except for the comparison zanamivir against placebo where the effect on mean nasal titres at 48 hours since randomisation is not significant when analysed using a fixed-effect model. However, treatment did not suppress viral excretion, apparently regardless of the dose. We found insufficient data to comment on the effects on nasal excretion of viruses of higher doses of medication.

There is insufficient evidence for oseltamivir 75 mg daily in preventing complications (pneumonia, bronchitis, otitis media, sinusitis) requiring antibiotics in influenza cases (RR 0.57, 95% CI 0.23 to 1.37) (Figure 6). There is also insufficient evidence for zanamivir in preventing complications of all types in influenza cases (RR 0.73, 95% CI 0.50 to 1.06). However, zanamivir is effective in preventing complications of all types in the ITT population (RR 0.69, 95% CI 0.49 to 0.96), although these observations are based on a single study (Makela 2000).

Figure 6. Forest plot of comparison: 2 NI versus placebo for treatment, outcome: 2.6 Complications - all types (influenza cases only).

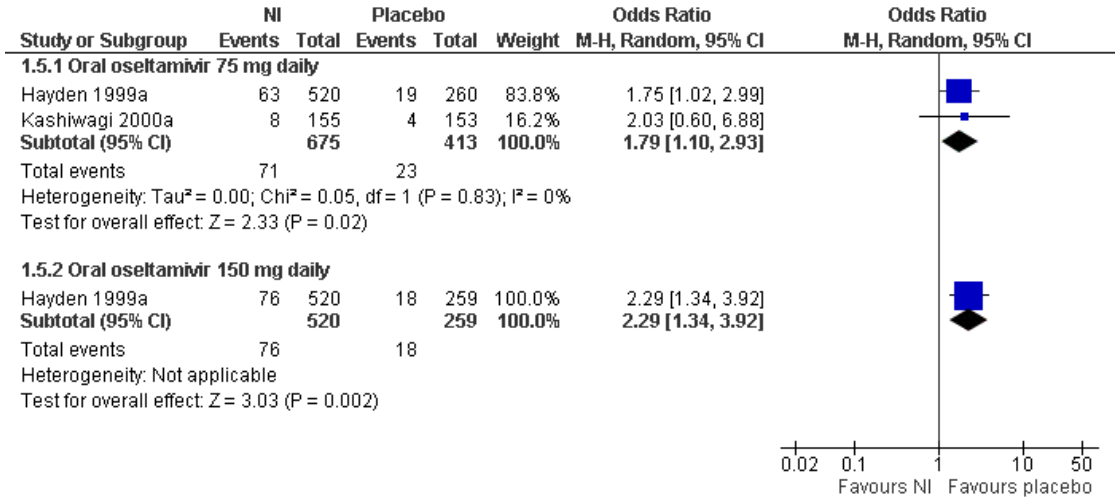


Oseltamivir is associated with nausea (OR 2.50, 95% CI 1.49 to 4.20). Finally, use of relief medications and antibiotics is unaffected by consumption of NIs (OR 0.82, 95% CI 0.60 to 1.11).

Evidence of harms

The trials identified only one serious adverse event (Nicholson 2000) (so labelled in the Japanese data, a patient with neutropenia), and, in particular, no neuropsychiatric events. Oseltamivir induced nausea (OR 1.79, 95% CI 1.10 to 2.93), especially at the higher dose of 150 mg daily (OR 2.29, 95% CI 1.34 to 3.92) (Figure 7). No statistically significant adverse event was found for zanamivir from the trials (Matsumoto 1999; MIST 1998; Monto 1999b; Puhakka 2003).

Figure 7. Forest plot of comparison: 1 NI versus placebo for prophylaxis, outcome: 1.5 Adverse events - nausea.



Two published studies reported additional retrospective comparative safety data on oseltamivir (Blumentals 2007; Toovey 2008). Their data suggest an incidence of neuropsychiatric adverse events per 1000 adults aged between 18 to 49 at 14 days and 30 to 40 at 30 days (Blumentals 2007) and for neuropsychiatric adverse events in prospective clinical trials, an incidence of 0.5% (Toovey 2008).

AERS-1includes 2275 adverse event reports for oseltamivir and 453 for zanamivir (excluding follow up reports on the same individual event) generated worldwide between December 1999 and July 2009 (the month our request was answered). Unfortunately it indicates neither reporting country nor how long the event occurred before receipt of the report by the FDA. The period from 2004 onwards overlaps with AERS-2, which has reports from January 2004 to March 2009, indicating both initial and follow up reports, and reporting the date of the adverse event (FDA 2009b; FDA 2009c). From July 2005 it indicates the reporting country. From July 2005 to March 2009, 1205 initial adverse events occurred. Most (681, 56.5%) were reported from Japan, followed by the United States (390, 32.4%). Most (1109, 92.0%) were for oseltamivir (perhaps reflecting its higher use). A disproportionate amount of reports are for people aged less than 20 (with data on age missing for many).

DISCUSSION

Summary of main results

Role of NIs in seasonal influenza

We have assembled a good-quality up to date evidence base of the prophylactic and treatment effects of NIs. These compounds have low effectiveness, high efficacy and appear to be well tolerated, with the possible exception of oseltamivir-induced nausea and vomiting and zanamivir-induced diarrhoea. Existing trials on NIs were clearly designed and undertaken within a registration and regulation perspective. This is reflected in the cryptic reporting of continuous outcome data which forced us to resort to summary measures such as hazard ratio (HR), which although methodologically virtuous, may not be relevant to workers in the field. Onset of resistance is a possibility.

Although none of the studies included in the review reported it, Kiso and colleagues found an 18% isolation rate of NI-resistant A/H3N2 viruses in 50 very young children at day 4 of treatment, and a high prolonged viral excretion even after five days of treatment (Kiso 2004). Resistance to oseltamivir is reported to be the around 0.5% from other trials in the Roche database (Ward 2005). Recently resistance of H1N1 viruses to oseltamivir has been reported from 59/437 (14%) isolates from nine European countries (Lackenby 2008). Given the highly selective nature of the isolates it is not possible to generalise the data. However the onset of resistance is a further reason against the routine use of neuraminidase inhibitors.

NIs affect influenza symptoms, either preventing their appearance or curtailing their duration and, although we found clear evidence of their capacity to interrupt transmission of seasonal influenza in households, NIs do not prevent infection and decrease - but do not interrupt - nasal shedding of seasonal influenza viruses. We cannot

explain how NIs can affect respiratory complications of seasonal influenza such as bronchitis and pneumonia while not preventing infection and this effect should be further studied. An explanation for what we have observed is a possible effect in preventing a proportion of NI recipients to seroconvert into symptomatic influenza cases. This would explain the observed effects of NIs on serious complications and interruption of transmission in households during seasonal influenza. Whichever explanation is chosen, prophylactic use of NIs in a serious epidemic or a pandemic may enhance vulnerability to infection by preventing seroconversion and facilitating the selection of NI-resistant mutant viruses. Because of their low effectiveness and the possibility of the onset of resistance we conclude that NIs should not be routinely used in seasonal influenza. In the case of a serious localised confirmed epidemic, NIs could be used to prevent serious complications.

Our inability to provide a satisfactory response to the observations made in the Hayashi challenge, compounded by the inability of corresponding authors or the manufacturers to provide their original data, (for the latter, because it was contingent on our signing a secret confidentiality agreement), has undermined our confidence in our previous findings Cooper 2003. The treatment effects of oseltamivir now seem less credible.

NIs had low effectiveness, high efficacy against symptoms (shortening the illness by half to one day, and preventing symptoms from appearing), and initially appeared to be well tolerated (with the possible exception of oseltamivir-induced nausea and vomiting and zanamivir-induced diarrhoea).

Commercial interests may explain the cryptic reporting of continuous outcome data which forced us to resort to summary measures such as hazard ratio (HR). A surprising finding is the very high percentage (from 57% to 78%) of influenza in the ITT populations of the neuraminidase treatment trials. We remain at a loss to explain this (Jefferson 2009a) and questions to authors and pharmaceutical company remain unanswered or unsatisfactory, (WebExtra).

Viral resistance is monitored by several organisations. One recently reported resistance of seasonal A/H1N1 to oseltamivir at 98% of 259 tested specimens, but no resistance for the 26 novel A/H1N1 tested, or for any of 285 specimens to zanamivir (ECDPC 2009). Yet resistance was reported as 0.5% from other trials in the Roche database (Ward 2005). The risk of resistance is one reason to advise against routine use of neuraminidase inhibitors except in life-threatening situations.

Role of NIs in avian influenza

We identified no comparative evidence of the role of NIs in avian A/H5N1 influenza or for the current novel A/H1N1 pandemic. Oseltamivir was used against three subtypes of avian influenza viruses with proven bird-to-human and human-to-human transmission: A/H5N1, A/H7N7 and H7N3. The virological and transmission profile of avian H5N1 influenza is not clear. One review reports that experience from the cases of avian influenza transmitted to man in South East Asia suggests that viral shedding commences before symptoms appear and ceases after 48 hours from onset of symptoms (Yuen 2005). The WHO-led review of H5N1 influenza cases suggests that viral shedding and infectivity of index cases could be protracted (WHOWC 2005). What appears clear however, is that viral load can be up to 10 times greater than in seasonal influenza (WHOWC 2005). In the South East Asia outbreaks, use of oseltamivir was not associated with any obvious effect on mortality, although this could be due to late commencement of therapy and high initial viral load. Resistance to oseltamivir was detected in up 16% of children given the drug (WHOWC 2005), accordingly with evidence from Japan (Kiso 2004), a country with very high NI prescription rates, and in two out of eight Vietnamese people aged eight to 35 years (de Jong 2005).

The apparently common feature favouring the selection of resistant viruses is immunological naivety to the infecting viral subtype. A large outbreak of avian A/H7N7 influenza with bird-to-human and human-to-human transmission took place in chicken farms in the Netherlands between February and June 2003. Eighty-five of the 453 people who reported symptoms (mainly ILI and/or conjunctivitis) had A/H7N7 isolation from lacrimal fluid and/or upper airway swabs. Among other measures, PEP with oseltamivir 75 mg was started. Ninety people in the case registry probably had prophylactic treatment. Avian influenza virus infection was detected in one of 38 (2.6%) people who used oseltamivir, compared with five of 52 (9.6 %) who reported that they had not taken prophylactic medication. The difference was not significant (P value 0.38), probably because of small numbers and of the late nature of the commencement of PEP (Koopmans 2004). A similar outbreak of A/H7N3 took place in British Columbia, Canada in 2004. Twelve possible cases (22% of total) reported taking prophylactic oseltamivir at symptom onset, and 11 (20%) received oseltamivir for treatment. Maximum duration of oseltamivir assumption is thought to have been 12 weeks (Ward 2005). The remaining 22 patients with suspected cases were identified more than 48 hours after onset or refused treatment. All recovered fully (Tweed 2004). Evaluation of the effects of oseltamivir was outside a formal study and in all three cases data on the effectiveness of oseltamivir are insufficient to reach a conclusion. The use of NIs in avian influenza or in a possible pandemic is not supported by any credible data at present and we have doubts as to the generalisability of the evidence from seasonal influenza to avian influenza. Given the circumstances (ad hoc studies carried out during actual localised epidemics of avian influenza and the future characteristics of any pandemic) this is not surprising.

It should be remembered that at times the manufacturer makes no claims for oseltamivir to influence symptoms and complications: "Tamiflu has not been proven to have a positive impact on the potential consequences (such as hospitalisations, mortality, or economic impact) of seasonal, avian, or pandemic influenza"

(Doerler 2009). Since NIs do not prevent infection or stop nasal viral excretion, they may be a sub-optimal means of interrupting viral spread in a pandemic. If used to contain a severe pandemic outbreak, NIs should be part of a package of measures to interrupt spread, including physical measures (Jefferson 2009d), rather than used alone. Finally, the inability of NIs to prevent infection and to suppress viral nasal excretion raises doubts as to their effectiveness in interrupting viral spread in a pandemic, although NIs may have a role in addressing symptoms and complications. We conclude that in a pandemic, NIs should be used within a package of measures to interrupt spread, that is to say, together with barrier, distance and personal hygiene measures.

Possible rare harms associated with NIs

A key limitation of the post-marketing pharmaco-vigilance data we obtained from FDA is the likely under-representation of non-USA-generated reports. Manufacturers are not required to inform FDA of non-USA events that are not "both serious and unexpected" (FDA 2009a). This has important implications for evaluating the complete safety profile of oseltamivir, as 79% of global consumption has occurred outside of the USA (76% in Japan) (Toovey 2008). Of particular concern are neuropsychiatric adverse events (NPAEs) known to the manufacturer but not in the AERS database. The Roche Global Safety Database contains reports of 2466 NPAE patients between 1999 and 15 September 2007 of which they classified 562 (23%) as "serious" (Toovey 2008). However, the total AERS database (all types of adverse events) during this time period contains only 1805 reports.

Another important limitation of the AERS database is the FDA's practice of not registering into AERS non-electronically submitted reports of non-serious adverse events three years after a drug's initial approval (personal correspondence with FDA 14 October 2009). There is a possible association with NIs and the onset of rare harms. According to a review of phase IV evidence from eight cases (adolescents and adults) by Hama (Hama 2008), oseltamivir may induce sudden behavioural changes in recipients including hallucination and suicidal tendencies and sudden death while sleeping. This evidence comes hard on the heels of the review ordered by the Japanese government which is in part triggered by the 567 serious neuropathic cases received since the 2001 launch of the drug and May 2007 (Hama 2008). However it is estimated that > 36 million doses have been prescribed since 2001 (Toovey 2008), making such harms (even if confirmed) rare. These findings are similar to our review of the US AERS data (Jefferson 2009b). We therefore found under-reported evidence of varied quality which could not answer concerns about the toxicity of NIs, especially oseltamivir. Governments should set up studies to monitor the safety of oseltamivir (Jefferson 2009b).

In the course of conducting this review it was discovered that Chugai Pharmaceuticals Co., Ltd. a Japanese subsidiary drug manufacturer controlled by Hoffmann La Roche Ltd. had published adverse event data from randomised trials of oseltamivir on its web site. Data from prophylaxis trials comes from Hayden 1999a as well as two trials in the elderly (one unpublished). Notable adverse events are presented in Table 1 where there is strong evidence of increased incidence of nausea and vomiting due to oseltamivir as well as some evidence of an increased incidence of headache, pain in extremities, earache, major psychotic events, hyperglycaemia, and renal/urinary tract adverse events. Data from treatment trials comes from Nicholson 2000 and Treanor 2000, as well as from an unpublished study of otherwise healthy adults. These data, shown in Table 2, show strong evidence of increased incidence of nausea and vomiting due to oseltamivir.

Table 1. Adverse events in randomised controlled trials of oseltamivir for prophylaxis (75 mg o.d. group of WV15673/697, WV15708 and WV15825#)

Type of event (during on-treatment unless indicated as "+off") *a	Placebo (n = 973) n (%)	Oseltamivir 75mg o.d. (n = 986) n (%)	P-value (Fishers exact)
All AEs	1780	1933	
Patients with any AE	673 (69.2)	717 (72.7)	0.091
Nausea	50 (5.1)	92 (9.3)	< 0.001
Vomiting	9 (0.9)	27 (2.7)	0.004
Diarrhoea	38 (3.9)	49 (5.0)	0.27
All GI tract	155 (15.9)	214 (21.7)	0.001

Table 1. Adverse events in randomised controlled trials of oseltamivir for prophylaxis (75 mg o.d. group of WV15673/697, WV15708 and WV15825#) (*Continued*)

Headache	243 (25.0)	286 (29.0)	0.047
All neurological	270 (27.7)	314 (31.8)	0.048
Pain in extremities	5 (0.5)	16 (1.6)	0.026
Eearache	2 (0.2)	11 (1.1)	0.022
Aall ear and vestibular	8 (0.8)	22 (2.2)	0.015
Major psychotic *b	0 (0.0)	5 (0.5)	0.062
Major psychotic +off *c	1 (0.1)	8 (0.8)	0.039
+Major psychiatric *d	7 (0.7)	17 (1.7)	0.062
All psychiatric	13 (1.3)	24 (2.4)	0.096
All psychiatric +off	18 (1.8)	31 (3.1)	0.082
Mild psychiatric *e	6 (0.6)	9 (0.9)	0.61
Hyperglycaemia +off *f	0 (0.0)	8 (0.8)	0.008
Renal/urinary tract *g	3 (0.3)	15 (1.5)	0.007
Upper respiratory infection	51 (5.2)	57 (5.8)	0.62
Influenza	41 (4.2)	46 (4.7)	0.66
Influenza like illness	23 (2.4)	19 (1.9)	0.54
Fever (general system)	33 (3.4)	28 (2.8)	0.52
Viral infection	5 (0.5)	4 (0.4)	0.75
All infections	227 (23.3)	234 (23.7)	0.87

*a?"+off": including events during off-treatment period.
*b: major psychotic disorders?hallucination, Korsakov psychosis, schizophrenia, psychosis NOS, attempted suicide?
*c: one psychosis NOS in placebo group and hostility, hallucination aggravated and delusion in Tamiflu group were added.
*d?*a+b+major psychiatric events(depression, depression worsened, intrinsic depression, confusion, bipolar mood disorders).
*e?mild psychiatric events: all others that are not included in *a,*b,*c and *d? anxiety, alcoholism, sleep disorder, stress symptoms, restlessness are included.
*f? 4 hyperglycaemia and 3 diabetes aggravated during on-treatment, and one diabetes aggravated during off-treatment period.
*g? one nephrotic syndrome and one acute renal failure in Tamiflu group.

#Sources: Chugai Pharm Co 2004. New drug approval package (NAP) of oseltamivir (in Japanese); oseltamivir capsule for prevention (2004) (in Japanese): available at: http://www.info.pmda.go.jp/shinyaku/g040703/index.html?submit3=%C9%BD%BC%A8
Hama R. Re: Oseltamivir: psychotic and neurological adverse reactions in the randomized controlled trials Rapid response: http://www.bmj.com/cgi/eletters/339/dec07˙2/b5106#227187

Table 2. Comparison of adverse events in healthy adults (< 65 years) in oseltamivir treatment trials (WV15670,WV15671,WV15730)*

Type of event	Placebo (n = 466) n (%)	75mg b.i.d. (n = 479) n (%)	P-value (Fishers exact)
Vomiting	15 (3.2)	57 (11.9)	<0.001
Nausea	29 (6.2)	70 (14.6)	<0.001
Insomnia	3 (0.6)	7 (1.5)	0.34
Constipation	1 (0.2)	4 (0.8)	0.37
Back pain	2 (0.4)	4 (0.8)	0.69
Type of dizziness	2 (0.4)	4 (0.8)	0.69
Headache	11 (2.4)	13 (2.7)	0.84
Pharyngitis	5 (1.1)	6 (1.3)	1.0
Stomach ache	11 (2.4)	12 (2.5)	1.0
Fatigue	7 (1.5)	6 (1.3)	0.79
Herpes simplex	5 (1.1)	4 (0.8)	0.75
Fever	4 (0.9)	2 (0.4)	0.45
Cough	10 (2.1)	7 (1.5)	0.47
Dizziness	16 (3.4)	11 (2.3)	0.33
Nasal congestion	10 (2.1)	5 (1.0)	0.20
Diarrhoea	40 (8.6)	35 (7.3)	0.47

*Source: PMDA website document, Tamiflu 75 mg, Chugai document, p.294

Overall completeness and applicability of evidence

We have concerns about the difference between efficacy (treatment

response to influenza virus infection) and effectiveness (the real-life response to influenza-like illness, when real cases of influenza are indistinguishable from other causative agents not responsive to neuraminidase inhibitors) (Smith 2006). Understanding the proportion of influenza-like illness caused by both seasonal and epidemic influenza is critical to generalising the results of this review to clinical practice. The finding of treatment effectiveness for the neuraminidase inhibitors may be enhanced by the high percentage of influenza-like illness caused by influenza in some of the included trials -for example, up to 80% (Kashiwagi 2000b).

Quality of the evidence

Only five trials were judged adequate by usual Cochrane Collaboration methods (Higgins 2008b): one prophylaxis (Monto 1999a), and four treatment trials (Makela 2000; MIST 1998; Nicholson 2000; Treanor 2000). There was risk of bias in most trials, arising from poor descriptions of the methods (Aoki 2000; Boivin 2000; Kaiser 2000; Kaiser 2003; Hayden 1999a; Kashiwagi 2000a; Kashiwagi 2000b), such as no description of loss of follow up and blinding (Kaiser 2000). Attempts to address shortcomings were unsuccessful: although four out of five first authors of oseltamivir trials responded to our contact, none had original data and referred us to the manufacturer (Roche).

Data about the effectiveness against influenza complications confused us. After studying available FDA and EMEA regulatory product information documents, we asked the EMEA for the basis behind its decision to approve statements that oseltamivir reduces lower respiratory tract complications (EMEA 2009). Answers did not resolve this satisfactorily. We contacted the manufacturer (Roche), asking for the complete complications data, in particular the unpublished data used by Kaiser et al (Kaiser 2003) as indicated in the Hayashi Feedback comment. In response, the lead review author was sent a confidentiality agreement which included a clause forbidding ever mentioning the confidentiality agreement's very existence (WebExtra). We felt signing might compromise our aims. We persisted with Roche, who provided excerpts from company study reports apparently authored by people who did not appear in the published trials, and with insufficient detail to understand some data (for example, complication data from several trials were combined). This precluded us from addressing the Hayashi Feedback comment. It also meant we were obliged to now disregard a Roche-funded review of 10 trials containing a mixture of published and unpublished data (Kaiser 2003) that is being promoted by the manufacturer (Burns 2009) and cited in US influenza treatment recommendations (Burns 2009).

Potential biases in the review process

In our 2005 review (Jefferson 2006) we failed to resolve the questions posed by Hayashi, the numerous inconsistencies found during the review process (Doshi 2009) and to assess the harms profile of oseltamivir in a satisfactory manner. This in our view, may present an uncertain but perhaps optimistic view of the performance of oseltamivir.

Agreements and disagreements with other studies or reviews

Our review is now in disagreement with the conclusions of the Burch 2009, Tappenden 2009, and Turner 2003 reviews as our investigations could not answer the Hayashi comment and we were forced to exclude the Kaiser et al 2003 (Kaiser 2003) data on the effects of oseltamivir on complications

AUTHORS' CONCLUSIONS

Implications for practice

We do not recommend NIs for routine use in seasonal influenza except for life-threatening illness, and in circumstances where they used as an adjunct to other public health measures. We urge caution in the administration of NIs until some of the problems such as psychotropic effects and resistance have been clarified. Updating this Cochrane review has increased uncertainty about the safety of NIs, their capacity to interrupt viral transmission, or to affect complications rates.

Implications for research

To provide that, adequate trials should be carried out to test NIs against a viable alternative for symptoms and duration of illness (such as a non-steroidal anti-inflammatory drug, or a statin) (Frost 2007), and compare its performance against hand washing and masks to interrupt influenza transmission (Jefferson 2009d), and powered to detect potentially rare adverse events.

ACKNOWLEDGEMENTS

Thanks to Dr Aoki for helpful comments. We thank Prof Jon Deeks for co-authoring the original and first update of this review (Jefferson 1999; Jefferson 2000). We thank Vittorio Demicheli and Daniela Rivetti for their work on previously published versions of this Cochrane review (Jefferson 1999; Jefferson 2006; Jefferson 2009b) and Carlo Di Pietrantonj for his work on previously published versions of this Cochrane review (Jefferson 2006; Jefferson 2009c).

The authors wish to thank the following for commenting on the 2008 update: Janet Wale, John Bartlett, Sree Nair and Tom Fahey.

We wish to thank the following for commenting on the 2009 update: Janet Wale, Sree Nair and Tom Fahey.

We thank Alessandro Rivetti for running the searches on this 2009 update for effectiveness studies, and Liz Dooley for assisting with applying the inclusion criteria and editing the text.

We gratefully acknowledge funding for the 2009 update by the UK National Institute for Health Research (NIHR) and the National Health and Research Council (NHMRC) of Australia.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aoki 2000

Methods	Multicentre, randomised, double-blind parallel group study, performed in 14 countries in Europe and North America during the 1995 - 1996 winter.
Participants	One thousand two hundred and fifty six patients were included in study, of which 722 had laboratory confirmed influenza. The report only includes data for the 722 influenza cases. Participants were healthy individuals over 13 years old with acute influenza like illness (ILI) lasting less than 48 hours. The patients had to be able to use the inhaler and nasal devices. Patients with unstable chronic illness (for example, hospitalised) or were pregnant or breast feeding were excluded. Randomisation was carried out with an allocation schedule of 2:2:1:1 respectively
Interventions	Treatment lasted for five days
Outcomes	Serological: Serum samples were collected on days 1 and 21, and assayed for the presence of anti-influenza antibodies by haemagglutination inhibition Effectiveness: ILI (feverishness and at least two of the following symptoms: headache, myalgia, cough, or sore throat). Productivity Health status Sleep quality Healthcare utilisation Treatment satisfaction Social functioning Physical functioning Role functioning Body pain Current health perception Psychological distress The clinical efficacy of zanamivir and was reported is the Monto 1999c trial Safety outcomes are not reported
Notes	The authors conclude that zanamivir treatment reduced absenteeism, improved patient productivity and well being, and reduced the additional use of healthcare resources in patients with influenza. It is very difficult to understand the basis for this conclusion when Table II shows equal proportion of influenza cases throughout the arms. The use of aggregate measures such as lest-squares mean scores for health status indicators and presentation in histogram form makes interpretation very difficult

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Boivin 2000

Methods	Double-blind, randomised, placebo controlled, multi centre sub-study, part of the MIST study, assessing the relationship between alleviation of all clinical important symptoms (as defined by no fever and other flu symptoms recorded as absent or mild for at least 24 hours) and reduction of viral load. The study was conducted during the 1997-1998 season in Québec and Winnipeg, Canada
Participants	Thirty-five patients were enrolled. 27 (77%) had an influenza virus infection laboratory-confirmed on day 1. All subjects had influenza A virus H3 infections. 10 received a placebo, 17 received zanamivir. Three influenza virus positive high-risk subjects were enrolled (2 in the placebo, 1 in zanamivir group). Healthy adolescents and adults, older than 12 years, and high risk subjects (defined as those with chronic respiratory, cardiovascular, or renal disease) with naturally occurring influenza A virus infections
Interventions	Inhaled zanamivir 10 mg 2 x daily for 5 days
Outcomes	Laboratory: serial swabs viral resistance insurgence analysis viral load Effectiveness: fever time to alleviation of symptoms Safety: no safety outcomes are mentioned
Notes	The authors conclude that: 1) zanamivir produced a rapid antiviral effect following inhalation, and this was noted as early as 12 hours after beginning treatment, 2) the decrease in virus load induced by zanamivir correlated with a significant reduction in the median time to alleviation of symptoms. 3) neither phenotypic nor genotypic assays detected any evidence of emergence of zanamivir-resistant strains during therapy. This is a sub-study of the pivotal treatment trial MIST. The claim of the relation between decreased viral load and alleviation of symptoms does not appear to be substantiated in the text of the report. All outcomes reported are non-clinical

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hayden 1997

Methods	Two multi centre trials in North America (38 centres, 220 individuals) and Europe (32 centres, 197 individuals) conducted during the 1994-1995 influenza season. Both trials assessed the treatment effects of zanamivir using a randomised, double-blind, placebo controlled design.
Participants	Otherwise healthy individuals with symptoms suggestive of influenza persisting longer than 48 hours. Mean ages of subjects in the three arms were 31 to 33 years
Interventions	Participants were randomised to receive either 10 mg of inhaled zanamivir by mouth plus 6.4 mg by intranasal spray or 10 mg of inhaled zanamivir and intranasal placebo spray or aqueous placebo by both

Hayden 1997 (*Continued*)

	routes twice daily for five days. During convalescence HAI titres were assessed and 262 individuals had laboratory confirmed influenza. Of these, 56% were due to A/H3N2 and 44% to B virus
Outcomes	Overall nine placebo patients and ten from each of the other arms withdrew or were lost to follow up (explained in the text as failure to at tend for the follow up visits). The major outcome assessed in the trial was "time to alleviation of major symptoms" (defined as absence of fever and headache, muscle ache, sore throat and cough). Additionally, time to resumption of usual activities are also reported
Notes	Individuals who commenced treatment 30 hours or less from the onset of illness fared significantly better than those who commenced later. Both interventions significantly shortened duration of illness compared to placebo (5.3 and 5.4 days compared to 6.3 days). Inhaled and intranasal zanamivir significantly shortened non-effective time compared to placebo. Importantly, no effect was seen on non-influenza infected patients (although the data are not presented in the text). Adverse effects are presented in the text as overall and broken down by generalised (respiratory tract and gastrointestinal) and local (perinasal). The authors conclude that zanamivir is safe and effective treatment against influenza A and B if given early in the illness. Although clearly randomised, no details of allocation or double blinding are given. The intention to treat analysis has clearly taken place

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hayden 1999a

Methods	Multicentre randomised double-blind placebo-controlled preventive phase III trials of oseltamivir. Follow up was 8 weeks. Medication continued for 6 weeks after recognition of the outbreak in the study area. Randomisation and allocation were carried by using a computer-generated sequence. Due to the low incidence of influenza (2.4% or 38/1559) the data from the two studies were combined. The study was conducted during the winter of 1997-1998 in Virginia, Texas and Kansas with circulating A/Sydney/5/97 H3N2 strain
Participants	One-thousand five-hundred and fifty-nine healthy unvaccinated adults aged 18 to 65. There were 33 withdrawals from the treatment arms and 21 from the placebo arm
Interventions	Oral oseltamivir 75 mg daily (n = 520), or twice daily (n = 520) or placebo (n = 519) for six weeks. Acetaminophen could also be taken by protocol agreement
Outcomes	Serological/Laboratory: viral isolation and paired sera for antibody titres were taken Effectiveness: influenza (presence of ILI symptoms and culture within two days of symptom onset and/or antibody rise) asymptomatic influenza (antibody rise in the absence of symptoms) ILI: oral temp of 37.2 degrees C or more with at least one respiratory (cough, sore throat, coryza) or one constitutional symptom (aches, fatigue, headache, chills, sweats) Safety: study withdrawals:

Hayden 1999a (*Continued*)

	withdrawals due to Aminotransferase concentration increase withdrawals due to gastrointestinal events headache nausea vomiting
Notes	The authors conclude that protection of 76 per cent is satisfactory given the low level of influenza activity. The study is reasonably reported but procedures for double blinding are not described and effectiveness outcomes are very confusingly named and described

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hayden 2000a

Methods	Multicentre, double-blind, randomised, placebo-controlled PEP trial that took place during the 1998 to 1999 winter in the USA
Participants	Two hundred and twenty one index cases aged 18 to 20 and 837 family contacts aged around 25 to 26 years in 337 families (168 assigned to placebo and 169 to zanamivir)
Interventions	Index cases received either inhaled zanamivir 10 mgs daily or placebo for five days. Family contacts received either zanamivir 10 mgs daily or placebo for ten days
Outcomes	Serological: serum assays, PCR and culture (with resistance assay) Effectiveness: ILI Efficacy: Influenza and duration of symptoms Safety: not better defined but authors report a profile similar to placebo
Notes	The authors conclude that zanamivir was 79% (57% to 89%) effective and 72% (42% to 87%) effective in preventing contacts from developing symptomatic influenza and 53% (27% to 70%) effective and 48% (15% to 68%) efficacious in symptomatic and asymptomatic influenza. Zanamivir shortened duration of symptoms by 2.5 days. There was no evidence of the onset of resistance. Allocation concealment is not described

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Hayden 2004

Methods	(WV 16163) Multicentre, open-cluster randomised trial conducted in Europe and North America during the 2000-2001 influenza season. The aims of the study were to assess the effects of post-exposure prophylaxis (PEP) with oseltamivir compared with standard treatment (oseltamivir if symptoms occurred in contacts) and the possible onset of resistance. Eligible households had a maximum of 3 and a minimum of 8 members, including at least 1 index case and at least 2 eligible contacts aged 1 year or more. Children aged younger than 1 year were excluded. Randomization was stratified by the presence or absence of an infant (aged younger than 1 year) in the household and by the presence or absence of a second index case (IC) in the household. ICs and contacts recorded symptoms twice daily on diary cards for 30 days
Participants	Eight-hundred and twelve healthy and non-pregnant household contacts of 298 index cases presenting with an influenza-like illness (temperature 37.8C or more plus cough and/or coryza) during a documented community influenza outbreak were randomised by household (n = 277). There were 20 contact exclusions, 11 because of lack of information and 9 due to lack of laboratory infected status data
Interventions	PEP with oseltamivir for 10 days or treatment at the time of developing illness (expectant treatment) during the postexposure period beginning within 48 h of the reported onset of symptoms in the index case. All index cases received oseltamivir treatment twice daily for 5 days. Contacts in the expectant treatment arm were also given a standard 5-day treatment course if illness developed (adults and adolescents older than 12 years received 75 mg oseltamivir capsules twice daily, whereas children aged 1 to 2, 3 to 5, and 6 to 12 years received 30, 45, and 60 mg oseltamivir suspension, respectively, twice daily). A second course of treatment could be provided in the event that the subject developed an ILI after the completion of the first course of oseltamivir
Outcomes	Serological: throat and nose swabs and paired serum samples for determining influenza strain-specific hemagglutination-inhibition (HAI) antibody titers Effectiveness: percentage of households with at least 1 secondary case of influenza during the 10-day period after the start of treatment in the ICs (primary efficacy outcome) Percentage of households with at least 1 secondary case of ILI during the 10-day period after the start of treatment in the ICs Both outcomes were also calculated for individual contacts and for children aged 1 to 12 years. Duration of illness (time to alleviation of symptoms for treated ICs and for ill contacts: the first 24 h period in which the severity of all influenza symptoms were remained as mild or none) Efficacy analyses were carried out for: intention-to-treat index-infected (ITTII) population defined as those households and contacts of laboratory-confirmed, influenza-infected ICs. Subpopulation of contacts who were virus-negative at baseline (ITTIINAB) Overall intention-to-treat (ITT) population (all randomised households and contacts, regardless of infection status in the IC). Safety: withdrawals nausea vomiting The data for children aged 1 to 12 were not extracted

Hayden 2004 (*Continued*)

Notes	The authors conclude that oseltamivir is safe and effective in interrupting household transmission. A very confusing report with unclear alternative interventions and outcomes which had to be pieced together from fragments of text. Randomisation details are lacking together with cluster co-efficient data

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Kaiser 2000

Methods	Multicentre, double-blind, placebo-controlled randomised controlled trial. The trial assessed the prophylactic activity of zanamivir after presumed exposure to influenza in the community. The study was conducted from November 1995 to March 1996 in Europe and North America when A/H3N2 was the predominant strain
Participants	Five hundred and seventy five asymptomatic subjects aged 13 to 65 years (mean age 34 to 35 years) who had been in close contact with index cases of influenza like illness of no longer than 4 days duration (ILI was defined as temp of 37.8C or more or feverishness with at least two of the following: headache, myalgia, cough and/or sore throat). No withdrawals are mentioned
Interventions	Participants were randomised to four treatment groups: 1) 2 intranasal sprays of zanamivir (16 mg/mL) per nostril (0.1 mL per spray) plus 2 placebo inhalations 2) 2 zanamivir inhalations (5mg per inhalation) plus 2 placebo sprays per nostril 3) inhaled and intranasal zanamivir 4) 2 placebo inhalations and 2 placebo sprays per nostril All were self administered for 5 days
Outcomes	Serological/laboratory: serum samples (days 1 and 21) and viral upper airways samples were taken Effectiveness: six point scale of influenza like symptoms ILI, including: - headache sore throat feverishness, muscle aches, cough, nasal congestion, weakness loss of appetite Observations were recorded twice daily for 10 days Safety: no detailed outcome data are reported
Notes	The authors conclude that short term treatment with intranasal zanamivir was ineffective. However, inhaled zanamivir treatment reduced the rate of influenza, which was 2% to 3% among zanamivir recipients versus 6% among placebo recipients. The results in the text are reported in a very confusing fashion. It is likely that "influenza at 21 days" and "Symptomatic or asymptomatic influenza 21 days after initiation" are the same outcome reported twice differently in the text and table 2. Because of the possibility of error, data on asymptomatic influenza have not been extracted

Kaiser 2000 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kashiwagi 2000a

Methods	Double-blind placebo-controlled randomised controlled trial of the preventive effects of oseltamivir against influenza A and B. The study was carried out in 33 centres in Japan. Both H3N2 and H1N1 were co-circulating at a low level the time with H3N2 accounting for 10 of the 13 cases in the placebo arm of the trial. Follow up and administration of the drug was for 42 days, with a further post-administration of 57 days' duration
Participants	Three hundred and eight healthy subjects aged 16 to 89 (mean 34 years), predominantly non-smokers. There were three withdrawals in the intervention arm (one each for adverse events, protocol violation and voluntary withdrawal)
Interventions	Oral oseltamivir (Roche) 75 mg or placebo daily for six weeks
Outcomes	Serological: viral antibody titres Effectiveness: Group 1: participants with fever of 37.5 degrees C or more and at least two other influenza symptoms with laboratory confirmed influenza Group 2: participants without fever of 37.5 degrees C or more or at least two other influenza symptoms with laboratory confirmed influenza Group 3: participants with no symptoms or signs with laboratory confirmed influenza Group 4: participants with symptoms without laboratory confirmed influenza Safety: diarrhoea, abdominal pain upper, nausea, abdominal pain, vomiting, abdo. distension, stomatitis, loose stools, retching, sore throat, faecal abnormality, gingivitis, constipation, oral discomfort, tooth loss, tooth ache, gingival oedema, dyspepsia, food poisoning, oesophagitis, glossitis, enterocolitis, headache, sneezing, dizziness, somnolence, insomnia, paraesthesia, cough, rhinorrhea, epistaxis, allergic rhinitis, nasal passage irritation, nasal congestion, tonsillitis. Other adverse events are grouped by infectious, local, musculoskeletal, reproductive, metabolic, cutaneous, injury and poisoning, eye, vascular, ENT, renal. An extensive list of laboratory and diagnostic tests is reported
Notes	The authors conclude that oseltamivir is safe and effective in the prevention of influenza. Despite not being able to consult the text, the tables and abstract report sufficient information. The study appears well designed and well reported

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kashiwagi 2000b

Methods	Double-blind placebo-controlled randomised trial of the treatment effects of oseltamivir against influenza A and B. The study was carried out in 79 centres in Japan. Both H3N2 and H1N1 were co-circulating at the time with H3N2 accounting for nearly 60% of infections in both arms of the trial. Follow up and administration of the drug was for 5 days, with a further post-administration of 21 days' duration
Participants	Three hundred and sixteen subjects were enrolled, 162 in the placebo arm and 154 in the active arm (including one in the placebo arm was given the study drug by mistake). There were 3 withdrawals from the active arm (one each for overdosing not turning up for follow up and voluntary withdrawal) and 11 from the placebo arm (4 for adverse events, 4 for voluntary withdrawal, 1 was given the study drug by mistake, 1 "other" and 1 for not turning up for follow up) so 151 in each arm completed the trial. Participants were aged 16 to 89 (mean age 35.5 in the active arm and 33.6 in the placebo arm). Five were inpatients. One hundred and twenty two participants were infected with influenza and 130 in the placebo arm. These represented the ITTI population
Interventions	Oral oseltamivir (Roche) 75 mg or placebo twice daily for five days. In the ITTI population, administration took place within 36 hours of onset of symptoms for all but 8 in the active arm and 5 in the placebo arm
Outcomes	Serological: viral antibody titres Effectiveness: time to resolution of illness (ITTI) time to resolution of symptoms (ITTI) cases of influenza (ITTI) influenza viral titre severity (symptom scores) Safety: diarrhoea, abdominal pain upper, nausea, abdominal pain, vomiting, abdo. distension, stomatitis, loose stools, retching, sore throat, faecal abnormality, gingivitis, constipation, dry mouth, oral pain, tooth ache, gingival oedema, dyspepsia, tongue coated, oesophagitis, glossitis, enterocolitis, headache, sneezing, dizziness, somnolence, insomnia, paraesthesia, cough, rhinorrhea, dizziness, grand mal convulsion, epistaxis, allergic rhinitis, nasal passage irritation, nasal congestion, tonsillitis. Other adv events are grouped by infectious, local, musculoskeletal, reproductive, metabolic, cutaneous, injury and poisoning, eye, cardiac, ENT, renal. An extensive list of laboratory and diagnostic tests is reported
Notes	The authors concluded that oseltamivir is safe and effective in reducing length of illness. Lack of translation of parts of the text make assessment of quality difficult. The imbalance in denominators is not explained

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Li 2003

Methods	Double-blind randomised placebo-controlled trial to assess the efficacy of oseltamivir in the treatment of naturally occurring influenza. Background rates of infections are not described, nor strains isolated from participants are described
Participants	Four hundred and seventy eight healthy adults aged 18 to 65 with symptoms consistent with influenza (fever of 37. 8 degrees C or more, plus at least two others: coryza/nasal congestion, sore throat, cough, myalgia/muscles aches and pain, fatigue, headache or chills/sweats). People with influenza vaccination less than 12 months before the study were excluded. Sixteen participants were lost to follow up or refused to continue the trial, 3 were excluded prior to taking medication because they did not meet the entry criteria, and 8 were excluded because of protocol violation. Four hundred and fifty one individuals were analyzed for efficacy as the ITT population (216 oseltamivir and 235 placebo) with 273 individuals were identified as influenza infected through laboratory test and were regarded as the ITTI population (134 oseltamivir and 139 placebo). For the safety analysis, 459 individuals were included (137 oseltamivir group with influenza, 84 oseltamivir group without influenza, 141 placebo group with influenza, and 97 placebo group without influenza)
Interventions	Oral oseltamivir phosphate or placebo (Roche) 75 mg bid for 5 days
Outcomes	Serological: culture or serological tests were used to confirm influenza cases (symptoms and a positive culture on day 1 and/or = 4 fold increase in HAI antibody between baseline and day 21 of the study). Viral cultures were performed on all participants: 224 positive and 254 negative. Of 224 individuals with positive culture, serum HAI antibodies on days 1 and 21 were completed in 160 individuals (133 positive, 27 negative). Of 254 with negative cultures, HAI antibodies were completed in 146 individuals (58 positive, 88 negative) . Effectiveness: the primary outcome was time to resolution of symptoms (from the onset of symptoms to the time that all symptoms were resolved). A symptom severity scale was used (0 = no problem, 1 = minor, 2 = moderate, 3 = severe). Symptoms scores are reported as median areas under the curve of decreased total score and cumulative alleviation proportion by arm as survival curve Logrank test Safety: nausea, upset upper abdomen, vomiting, vertigo, insomnia, and rash were reported with an increased frequency in the active arm but the difference was not significant. Numerators are not reported. Follow up took place at days 3, 6, 8 and 21 (vital signs and laboratory examinations included blood routine, urine routine, liver and renal function)
Notes	The authors conclude that oseltamivir is well tolerated and efficacious in relieving symptoms within 36 of onset of influenza and could be used routinely on all symptomatic subjects during an outbreak. A very badly reported trial, with impenetrable outcome reporting

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Makela 2000

Methods	Randomised double-blind, placebo-controlled trial to assess the effectiveness of zanamivir in the treatment of subjects presenting with influenza symptoms during a period of influenza activity. The trial took place in 11 European countries during the winter of 1997-1998. The predominant strain was A/H3N2. Follow up was up to 28 days
Participants	Three hundred and fifty six patients aged 12 or more. Patients presenting with acute febrile influenza-like illness. Patients were required to have a fever (37.8C or more for patients aged less than 65, 37.2C or more for patients aged 65 or more, with at least two of the following symptoms: headache, myalgia, cough and sore throat. They had to start therapy within 2 days of symptom onset. Women who were pregnant or at risk of pregnancy were excluded
Interventions	Within two days of onset of typical influenza symptoms and received orally inhaled zanamivir 10 mg via diskhaler twice daily for five days or matching placebo
Outcomes	Serological: influenza was confirmed by diagnosis of virus culture, virus isolation, seroconversion, or by virus detection PCR. Influenza A subtyping was performed by serology and PCR Effectiveness: time until alleviation of clinically significant symptoms of influenza time to alleviation and no use of relief medication, time to return to normal activities influenza high risk influenza positive Safety: bronchitis sinusitis diarrhoea pharyngitis nausea and vomiting pneumonia
Notes	The authors conclude that zanamivir is effective in reducing the duration and severity of influenza illness and is well tolerated. No age breakdown is given and the whole text gives the idea of careful editing to enhance effect of zanamivir. Reporting of clinical outcomes is in the format of Area Under the Curve (AUC)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Matsumoto 1999

Methods	Double-blind, randomised, placebo-controlled trial of the treatment efficacy of inhaled and intranasal zanamivir for five days. Follow up was up to 28 days. ITT analysis was carried out. The study was carried out in 28 centres in Japan during January to March 1995. The dominant strain was A/H3N2

Matsumoto 1999 (*Continued*)

Participants	One hundred and sixteen healthy subjects aged 16 to 65 recruited in 28 centres randomised to three arms. Participants with a set list of symptoms who presented themselves to their family doctor within 36 hours of onset were enrolled. Two participants dropped out from arm 1 and 2 from arm 3 because of lack of improvement
Interventions	Zanamivir (Nippon Glaxo) dry powder (5 mg/inhalation) or matching placebo or aqueous intranasal spray (1.6 mg/spray) or matching placebo were administered. Participants received either two inhalations (10mgs) plus intranasal placebo, or 10 mg inhaled zanamivir plus two spray per nostril (6.4 mg) or double placebo for five days. As initial analysis failed to detect any difference between arm 1 and arm 2, the data from the two arms was compared with placebo
Outcomes	Serological: serology and virological samples were taken and influenza viruses identified with PCR. Effectiveness: participants were instructed in the use of diaries to record symptoms. - Time to alleviation of: fever, headache and myalgia, cough and sore throat (used in the text as corporate indicator of lower fever, headache and myalgia). - Time to resumption of normal activities Safety: possible adverse events hoarse voice, headache, diarrhoea
Notes	The authors conclude that participants in the active arms recovered faster by one day compared to placebo recipients (3 days instead of four). Continuous outcomes are summarised in the text either median and interquartile ranges (time to alleviation) or as Kaplan-Meyer plots (time to resumption of normal activities). Average reporting quality but randomisation and double blinding are not described

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

MIST 1998

Methods	Multi-centre randomised placebo-controlled trial of the treatment and safety effects of zanamivir in healthy adults with ILI and influenza. Randomisation and allocation were centralised. Concealment was by means of sealed envelopes on site. Follow up was 28 days and symptoms were self-recorded with diaries. The study was conducted in 1997 in Australia, New Zealand and South Africa, with A/H3N2 being the dominant viral strain
Participants	Four hundred and fifty five healthy and non-pregnant persons aged 12 or more (mean 37 years) with influenza symptoms of no more than 36 h (temp of higher than 37.8 degrees C or feverishness or both and at least two of the following myalgia, sore throat, cough, headache). There were 76 participants

MIST 1998 (*Continued*)

	(57 with respiratory diseases,15 aged 65 or more, 11 with a metabolic disease, 8 hypertensives and 2 immunocompromised) There were 58 withdrawals: 31 for adverse events (27 in the zanamivir arm and 4 on placebo), withdrawn consent (5 and 3), loss to follow up (7 and 10) and 2 because of protocols violation (1 and 1)
Interventions	Inhaled zanamivir 10 mg bd or placebo for five days. An antipyretic and antitussive were also dispensed with a request not be used routinely
Outcomes	Serological/Laboratory: viral cultures and paired antibody titre estimations Effectiveness: symptoms (duration and severity): feverishness, cough, headache, sore throat, myalgia, nasal congestion, weakness and anorexia were rated on a 4-point scale (0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe) temp sleep disturbance ability to perform normal activity complications antibiotic use Safety: adverse events bronchitis cough sinusitis LRTC diarrhoea nausea and vomiting
Notes	The authors conclude that zanamivir was effective and well-tolerated. A well reported study although safety outcome definitions are not given and it is difficult to see how adv events such as bronchitis could be distinguished from influenza disease. The format of reporting of outcomes ay lead to considerable loss of data

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Monto 1999a

Methods	Double-blind randomised, placebo-controlled trial assessing the effects of zanamivir, administered once daily, in the prevention of influenza infection and disease. Follow up was for 35 days. Randomisation was stratified in blocks of 10 for each site and participant were assigned sequentially to pre-randomised packaged drug or placebo. The study was conducted during the 1997-1998 influenza season in two Midwest university communities, United States (Universities of Michigan and Missouri). A/Sydney/5/97 H3N2 was the dominant strain
Participants	One thousand one hundred and seven healthy adults, mean age 29, range 18 to 69 years, mainly students or community volunteers. 1107 included in the ITT analysis. Eleven discontinued the trial for adverse events, 16 for consent withdrawal or loss to follow up. Follow up was for up to 28 days with a final visit at day 35
Interventions	Zanamivir 10 mg or placebo for six days or more up to 28 days, administered by self-activating inhalation once daily using a Diskhaler device
Outcomes	Serological/Laboratory: serum samples and paired sera for antibody titres Effectiveness: influenza if had 2 of the following recorded successively in at least 3 diary entries: cough, headache, sore throat, myalgia, feverishness or temp of at least 37.8 C with a rise in antibody titres and/or viral isolation febrile influenza if temp of at least 37.8 degrees C with a rise in antibody titres and/or viral isolation febrile illness if only temp of at least 37.8 degrees C Safety is not mentioned in detail, only as any adverse event
Notes	The authors conclude that zanamivir administered once daily is efficacious and well tolerated in the prevention of influenza for a 4-week period in healthy adults. A reasonably reported study

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Monto 1999b

Methods	Double-blind randomised placebo-controlled multi-centre parallel group study. Follow up was for 21 days. The study was conducted in November to March 1996 in North America and Europe. The dominant strains were A/H3N2 and A/H1N1
Participants	One thousand two hundred and fifty six healthy patients, aged 13 years or more (mean around 35 to 36 years) who had symptoms of influenza up to 48 h duration were enrolled. See below for definition of symptoms. There were seventy four withdrawals, these were for adverse events, lost to follow up and other reasons. Seven hundred and twenty two (57%) participants were found to have influenza. There were 158 participants described as high risk (n = 69 with asthma; n = 31 with cardiovascular disease; n = 18 had metabolic conditions; n = 39 were aged 65 or more
Interventions	Zanamivir 10 mg 2 x daily by oral inhalation plus 6.4 mg 2 x daily nasal spray versus zanamivir 10 mg 4 x daily by oral inhalation plus 6.4 mg 4 x daily by nasal spray versus placebo by both routes 2 x daily versus placebo by both routes 4 x daily. Placebo groups were combined for analysis. Medication was self

Monto 1999b (*Continued*)

	administered and patients were instructed to take the inhaled medication before the intranasal medication. All patients were provided with acetaminophen tablets and dextromethorphan cough suppressant but were instructed to avoid using these medications unless their symptoms became sufficient to warrant them
Outcomes	Serological: serum assays at days 1 and 21 and viral isolation from airways Effectiveness: oral temp severity of symptoms: rated on six point scale in which '0' corresponded to no symptoms and '5' corresponded to severe symptoms sleep disturbances level of ability to perform normal activities health questionnaire time to alleviation of clinically significant symptoms, defines as the absence of feverishness, a temperature less than 37.8C and a score of 0 (none) or 1 (mild) for other major symptoms (i.e., headache, myalgia, sore throat and cough) for at least 24 hrs or more time to return to normal activities use of acetaminophen and cough mixture to relieve symptoms Safety Diarrhoea Nausea and vomiting Nasal signs and symptoms Headaches Bronchitis Withdrawal due to possible adverse events
Notes	The authors conclude that zanamivir can significantly reduce the duration and overall symptomatic effect of influenza. A summarily reported trial with selective and heterogeneous reporting of outcomes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Monto 2002

Methods	Double-blind randomised placebo controlled PEP trial
Participants	Four hundred and eighty seven households with 1291 contacts aged 5 or more (mean age around 19 years)
Interventions	Inhaled zanamivir 10 mgs once daily for ten days. Index patients with ILI received symptomatic medication only
Outcomes	Serological: serum assays, PCR and culture (with resistance assay) Effectiveness: ILI Efficacy: Influenza Safety: not better defined but authors report a profile similar to placebo (no cases of bronchospasm are

Monto 2002 (*Continued*)

	reported in the intervention arm, but two are reported in the placebo arm)
Notes	The authors conclude that zanamivir is effective in prophylaxis and interrupting transmission (79% effectiveness and 81% efficacy - 64% to 90% - for households and 82% for individuals and was well tolerated. Zanamivir shortened duration of illness by 1.5 days. No viral resistance was reported. A reasonably reported trial

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Nicholson 2000

Methods	(WV 15670). Randomised double-blind placebo-controlled preventive phase IIIa trials of Ro 64-0796. WV 15670 was conducted in Europe, Canada and China during the 1997-1998 winter. 473 otherwise healthy individuals who presented with at least on respiratory and one constitutional symptom were randomised within 36 hours of onset. AH3N2 was the dominant strain
Participants	Seven hundred and twenty six healthy (apart from ILI symptoms) participants aged 18 to 65 were enrolled. Four hundred and seventy five participants had influenza (161, 158, 156 respectively). There were seven withdrawals for lack of compliance and 15 because of adverse events and 23 protocol violations
Interventions	Either oseltamivir 75 mg daily orally (n = 155), or twice daily (n = 157), or "matching" placebo (n = 161) for five days
Outcomes	Serological: culture and serological specimens were used to diagnose influenza infection. Effectiveness: the main outcome was the time to alleviation of symptoms expressed in days and type and incidence of adverse events. Additionally severity of illness was also assessed by means of a symptom score and antibiotic use was recorded in each arm. influenza was defined as viral isolation and/or antibody titre (at 3/52 interval) increase. The laboratory assessment was done in a blinded fashion Safety: nausea vomiting (reported as mean frequencies by arm). all outcomes were assessed twice daily for 21 days
Notes	The authors conclude that the time to alleviation of symptoms was significantly reduced in the active arms. Equally there was a 30% reduction in the symptoms scores of the active arms of both trials. As in the prophylaxis/prevention trials of oseltamivir, nausea was the most reported systemic adverse event, especially at the higher dose. The methodological quality of the study is reasonable. Randomisation by centralised computer and robust allocation concealment procedures are explicitly mentioned in the text

Nicholson 2000 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Puhakka 2003

Methods	Multi-centre double-blind randomised placebo-controlled trial of treatment effects of zanamivir in Finnish armed forces conscripts Randomisation was computerised in blocks of 6. Only investigator-prescribed paracetamol was allowed. The study was conducted (2000-2001) over two influenza seasons with A/H3N2 and A/H1N1 respectively as dominant strains
Participants	Five hundred and eighty eight conscripts aged around 19 and mainly males, presenting with symptoms of ILI of less than 48 h duration with a temp of 38C or more and at least 2 of the following: headache, muscle/joint aches sore throat or cough during periods of influenza viral circulation. Surveillance was carried out throughout the influenza season. Diary cards were kept by participants for 28 days
Interventions	Inhaled zanamivir 5 mg per inhalation or placebo (lactose powder) bid for 5 days
Outcomes	Laboratory: real-time PCR, nasal and throat swabs (at 0, 8, 24 and 48h) and antibody titres (days 1 and 28) were collected Effectiveness: time to alleviation of symptoms (temp less than 37.8C and feverishness score as "none" and other symptoms recorded as 0 or 1 for 24 h) time to alleviation of symptoms with no use of relief medication (temp less than 37.8C and feverishness score as "none" and other symptoms recorded as 0 or 1 for 24 h in patients who have not taken relief medication) viral load use of relief medication severity of symptoms (overall symptoms, headache, cough, feverishness, sore throat, anorexia, muscle/joint aches and pains, weakness; on a scale: 0 = no symptoms; 1 = mild; 2 = moderate; 3 = severe) Complications: use of antibiotics for complications use of diagnostic procedures general well being was assessed using the - measure yourself medical outcomes - MYMOP questionnaire Safety: ILI symptoms that got worse bronchitis COPD or asthma that got worse Acceptability: ease of use of diskhaler device (data not extracted)

Puhakka 2003 (*Continued*)

Notes	The authors conclude that zanamivir significantly reduces viral load, however startling improvements in symptoms could not be observed because of the characteristics of this very healthy population. In the discussion the authors observe the short and benign duration of the illness (median 2.33 d in the placebo arm). A reasonably reported study with no mention of blinding procedures. Data are not reported for a number of outcomes (for example, general well-being, use of relief medication, etc) for which data were apparently collected

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Treanor 2000

Methods	(WV 15671) Multicentre double-blind placebo-controlled randomised trial of the efficacy of oseltamivir in cases of influenza of 36 hours' duration or more. Randomisation and allocation were centralised through an automated phone programme. Although the aim of the study is to test the efficacy of the drug, data for both efficacy influenza) and effectiveness (ILI) are reported. The study was conducted between January and March 1998 in the USA. A/H3N2 was the dominant viral strain
Participants	Six hundred and twenty nine unvaccinated previously healthy adults aged 18 to 65 presenting within 36 h of symptom onset (oral temp 38 degrees C or more and at least one of the following: cough, sore throat, nasal symptoms and headache, malaise, myalgia, sweats/chills, fatigue). There were 46 withdrawals (16, 19 and 11 respectively) Follow up was 21 days, with twice daily observations recorded on diaries
Interventions	Oral oseltamivir 75 mg or 150 bd or placebo for 5 days
Outcomes	Serological/laboratory: viral culture for airway swabs and antibody titres at days 1 and 21 Effectiveness: symptom severity (graded on a 4 point scale) ability to perform usual activities and health status (11-point visual analogue scales) oral temp number and type of complications Safety: nausea vomiting withdrawals due to adverse effects
Notes	The authors conclude that oseltamivir reduces duration of illness and may reduce complications. Convoluted reporting and extensive use of medians may lead to loss of important data

Risk of bias

Item	Authors' judgement	Description

Treanor 2000 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Welliver 2001

Methods	Multicentre double-blind placebo-controlled cluster randomised controlled trial (C-RCT) of the effects of oseltamivir in the interruption of transmission of influenza in families. The study was conducted in the winter of 1989-1999 in North America and Europe (76 centres)
Participants	Three hundred and seventy four households (962 healthy contacts with a mean age of 33, minimum 2 members and maximum 8 members per household) of 377 index cases (ICs) presenting within 48h of onset of cough and coryza. Children aged up to 12 were enrolled only if other contacts in the household met the enrolment criteria. A household represented a cluster (all members were randomised to the same treatment). There were 4 withdrawals due to contact not taking study medication and 7 withdrawals due to adverse events (5 in the active and 2 in the placebo arm)
Interventions	Oseltamivir 75 mg die or placebo within 48 h of symptom onset for 7 days and 500 mg of acetaminophen if needed. ICs were not treated
Outcomes	Serological: nasal swabs and paired antibody titres Effectiveness: proportion of contacts of IC with influenza within days 1 to 7 of the intervention ILI (oral temp of 37.2 degrees C or more and at least cough, nasal congestion or sore throat and headache, fatigue, chills or myalgia within 24 h) influenza (ILI plus laboratory confirmation) Safety: GI adverse events nausea withdrawals due to adverse events
Notes	The authors conclude that oseltamivir was well tolerated and prevented spread of influenza. Poor reporting of randomisation, cluster correlation calculations and allocation procedures

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

h: hour
ENT: ear, nose and throat
bd: twice daily
bid: twice daily
d: day
ILI: influenza-like illness
ITTI: intention-to-treat index

ITTII: intention-to-treat index-infected
IC: index cases
ITTIINAB: intention-to-treat index-infected virus-negative at baseline

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ambrozaitis 2005	Prevention of transmission placebo-controlled RCT in elderly in long term care facilities
Aoki 2003	No control arm (Roche study code WV 76006)
Barroso 2005	Viral challenge study on new NI peramivir
Bettis 2006	Data from 1997-1999 registration studies already in review
Bijl 2007	No data presented
Blumentals 2007	Contains retrospective, observational data
Calfee 1999	Experimental influenza only
Cass 1999	No denominator breakdown by arm
Fuyuno 2007	News piece
Hama 2008	Review of Phase IV data
Hayden 1999b	Experimental influenza only
Hayden 2000b	Experimental influenza only
Ison 2003	Population of persons with underlying medical conditions
Kaiser 2003	Unable to determine the number of healthy adults experiencing complications in each study nor the number of patients experiencing one of more of "bronchitis, lower respiratory tract infection, or pneumonia" presenting to each study
Kawai 2005	Prospectve cohort study non comparative with all oseltamivir exposure
Kawai 2006	Non comparative cohort study
Kawai 2007a	Porospective cohort study all treated with zanamivir
Kawai 2007b	Retrospective cohort
Kawai 2007c	Non comparative study with sole exposure to oseltamivir

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Kawai 2008	Prospective cohort study with oseltamivir versus nothing
LaForce 2007	Placebo controlled RCT in elderly
Li 2001	Same data set as Li 2003
Li 2004	Redundants publication of Li 2003
Lin 2006	Very small RCT high risk oseltamivir versus do-nothing
Macfarlane 2005	Editorial
Massarella 2000	Phase 2a study with no safety outcomes reported
Monto 1999c	Meta-analysis. No original data presented
Murphy 2000	At risk participants
Peng 2000	Dose-ranging study
Sato 2005	Children admitted to hospital with A/B diagnosis subsequently randomised to oseltamivir, zanamivir, or do-nothing
Sato 2008	Prospective cohort study in children
Toovey 2008	Review. Contains retrospective, observational data

DATA AND ANALYSES

Comparison 1. NI versus placebo for prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza-like illness	4	3549	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.59, 1.44]
1.1 Oral oseltamivir 75 mg daily	2	1088	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.45, 3.66]
1.2 Oral oseltamivir 150 mg daily	1	779	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.25, 3.95]
1.3 Inhaled zanamivir 10 mg daily	2	1299	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.49, 1.19]
1.4 Intranasal zanamivir 0.32 mg daily	1	189	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.21, 2.95]
1.5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily	1	194	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.58]
2 Influenza (symptomatic)	4	3549	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.23, 0.48]
2.1 Oral oseltamivir 75 mg daily	2	1087	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.12, 0.48]
2.2 Oral oseltamivir 150 mg daily	1	780	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.67]
2.3 Inhaled zanamivir 10 mg daily	2	1299	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.18, 0.59]
2.4 Intranasal zanamivir 0.32 mg daily	1	189	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.25, 2.37]
2.5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily	1	194	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.17, 2.53]
3 Influenza (symptomatic and asymptomatic)	4	3549	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.49, 0.76]
3.1 Oral oseltamivir 75 mg daily	2	1087	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.31, 0.68]
3.2 Oral oseltamivir 150 mg daily	1	780	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.29, 0.80]
3.3 Inhaled zanamivir 10 mg daily	2	1299	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.91]
3.4 Intranasal zanamivir 0.32 mg daily	1	189	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.54, 2.08]
3.5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily	1	194	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.38, 1.56]
4 Influenza (asymptomatic)	3	2974	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.62, 1.12]
4.1 Oral oseltamivir 75 mg daily	2	1087	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.43, 1.26]
4.2 Oral oseltamivir 150 mg daily	1	780	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.35, 1.28]
4.3 Inhaled zanamivir 10 mg daily	1	1107	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.65, 1.47]
5 Adverse events - nausea	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

5.1 Oral oseltamivir 75 mg daily	2	1088	Odds Ratio (M-H, Random, 95% CI)	1.79 [1.10, 2.93]
5.2 Oral oseltamivir 150 mg daily	1	779	Odds Ratio (M-H, Random, 95% CI)	2.29 [1.34, 3.92]
6 Adverse events - vomiting	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Oral oseltamivir 75 mg daily	2	1088	Odds Ratio (M-H, Random, 95% CI)	2.28 [0.87, 5.95]
6.2 Oral oseltamivir 150 mg daily	1	780	Odds Ratio (M-H, Random, 95% CI)	3.57 [0.81, 15.82]
7 Adverse events - diarrhoea	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Oral oseltamivir 75 mg daily	1	308	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.28, 1.20]
8 Adverse events - abdominal pain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Oral oseltamivir 75 mg daily	1	308	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.49, 1.97]
9 Adverse events - others	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Oral oseltamivir 75 mg daily	1	308	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.59, 1.55]
10 Adverse events - withdrawals due to gastrointestinal events	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Oral oseltamivir 75 mg daily	1	779	Odds Ratio (M-H, Random, 95% CI)	3.51 [0.18, 68.21]
10.2 Oral oseltamivir 150 mg daily	1	780	Odds Ratio (M-H, Random, 95% CI)	3.52 [0.18, 68.47]

Comparison 2. NI versus placebo for treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to alleviation of symptoms (ITT)	9	4985	Hazard ratio (Random, 95% CI)	1.22 [1.14, 1.31]
1.1 Zanamivir	6	3188	Hazard ratio (Random, 95% CI)	1.24 [1.13, 1.36]
1.2 Oseltamivir	3	1797	Hazard ratio (Random, 95% CI)	1.20 [1.06, 1.35]
2 Time to alleviation of symptoms (influenza cases only)	11	3491	Hazard ratio (Random, 95% CI)	1.32 [1.26, 1.38]
2.1 Zanamivir	7	2117	Hazard ratio (Random, 95% CI)	1.33 [1.29, 1.37]
2.2 Oseltamivir	4	1374	Hazard ratio (Random, 95% CI)	1.30 [1.13, 1.50]
3 Time to return to normal activity (ITT)	4	2454	Hazard ratio (Random, 95% CI)	1.26 [1.14, 1.40]
3.1 Zanamivir	3	1827	Hazard ratio (Random, 95% CI)	1.28 [1.13, 1.45]
3.2 Oseltamivir	1	627	Hazard ratio (Random, 95% CI)	1.23 [1.02, 1.48]
4 Time to return to normal activity (influenza cases only)	4	1234	Hazard ratio (Random, 95% CI)	1.22 [1.07, 1.39]
4.1 Zanamivir	3	860	Hazard ratio (Random, 95% CI)	1.17 [1.00, 1.37]
4.2 Oseltamivir	1	374	Hazard ratio (Random, 95% CI)	1.34 [1.07, 1.67]
5 Complications - all types (ILI cases only)	1	79	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.19]
5.1 Zanamivir	1	79	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.19]

6 Complications - all types (influenza cases only)	4	1122	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.00]
6.1 Zanamivir	1	277	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.50, 1.06]
6.2 Oseltamivir	3	845	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.23, 1.37]
7 Complications - all types (ITT)	1	356	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.49, 0.96]
7.1 Zanamivir	1	356	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.49, 0.96]
8 Adverse events - cough	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Zanamivir	2	1043	Odds Ratio (M-H, Random, 95% CI)	1.40 [0.14, 13.49]
8.2 Oral oseltamivir 150 mg daily	1	273	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.53, 3.22]
9 Adverse events - headache	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Zanamivir	2	1352	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.39, 1.97]
9.2 Oral oseltamivir 150 mg daily	2	586	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.44, 1.87]
10 Adverse events - diarrhoea	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Zanamivir	4	2415	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.63]
10.2 Oral oseltamivir 150 mg daily	1	313	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.28, 1.13]
11 Adverse events - nasal symptoms (congestion, rhinitis, dry or sore throat)	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Zanamivir	3	2299	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.47, 2.06]
11.2 Oral oseltamivir 150 mg daily	1	273	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.51, 1.44]
12 Adverse events - nausea	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Zanamivir	3	2067	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.10]
12.2 Oral oseltamivir 150 to 300 mg daily	2	928	Odds Ratio (M-H, Random, 95% CI)	2.50 [1.49, 4.20]
13 Adverse events - vomiting (Oseltamivir)	2	928	Odds Ratio (M-H, Random, 95% CI)	2.60 [0.77, 8.80]
14 Adverse events - bronchitis or pneumonia	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Zanamivir	3	2299	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.24, 2.26]
15 Adverse events - all types	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Zanamivir	3	1159	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.14]
15.2 Oral oseltamivir 150 mg daily	1	313	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.05]
16 Use of relief medications and antibiotics	4	1830	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.60, 1.11]
16.1 Zanamivir	2	838	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.41, 1.01]
16.2 Oseltamivir	2	992	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.67, 1.52]
17 Mean nasal viral titres (at 24 hours since randomisation)	4	1002	Mean Difference (IV, Random, 95% CI)	-0.62 [-0.82, -0.41]
17.1 Zanamivir 10 to 20 mg daily	2	441	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.75, -0.06]
17.2 Oseltamivir 75 to 150 mg daily	2	561	Mean Difference (IV, Random, 95% CI)	-0.73 [-0.99, -0.47]
18 Mean nasal viral titres (at 48 hours since randomisation)	3	659	Mean Difference (IV, Random, 95% CI)	-0.63 [-1.13, -0.13]
18.1 Zanamivir 10 to 20 mg daily	2	441	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.58, 0.16]

18.2 Oseltamivir 150 mg daily	1	218	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.74, -0.14]

Analysis 1.1. Comparison 1 NI versus placebo for prophylaxis, Outcome 1 Influenza-like illness.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 1 Influenza-like illness

Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Oral oseltamivir 75 mg daily					
Hayden 1999a	5/520	4/260		9.4 %	0.63 [0.17, 2.31]
Kashiwagi 2000a	29/155	15/153		27.0 %	1.91 [1.07, 3.42]
Subtotal (95% CI)	**675**	**413**		**36.4 %**	**1.28 [0.45, 3.66]**
Total events: 34 (NI), 19 (Placebo)					
Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 2.34$, df = 1 (P = 0.13); $I^2 = 57\%$					
Test for overall effect: Z = 0.46 (P = 0.64)					
2 Oral oseltamivir 150 mg daily					
Hayden 1999a	6/520	3/259		8.6 %	1.00 [0.25, 3.95]
Subtotal (95% CI)	**520**	**259**		**8.6 %**	**1.00 [0.25, 3.95]**
Total events: 6 (NI), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 1.0)					
3 Inhaled zanamivir 10 mg daily					
Kaiser 2000	4/144	2/48		6.2 %	0.67 [0.13, 3.53]
Monto 1999a	30/553	39/554		32.6 %	0.77 [0.49, 1.22]
Subtotal (95% CI)	**697**	**602**		**38.8 %**	**0.76 [0.49, 1.19]**
Total events: 34 (NI), 41 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.87); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.19 (P = 0.23)					
4 Intranasal zanamivir 0.32 mg daily					
Kaiser 2000	7/141	3/48		9.3 %	0.79 [0.21, 2.95]
Subtotal (95% CI)	**141**	**48**		**9.3 %**	**0.79 [0.21, 2.95]**
Total events: 7 (NI), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.34 (P = 0.73)					
5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily					
Kaiser 2000	3/146	3/48		6.9 %	0.33 [0.07, 1.58]
Subtotal (95% CI)	**146**	**48**		**6.9 %**	**0.33 [0.07, 1.58]**
Total events: 3 (NI), 3 (Placebo)					

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Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 1.39 (P = 0.16)					
Total (95% CI)	**2179**	**1370**		**100.0 %**	**0.92 [0.59, 1.44]**
Total events: 84 (NI), 69 (Placebo)					
Heterogeneity: Tau^2 = 0.10; Chi^2 = 8.70, df = 6 (P = 0.19); I^2 =31%					
Test for overall effect: Z = 0.35 (P = 0.73)					

Analysis 1.2. Comparison 1 NI versus placebo for prophylaxis, Outcome 2 Influenza (symptomatic).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 2 Influenza (symptomatic)

Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Oral oseltamivir 75 mg daily					
Hayden 1999a	6/520	12/259		14.2 %	0.25 [0.09, 0.66]
Kashiwagi 2000a	5/155	21/153		14.8 %	0.24 [0.09, 0.61]
Subtotal (95% CI)	**675**	**412**		**29.0 %**	**0.24 [0.12, 0.48]**
Total events: 11 (NI), 33 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 4.10 (P = 0.000041)					
2 Oral oseltamivir 150 mg daily					
Hayden 1999a	7/520	13/260		16.2 %	0.27 [0.11, 0.67]
Subtotal (95% CI)	**520**	**260**		**16.2 %**	**0.27 [0.11, 0.67]**
Total events: 7 (NI), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.84 (P = 0.0046)					
3 Inhaled zanamivir 10 mg daily					
Kaiser 2000	4/144	4/48		7.3 %	0.33 [0.09, 1.28]
Monto 1999a	11/553	34/554		29.7 %	0.32 [0.17, 0.63]
Subtotal (95% CI)	**697**	**602**		**37.1 %**	**0.33 [0.18, 0.59]**

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Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 15 (NI), 38 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.66 (P = 0.00025)					
4 Intranasal zanamivir 0.32 mg daily					
Kaiser 2000	9/141	4/48		10.4 %	0.77 [0.25, 2.37]
Subtotal (95% CI)	**141**	**48**		**10.4 %**	**0.77 [0.25, 2.37]**
Total events: 9 (NI), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.64)					
5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily					
Kaiser 2000	6/146	3/48		7.3 %	0.66 [0.17, 2.53]
Subtotal (95% CI)	**146**	**48**		**7.3 %**	**0.66 [0.17, 2.53]**
Total events: 6 (NI), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
Total (95% CI)	**2179**	**1370**		**100.0 %**	**0.33 [0.23, 0.48]**
Total events: 48 (NI), 91 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.16$, df = 6 (P = 0.66); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.90 (P < 0.00001)					

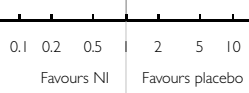
Analysis 1.3. Comparison 1 NI versus placebo for prophylaxis, Outcome 3 Influenza (symptomatic and asymptomatic).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 3 Influenza (symptomatic and asymptomatic)

Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Oral oseltamivir 75 mg daily					
Hayden 1999a	28/520	27/259		16.0 %	0.52 [0.31, 0.86]
Kashiwagi 2000a	11/155	29/153		10.1 %	0.37 [0.19, 0.72]
Subtotal (95% CI)	**675**	**412**		**26.1 %**	**0.46 [0.31, 0.68]**
Total events: 39 (NI), 56 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.81 (P = 0.00014)					
2 Oral oseltamivir 150 mg daily					
Hayden 1999a	27/520	28/260		16.0 %	0.48 [0.29, 0.80]
Subtotal (95% CI)	**520**	**260**		**16.0 %**	**0.48 [0.29, 0.80]**
Total events: 27 (NI), 28 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.82 (P = 0.0048)					
3 Inhaled zanamivir 10 mg daily					
Kaiser 2000	16/144	9/48		8.0 %	0.59 [0.28, 1.25]
Monto 1999a	53/553	77/554		31.6 %	0.69 [0.50, 0.96]
Subtotal (95% CI)	**697**	**602**		**39.6 %**	**0.67 [0.50, 0.91]**
Total events: 69 (NI), 86 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.58 (P = 0.010)					
4 Intranasal zanamivir 0.32 mg daily					
Kaiser 2000	28/141	9/48		9.6 %	1.06 [0.54, 2.08]
Subtotal (95% CI)	**141**	**48**		**9.6 %**	**1.06 [0.54, 2.08]**
Total events: 28 (NI), 9 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.17 (P = 0.87)					
5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily					
Kaiser 2000	21/146	9/48		8.8 %	0.77 [0.38, 1.56]
Subtotal (95% CI)	**146**	**48**		**8.8 %**	**0.77 [0.38, 1.56]**
Total events: 21 (NI), 9 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.46)					



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Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**2179**	**1370**		**100.0 %**	**0.61 [0.49, 0.76]**
Total events: 184 (NI), 188 (Placebo)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.87$, df = 6 (P = 0.33); $I^2 = 13\%$					
Test for overall effect: Z = 4.46 (P < 0.00001)					

Analysis 1.4. Comparison 1 NI versus placebo for prophylaxis, Outcome 4 Influenza (asymptomatic).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 4 Influenza (asymptomatic)

Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Oral oseltamivir 75 mg daily					
Hayden 1999a	22/520	15/259		20.9 %	0.73 [0.39, 1.38]
Kashiwagi 2000a	6/155	8/153		8.0 %	0.74 [0.26, 2.08]
Subtotal (95% CI)	**675**	**412**		**28.9 %**	**0.73 [0.43, 1.26]**
Total events: 28 (NI), 23 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.12 (P = 0.26)					
2 Oral oseltamivir 150 mg daily					
Hayden 1999a	20/520	15/260		20.0 %	0.67 [0.35, 1.28]
Subtotal (95% CI)	**520**	**260**		**20.0 %**	**0.67 [0.35, 1.28]**
Total events: 20 (NI), 15 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					
3 Inhaled zanamivir 10 mg daily					
Monto 1999a	42/553	43/554		51.1 %	0.98 [0.65, 1.47]
Subtotal (95% CI)	**553**	**554**		**51.1 %**	**0.98 [0.65, 1.47]**
Total events: 42 (NI), 43 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					

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Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**1748**	**1226**		**100.0 %**	**0.83 [0.62, 1.12]**
Total events: 90 (NI), 81 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.26$, df = 3 (P = 0.74); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.22 (P = 0.22)					

Analysis 1.5. Comparison 1 NI versus placebo for prophylaxis, Outcome 5 Adverse events - nausea.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 5 Adverse events - nausea

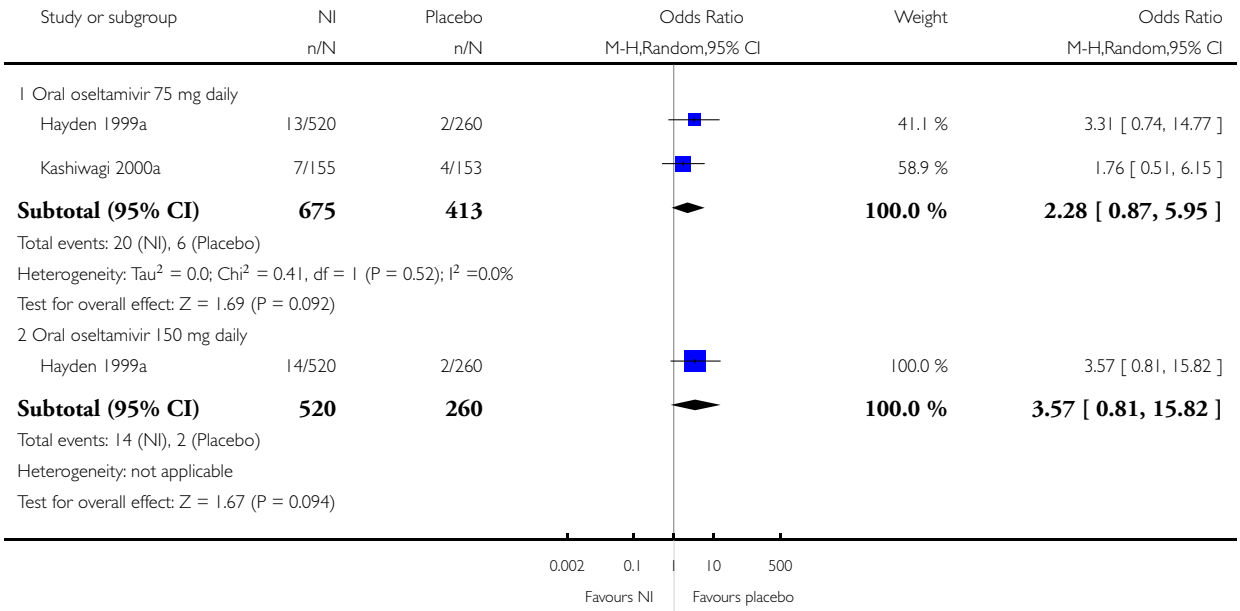
Study or subgroup	NI n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Oral oseltamivir 75 mg daily					
Hayden 1999a	63/520	19/260		83.8 %	1.75 [1.02, 2.99]
Kashiwagi 2000a	8/155	4/153		16.2 %	2.03 [0.60, 6.88]
Subtotal (95% CI)	**675**	**413**		**100.0 %**	**1.79 [1.10, 2.93]**
Total events: 71 (NI), 23 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.33 (P = 0.020)					
2 Oral oseltamivir 150 mg daily					
Hayden 1999a	76/520	18/259		100.0 %	2.29 [1.34, 3.92]
Subtotal (95% CI)	**520**	**259**		**100.0 %**	**2.29 [1.34, 3.92]**
Total events: 76 (NI), 18 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.03 (P = 0.0025)					

Analysis 1.6. Comparison 1 NI versus placebo for prophylaxis, Outcome 6 Adverse events - vomiting.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 6 Adverse events - vomiting

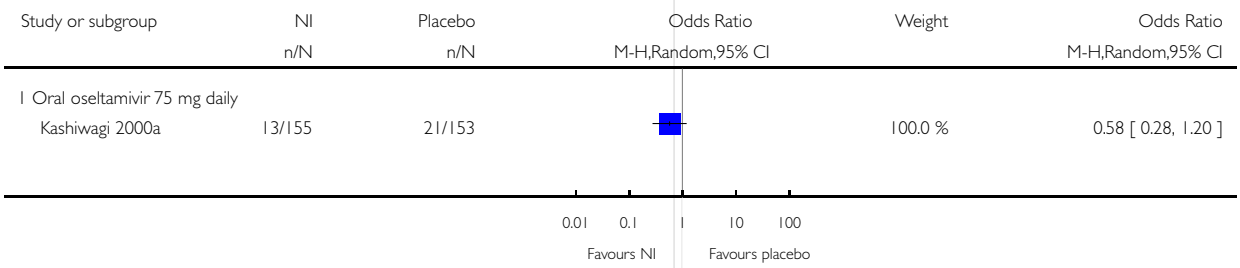


Analysis 1.7. Comparison 1 NI versus placebo for prophylaxis, Outcome 7 Adverse events - diarrhoea.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 7 Adverse events - diarrhoea

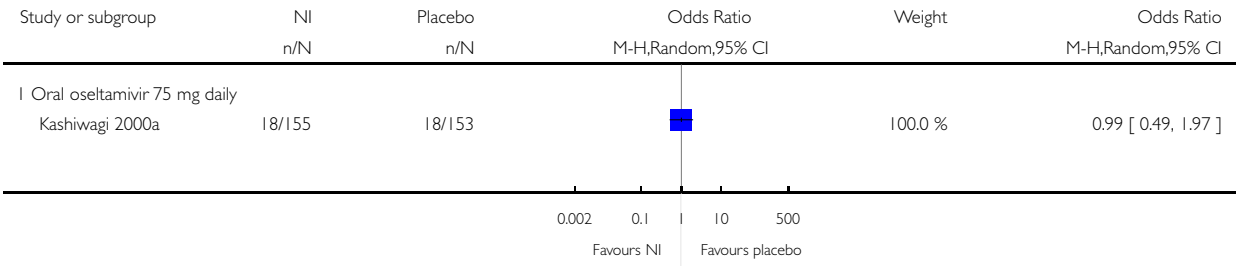


Analysis 1.8. Comparison 1 NI versus placebo for prophylaxis, Outcome 8 Adverse events - abdominal pain.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 8 Adverse events - abdominal pain

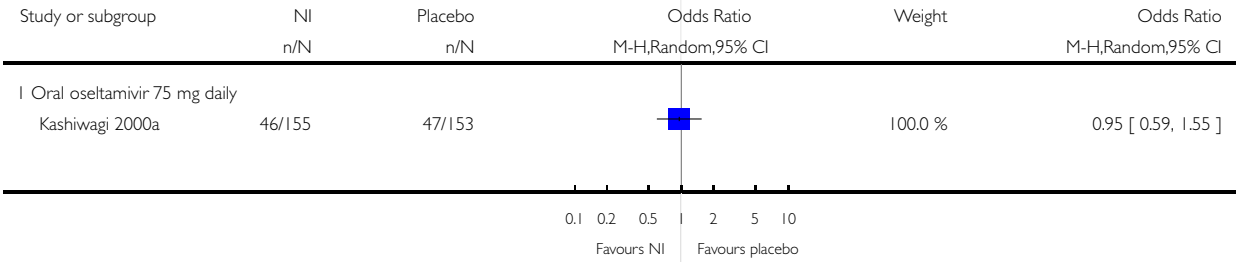


Analysis 1.9. Comparison 1 NI versus placebo for prophylaxis, Outcome 9 Adverse events - others.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 9 Adverse events - others

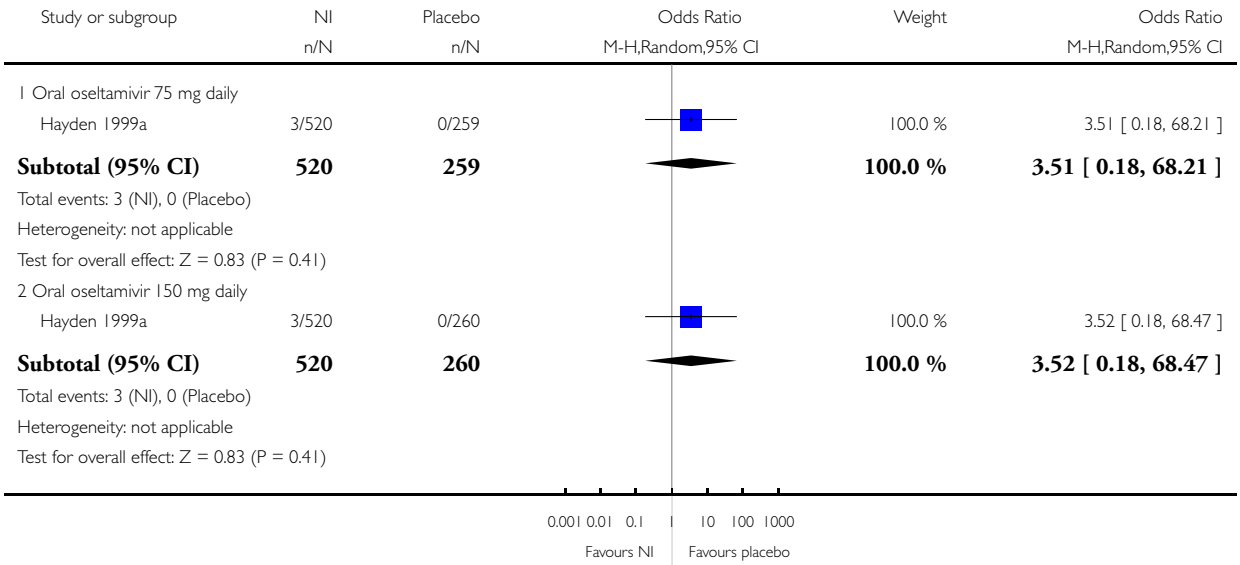


Analysis 1.10. Comparison 1 NI versus placebo for prophylaxis, Outcome 10 Adverse events - withdrawals due to gastrointestinal events.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 1 NI versus placebo for prophylaxis

Outcome: 10 Adverse events - withdrawals due to gastrointestinal events



Analysis 2.1. Comparison 2 NI versus placebo for treatment, Outcome 1 Time to alleviation of symptoms (ITT).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 1 Time to alleviation of symptoms (ITT)

Study or subgroup	NI N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio IV,Random,95% CI	Weight	Hazard ratio IV,Random,95% CI
1 Zanamivir						
Hayden 1997	273	144	0.105 (0.1183)		8.9 %	1.11 [0.88, 1.40]
Makela 2000	174	182	0.405 (0.1183)		8.9 %	1.50 [1.19, 1.89]
Matsumoto 1999	77	39	0.288 (0.2449)		2.1 %	1.33 [0.83, 2.16]
MIST 1998	227	228	0.262 (0.1048)		11.4 %	1.30 [1.06, 1.60]
Monto 1999b	834	422	0.154 (0.0744)		22.5 %	1.17 [1.01, 1.35]
Puhakka 2003	293	295	0.207 (0.8366)		0.2 %	1.23 [0.24, 6.34]
Subtotal (95% CI)					**54.0 %**	**1.24 [1.13, 1.36]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.41$, df = 5 (P = 0.49); $I^2 = 0.0\%$						
Test for overall effect: Z = 4.48 (P < 0.00001)						
2 Oseltamivir						
Li 2003	216	235	0.049 (0.0969)		13.3 %	1.05 [0.87, 1.27]
Nicholson 2000	484	235	0.216 (0.0854)		17.1 %	1.24 [1.05, 1.47]
Treanor 2000	418	209	0.253 (0.0894)		15.6 %	1.29 [1.08, 1.53]
Subtotal (95% CI)					**46.0 %**	**1.20 [1.06, 1.35]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.67$, df = 2 (P = 0.26); $I^2 = 25\%$						
Test for overall effect: Z = 2.96 (P = 0.0031)						
Total (95% CI)					**100.0 %**	**1.22 [1.14, 1.31]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.32$, df = 8 (P = 0.50); $I^2 = 0.0\%$						
Test for overall effect: Z = 5.64 (P < 0.00001)						

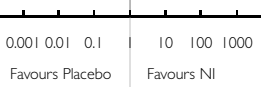
Analysis 2.2. Comparison 2 NI versus placebo for treatment, Outcome 2 Time to alleviation of symptoms (influenza cases only).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 2 Time to alleviation of symptoms (influenza cases only)

Study or subgroup	NI N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio IV,Random,95% CI	Weight	Hazard ratio IV,Random,95% CI
1 Zanamivir						
Boivin 2000	17	10	0.642 (0.3987)		0.4 %	1.90 [0.87, 4.15]
Hayden 1997	173	89	0.223 (0.1483)		2.6 %	1.25 [0.93, 1.67]
Makela 2000	136	141	0.47 (0.1378)		3.0 %	1.60 [1.22, 2.10]
Matsumoto 1999	44	29	0 (0.2863)		0.7 %	1.00 [0.57, 1.75]
MIST 1998	161	160	0.288 (0.016)		64.6 %	1.33 [1.29, 1.38]
Monto 1999b	481	241	0.241 (0.1)		5.6 %	1.27 [1.05, 1.55]
Puhakka 2003	222	213	0.153 (0.0959)		6.0 %	1.17 [0.97, 1.41]
Subtotal (95% CI)					**83.0 %**	**1.33 [1.29, 1.37]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.89$, df = 6 (P = 0.44); $I^2 = 0.0\%$						
Test for overall effect: Z = 18.52 (P < 0.00001)						
2 Oseltamivir						
Kashiwagi 2000a	122	130	0.287 (0.1264)		3.6 %	1.33 [1.04, 1.71]
Li 2003	134	139	0.036 (0.124)		3.7 %	1.04 [0.81, 1.32]
Nicholson 2000	314	161	0.32 (0.1048)		5.1 %	1.38 [1.12, 1.69]
Treanor 2000	245	129	0.379 (0.1095)		4.7 %	1.46 [1.18, 1.81]
Subtotal (95% CI)					**17.0 %**	**1.30 [1.13, 1.50]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.80$, df = 3 (P = 0.19); $I^2 = 37\%$						
Test for overall effect: Z = 3.61 (P = 0.00031)						
Total (95% CI)					**100.0 %**	**1.32 [1.26, 1.38]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.77$, df = 10 (P = 0.38); $I^2 = 7\%$						
Test for overall effect: Z = 11.37 (P < 0.00001)						



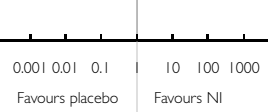
Analysis 2.3. Comparison 2 NI versus placebo for treatment, Outcome 3 Time to return to normal activity (ITT).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 3 Time to return to normal activity (ITT)

Study or subgroup	NI N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio IV,Random,95% CI	Weight	Hazard ratio IV,Random,95% CI
1 Zanamivir						
Matsumoto 1999	77	39	0.405 (0.2664)		4.0 %	1.50 [0.89, 2.53]
MIST 1998	227	228	0.251 (0.1378)		15.0 %	1.29 [0.98, 1.68]
Monto 1999b	834	422	0.234 (0.0761)		49.2 %	1.26 [1.09, 1.47]
Subtotal (95% CI)					**68.3 %**	**1.28 [1.13, 1.45]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.38$, df = 2 (P = 0.83); $I^2 = 0.0\%$						
Test for overall effect: Z = 3.83 (P = 0.00013)						
2 Oseltamivir						
Treanor 2000	418	209	0.204 (0.0948)		31.7 %	1.23 [1.02, 1.48]
Subtotal (95% CI)					**31.7 %**	**1.23 [1.02, 1.48]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.15 (P = 0.031)						
Total (95% CI)					**100.0 %**	**1.26 [1.14, 1.40]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.53$, df = 3 (P = 0.91); $I^2 = 0.0\%$						
Test for overall effect: Z = 4.38 (P = 0.000012)						



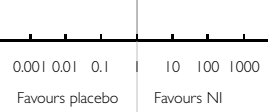
Analysis 2.4. Comparison 2 NI versus placebo for treatment, Outcome 4 Time to return to normal activity (influenza cases only).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 4 Time to return to normal activity (influenza cases only)

Study or subgroup	NI N	Placebo N	log [Hazard ratio] (SE)	Hazard ratio IV,Random,95% CI	Weight	Hazard ratio IV,Random,95% CI
1 Zanamivir						
Hayden 1997	173	89	0 (0.1483)		20.0 %	1.00 [0.75, 1.34]
Makela 2000	136	141	0.194 (0.1378)		23.1 %	1.21 [0.93, 1.59]
MIST 1998	161	160	0.251 (0.1378)		23.1 %	1.29 [0.98, 1.68]
Subtotal (95% CI)					**66.2 %**	**1.17 [1.00, 1.37]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.66$, df = 2 (P = 0.44); $I^2 = 0.0\%$						
Test for overall effect: Z = 1.91 (P = 0.056)						
2 Oseltamivir						
Treanor 2000	245	129	0.289 (0.114)		33.8 %	1.34 [1.07, 1.67]
Subtotal (95% CI)					**33.8 %**	**1.34 [1.07, 1.67]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.54 (P = 0.011)						
Total (95% CI)					**100.0 %**	**1.22 [1.07, 1.39]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.57$, df = 3 (P = 0.46); $I^2 = 0.0\%$						
Test for overall effect: Z = 3.03 (P = 0.0025)						

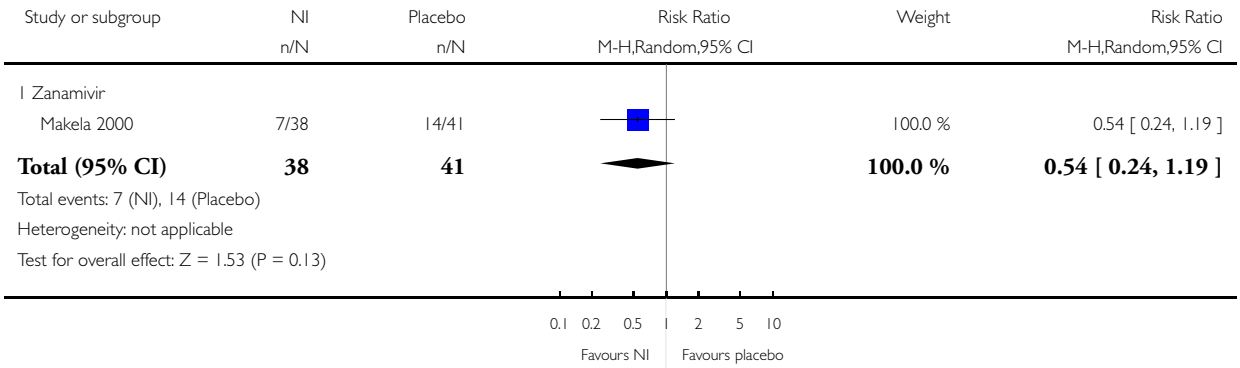


Analysis 2.5. Comparison 2 NI versus placebo for treatment, Outcome 5 Complications - all types (ILI cases only).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 5 Complications - all types (ILI cases only)

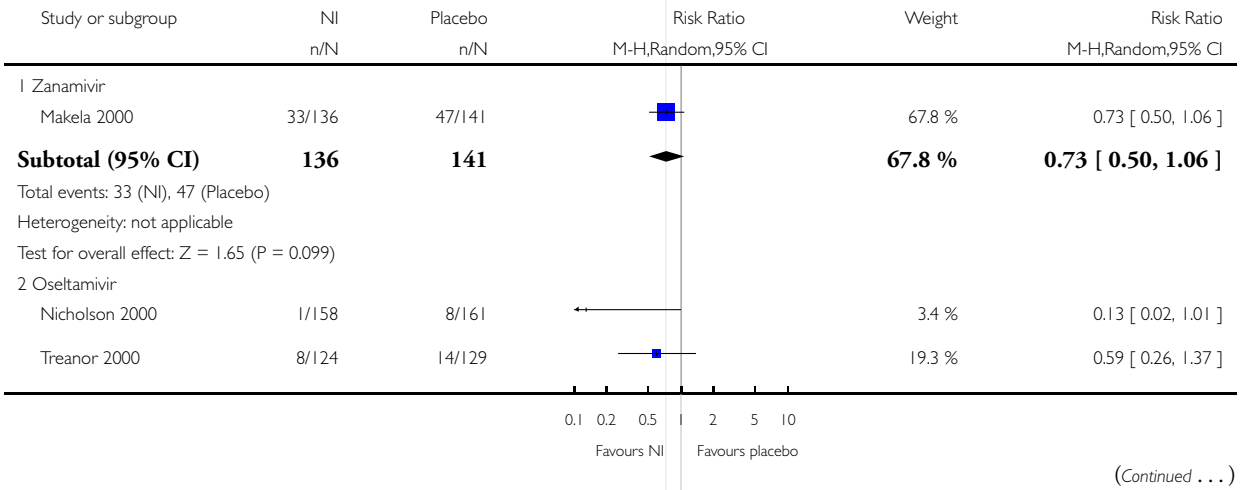


Analysis 2.6. Comparison 2 NI versus placebo for treatment, Outcome 6 Complications - all types (influenza cases only).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 6 Complications - all types (influenza cases only)



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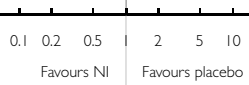
Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Li 2003	5/134	5/139		9.5 %	1.04 [0.31, 3.50]
Subtotal (95% CI)	**416**	**429**		**32.2 %**	**0.57 [0.23, 1.37]**
Total events: 14 (NI), 27 (Placebo)					
Heterogeneity: Tau^2 = 0.22; Chi^2 = 3.04, df = 2 (P = 0.22); I^2 =34%					
Test for overall effect: Z = 1.26 (P = 0.21)					
Total (95% CI)	**552**	**570**		**100.0 %**	**0.68 [0.46, 1.00]**
Total events: 47 (NI), 74 (Placebo)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 3.29, df = 3 (P = 0.35); I^2 =9%					
Test for overall effect: Z = 1.94 (P = 0.052)					



Analysis 2.7. Comparison 2 NI versus placebo for treatment, Outcome 7 Complications - all types (ITT).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 7 Complications - all types (ITT)

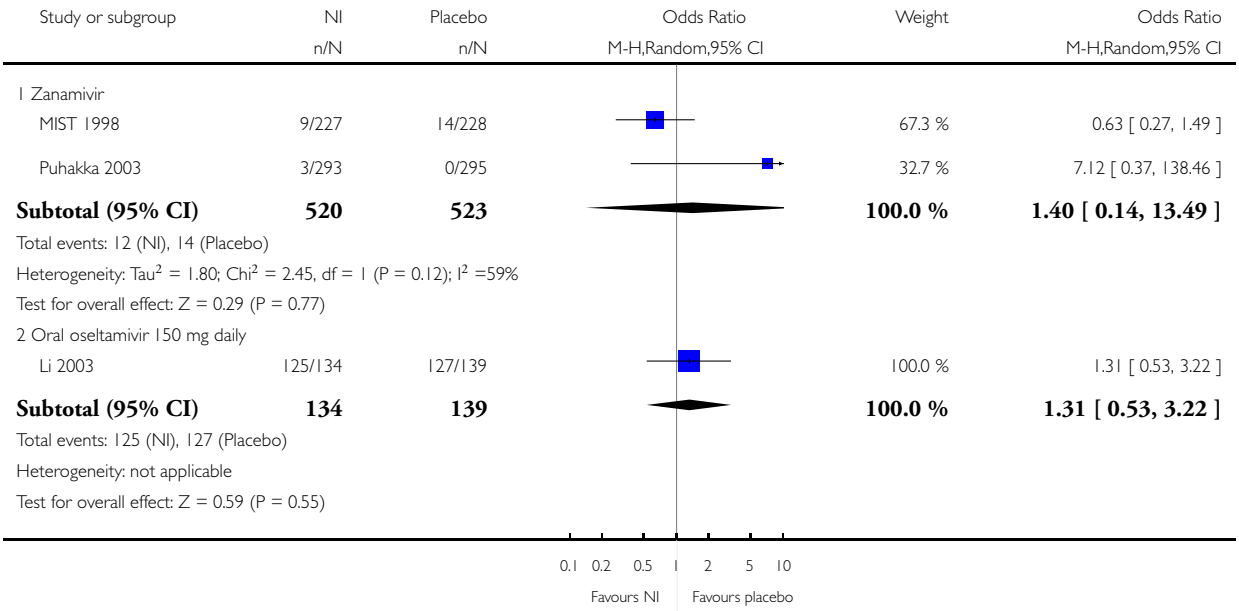
Study or subgroup	NI n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Zanamivir					
Makela 2000	40/174	61/182		100.0 %	0.69 [0.49, 0.96]
Total (95% CI)	**174**	**182**		**100.0 %**	**0.69 [0.49, 0.96]**
Total events: 40 (NI), 61 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.17 (P = 0.030)					

Analysis 2.8. Comparison 2 NI versus placebo for treatment, Outcome 8 Adverse events - cough.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 8 Adverse events - cough

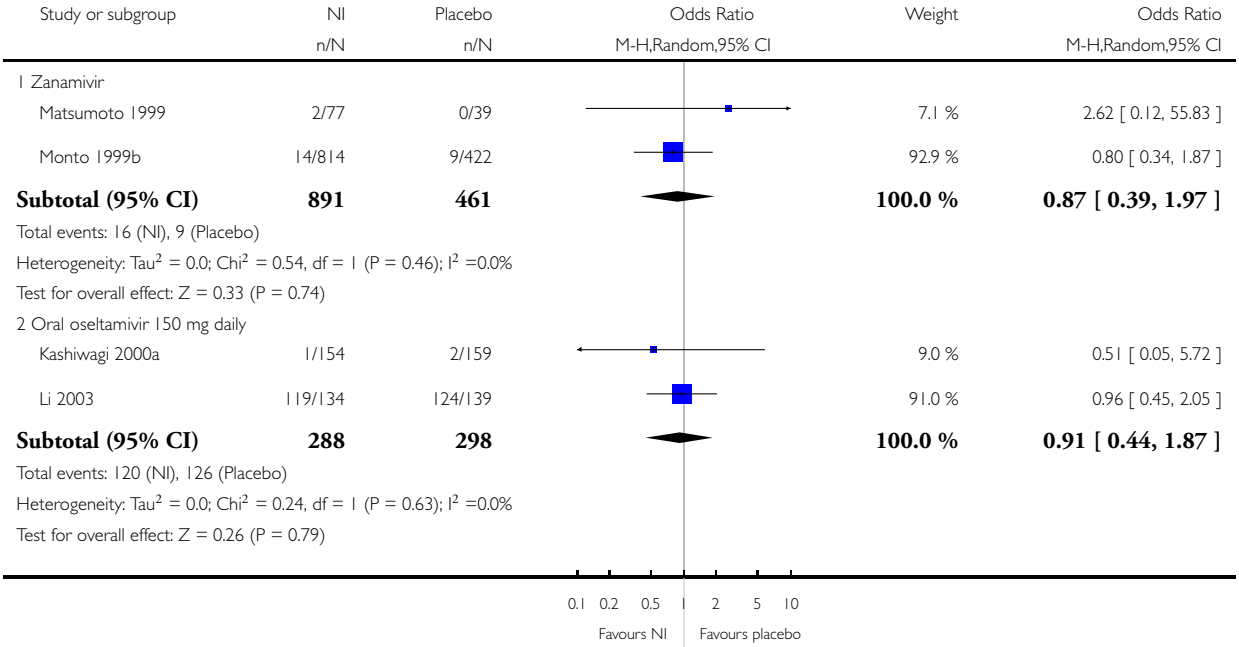


Analysis 2.9. Comparison 2 NI versus placebo for treatment, Outcome 9 Adverse events - headache.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 9 Adverse events - headache

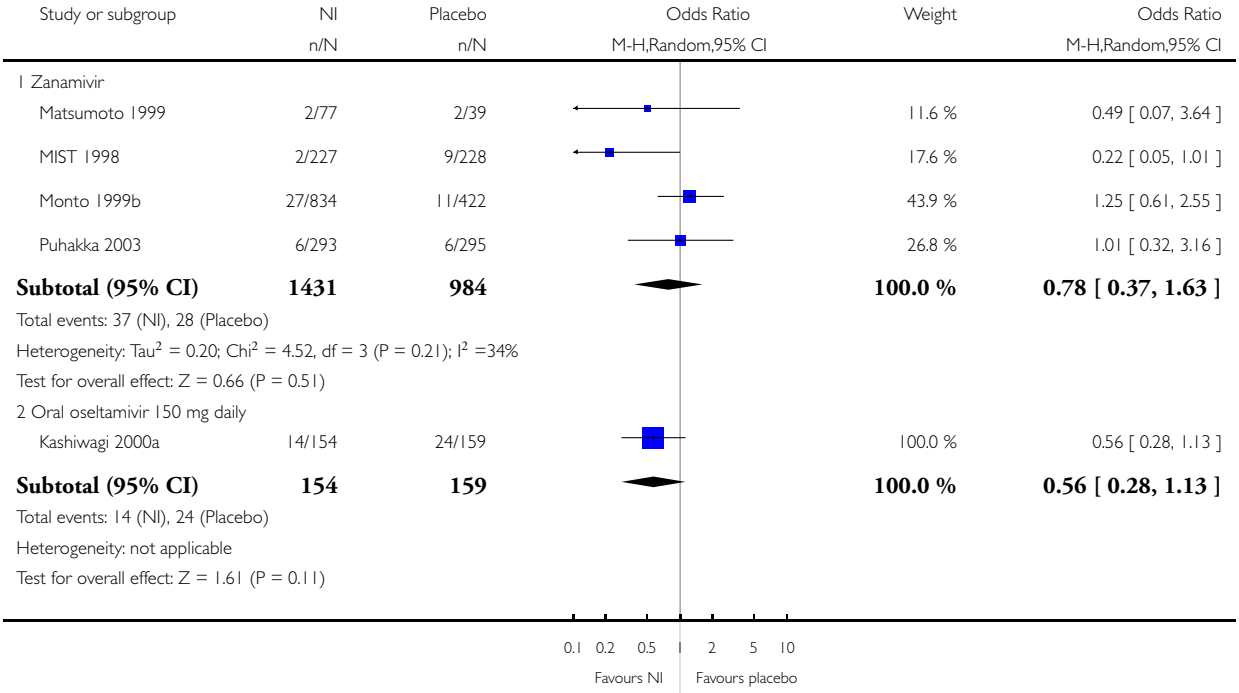


Analysis 2.10. Comparison 2 NI versus placebo for treatment, Outcome 10 Adverse events - diarrhoea.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 10 Adverse events - diarrhoea

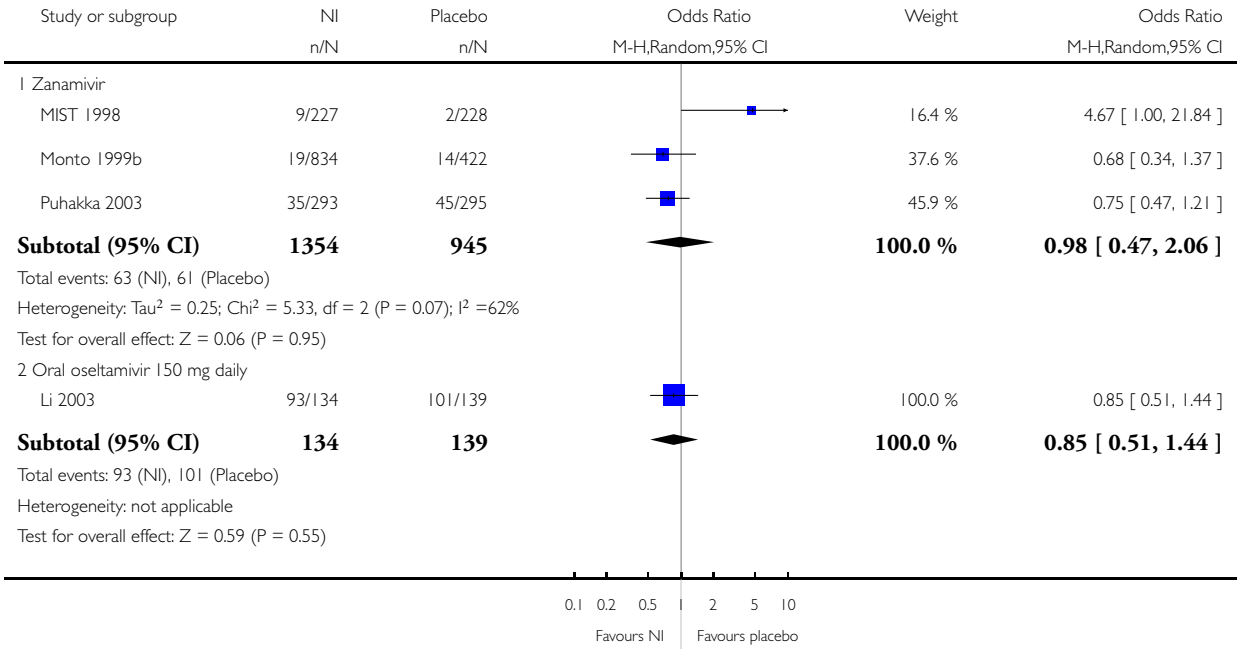


Analysis 2.11. Comparison 2 NI versus placebo for treatment, Outcome 11 Adverse events - nasal symptoms (congestion, rhinitis, dry or sore throat).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 11 Adverse events - nasal symptoms (congestion, rhinitis, dry or sore throat)



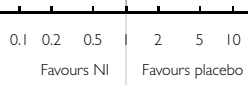
Analysis 2.12. Comparison 2 NI versus placebo for treatment, Outcome 12 Adverse events - nausea.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 12 Adverse events - nausea

Study or subgroup	NI n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Zanamivir					
Makela 2000	3/174	5/182		14.6 %	0.62 [0.15, 2.64]
MIST 1998	4/227	9/228		21.6 %	0.44 [0.13, 1.44]
Monto 1999b	20/834	14/422		63.8 %	0.72 [0.36, 1.43]
Subtotal (95% CI)	**1235**	**832**		**100.0 %**	**0.63 [0.36, 1.10]**
Total events: 27 (NI), 28 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.50, df = 2 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 1.63 (P = 0.10)					
2 Oral oseltamivir 150 to 300 mg daily					
Kashiwagi 2000a	8/154	5/159		20.7 %	1.69 [0.54, 5.28]
Treanor 2000	74/411	15/204		79.3 %	2.77 [1.54, 4.96]
Subtotal (95% CI)	**565**	**363**		**100.0 %**	**2.50 [1.49, 4.20]**
Total events: 82 (NI), 20 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.57, df = 1 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 3.46 (P = 0.00055)					

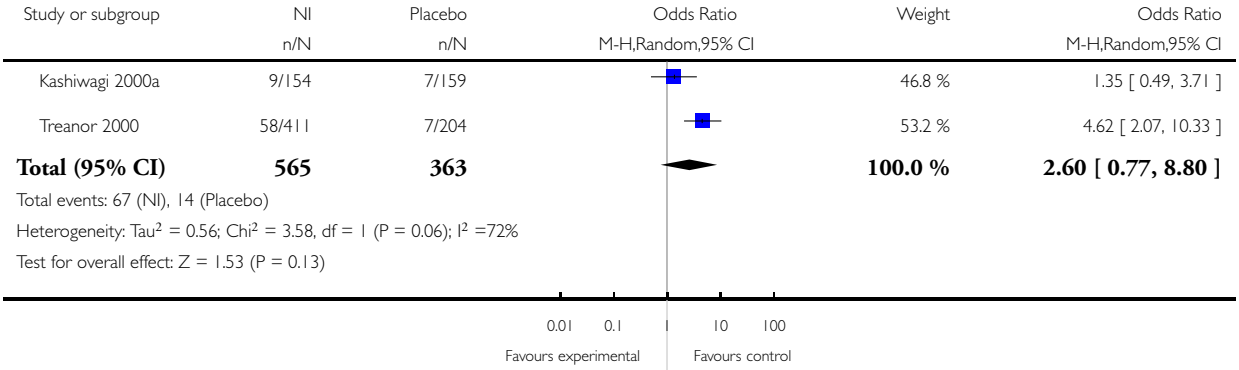


Analysis 2.13. Comparison 2 NI versus placebo for treatment, Outcome 13 Adverse events - vomiting (Oseltamivir).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 13 Adverse events - vomiting (Oseltamivir)

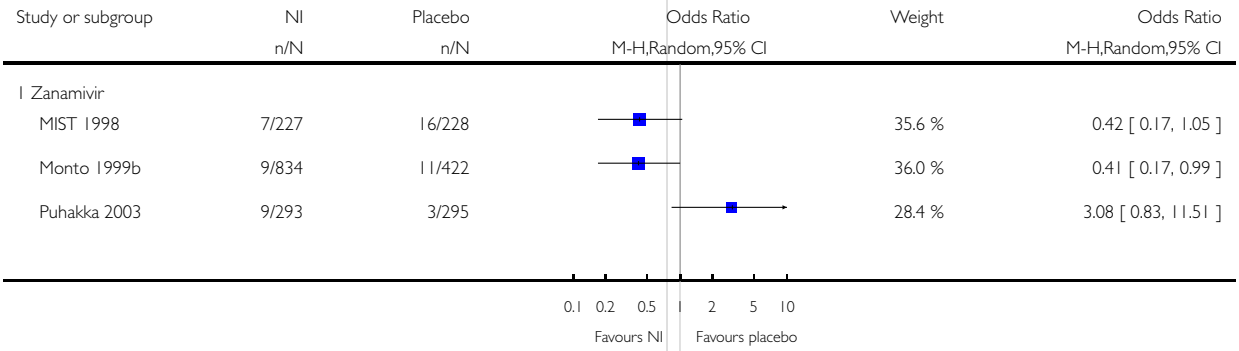


Analysis 2.14. Comparison 2 NI versus placebo for treatment, Outcome 14 Adverse events - bronchitis or pneumonia.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 14 Adverse events - bronchitis or pneumonia

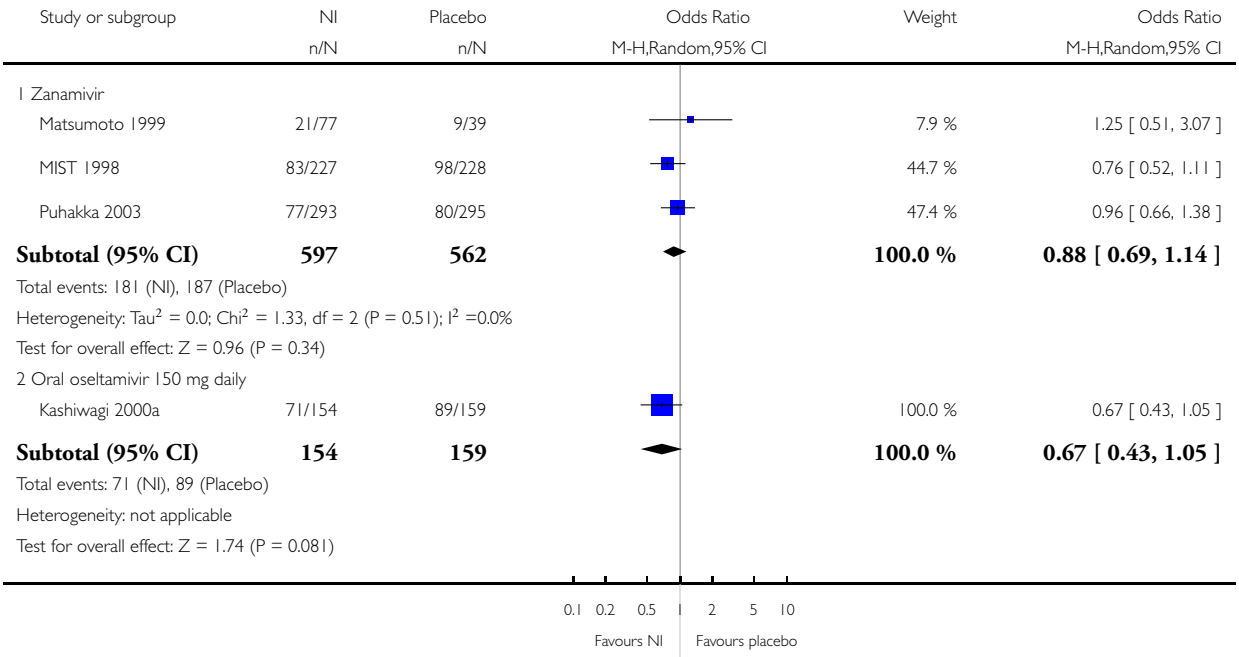


Analysis 2.15. Comparison 2 NI versus placebo for treatment, Outcome 15 Adverse events - all types.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 15 Adverse events - all types

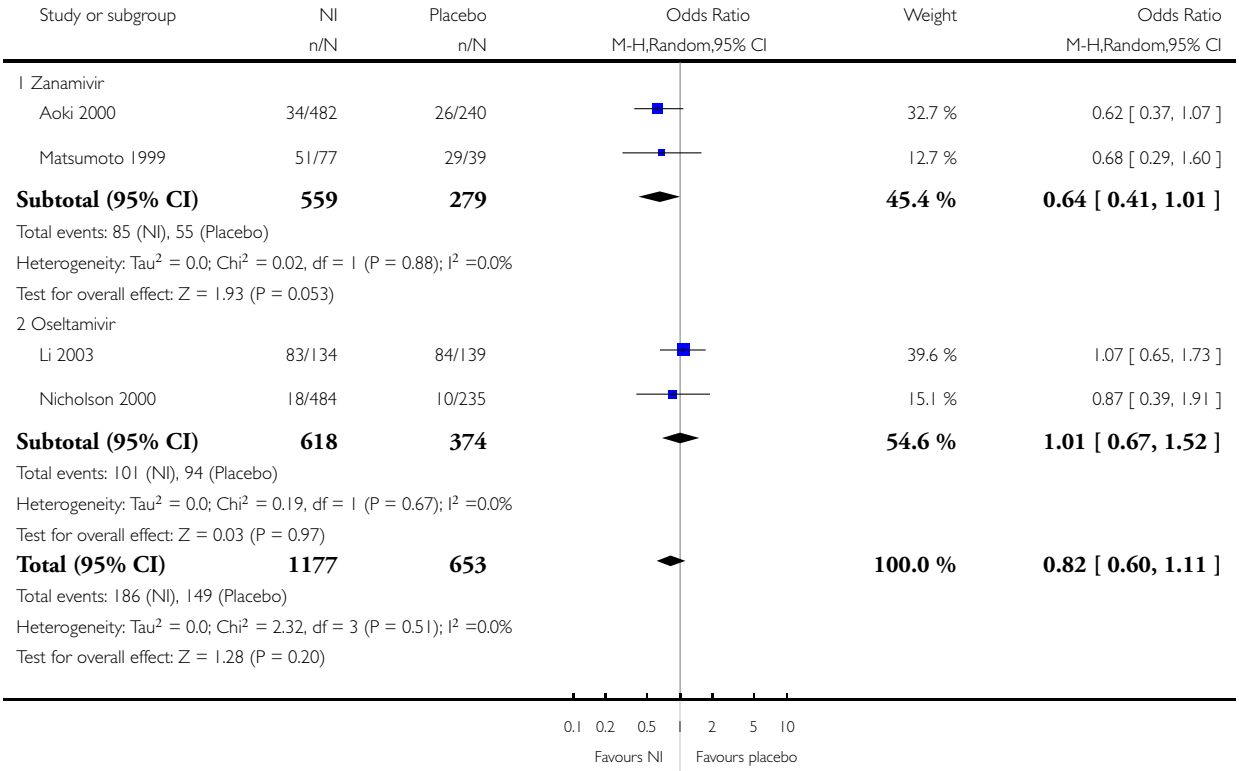


Analysis 2.16. Comparison 2 NI versus placebo for treatment, Outcome 16 Use of relief medications and antibiotics.

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 16 Use of relief medications and antibiotics



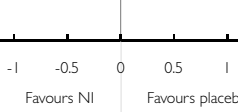
Analysis 2.17. Comparison 2 NI versus placebo for treatment, Outcome 17 Mean nasal viral titres (at 24 hours since randomisation).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 17 Mean nasal viral titres (at 24 hours since randomisation)

Study or subgroup	NI N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Zanamivir 10 to 20 mg daily							
Boivin 2000	17	2.19 (1.61)	10	2.79 (1.74)		2.5 %	-0.60 [-1.92, 0.72]
Puhakka 2003	212	3.67 (1.95)	202	4.06 (1.81)		33.2 %	-0.39 [-0.75, -0.03]
Subtotal (95% CI)	**229**		**212**			**35.7 %**	**-0.40 [-0.75, -0.06]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.27 (P = 0.023)							
2 Oseltamivir 75 to 150 mg daily							
Nicholson 2000	233	1.6 (1.9)	117	2.3 (2)		22.8 %	-0.70 [-1.14, -0.26]
Treanor 2000	140	1.55 (1.2)	71	2.3 (1.1)		41.5 %	-0.75 [-1.07, -0.43]
Subtotal (95% CI)	**373**		**188**			**64.3 %**	**-0.73 [-0.99, -0.47]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.51 (P < 0.00001)							
Total (95% CI)	**602**		**400**			**100.0 %**	**-0.62 [-0.82, -0.41]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.30$, df = 3 (P = 0.51); $I^2 = 0.0\%$							
Test for overall effect: Z = 5.78 (P < 0.00001)							

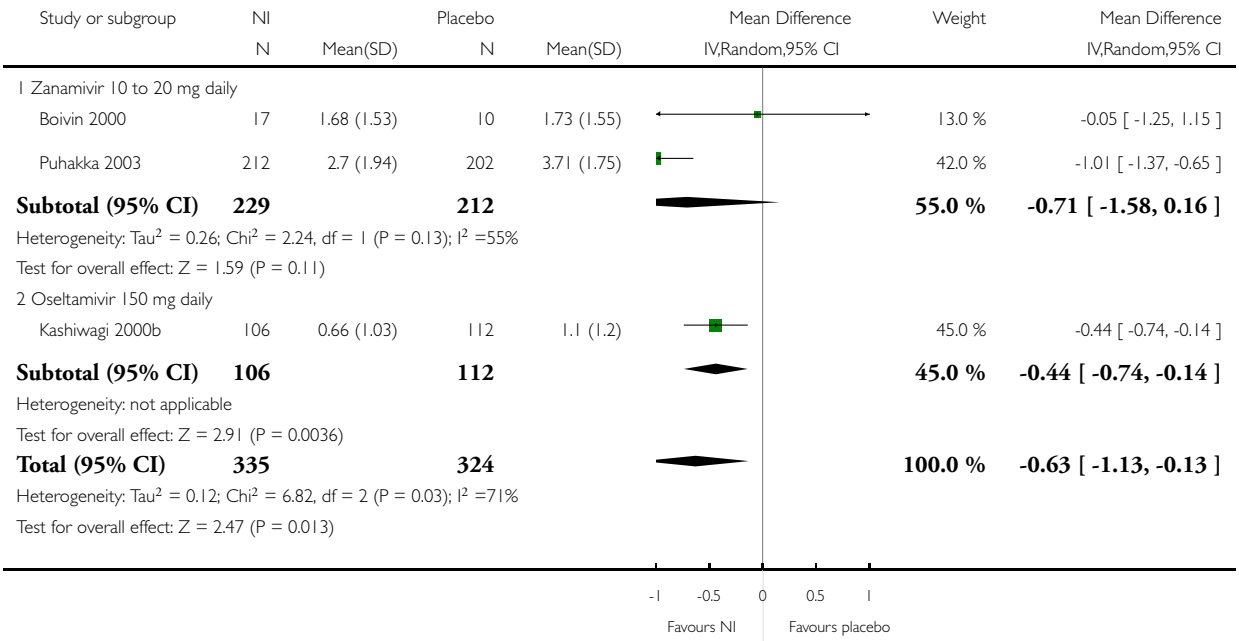


Analysis 2.18. Comparison 2 NI versus placebo for treatment, Outcome 18 Mean nasal viral titres (at 48 hours since randomisation).

Review: Neuraminidase inhibitors for preventing and treating influenza in healthy adults

Comparison: 2 NI versus placebo for treatment

Outcome: 18 Mean nasal viral titres (at 48 hours since randomisation)



APPENDICES

Appendix 1. EMBASE (WebSPIRS) search strategy

#1 explode 'influenza-' /
#2 (influenza* in ti) or (influenza* in ab)
#3 #1 or #2
#4 explode 'sialidase-inhibitor' /
#5 (neuraminidase inhibitor* in ti) or (neuraminidase inhibitor* in ab)
#6 explode 'oseltamivir-' /
#7 (oseltamivir in ti) or (oseltamivir in ab)
#8 explode 'zanamivir-' /
#9 (ozanamivir in ti) or (zanamivir in ab)
#10 #4 or #5 or #6 or #7 or #8 or #9
#11 #3 and #10

Appendix 2. Glossary of terms

- **Efficacy**: the impact of an intervention (drug, vaccines etc) on a problem or disease in ideal conditions - in this case the capacity of NIs to prevent or treat influenza and its complications.

- **Effectiveness**: the impact of an intervention (drug, vaccines etc) on a problem or disease in field conditions - in this case the capacity of NIs to prevent or treat ILI and its complications.

- **Influenza**: an acute respiratory infection caused by a virus of the Orthomyxoviridae family. Three serotypes are known (A, B and C). Influenza causes an acute febrile illness with myalgia, headache and cough. Although the median duration of the acute illness is three days, cough and malaise can persist for weeks. Complications of influenza include otitis media, pneumonia, secondary bacterial pneumonia, exacerbations of chronic respiratory disease and bronchiolitis in children. These illnesses may require treatment in a hospital and can be life-threatening especially in 'high-risk' people e.g. the elderly and people suffering from chronic heart disease. Additionally, influenza can cause a range of non-respiratory complications including febrile convulsions, Reye's syndrome and myocarditis. The influenza virus is composed of a protein envelope around an RNA core. On the envelope are two antigens: neuraminidase (N antigen) and hemagglutinin (H antigen). Hemagglutinin is an enzyme that facilitates the entry of the virus into cells of the respiratory epithelium, while neuraminidase facilitates the release of newly produced viral particles from infected cells. The influenza virus has a marked propensity to mutate its external antigenic composition to escape the hosts' immune defences. Given this extreme mutability, a classification of viral subtype A based on H and N typing has been introduced. Additionally, strains are classified on the basis of antigenic type of the nucleoprotein core (A, B), geographical location of first isolation, strain serial number and year of isolation. Every item is separated by a slash mark (e.g. A/Wuhan/359/95 (H3N2)). Unless otherwise specified such strains are of human origin. The production of antibodies against influenza beyond a conventional quantitative threshold is called **seroconversion**. Seroconversion in the absence of symptoms is called **asymptomatic influenza**.

- **Influenza-like illness (ILI)**: an acute respiratory illness caused by scores of different viruses (including influenza A and B) presenting with symptoms and signs which are not distinguishable from those of influenza. ILI does not have documented laboratory isolation of the causative agent and is what commonly presents to physicians and patients (also known as the flu")

- **Mean**: a measure of central tendency of a group of variables (such as age). It is calculated by adding all the individual values and then dividing by the number of values in the group.

- **Median**: a measure of central tendency of a group of variables (such as age). It is the halfway mark of a set of variables, the dividing point between lower and upper.

- **Randomised study**: when it appears that the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using random allocation - **randomised controlled trial (RCT)**. When the unit of allocation is a group (such as a family, or a military unit) the design is that of a **Cluster Randomised Trial (C-RCT).**

- **Quasi-randomised study**: when it appears that the individuals (or other experimental units) followed in the study were definitely or probably assigned prospectively to one of two (or more) alternative forms of health care using some quasi-random method of allocation (such as alternation, date of birth or case record number) - **clinical controlled trial (CCT)**

Appendix 3. Details of previous searches

In the original review, we searched the Cochrane Controlled Trials Register (CCTR) (*The Cochrane Library* 1999, issue 1), MEDLINE (in May 1999), EMBASE (1991 to 1998). We read the bibliography of retrieved articles in order to identify further trials. We hand searched the journal *Vaccine* from its first issue to the end of 1997. Given that NIs were still at the pre-registration developmental phase, to locate unpublished trials, we contacted both manufacturers. See below for the original search strategy.
The following search terms or combined sets in any language were used:
Influenza Route (oral)
route (parenteral)
Neuraminidase inhibitors
Oseltamivir
RO/GS 4104
Zanamivir

In the 2005 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, issue 3), MEDLINE (2004 to September, Week 4 2005), EMBASE (2003 to June 2005). We also contacted manufacturers, researchers in the field, and authors of studies evaluated in the review.
In the 2008 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, issue 2), MEDLINE (2005 to May, Week 4 2008), and EMBASE (2005 to May 2008).

Appendix 4. Adverse effects search strategies

CENTRAL Issue 3, 2009
#1MeSH descriptor Oseltamivir explode all trees
#2MeSH descriptor Zanamivir explode all trees
#3(oseltamivir or zanamivir or GS4071 or tamiflu or relenza):ti,ab,kw
#4neuraminidase NEXT inhibitor*:ti,ab,kw
#5(#1 OR #2 OR #3 OR #4)
#6safe or safety:ti,ab,kw
#7side NEXT effect*:ti,ab,kw
#8(adverse or undesirable or harm* or serious or toxic) NEAR/3 (effect* or reaction* or event* or outcome*):ti,ab,kw
#9MeSH descriptor Product Surveillance, Postmarketing explode all trees
#10MeSH descriptor Adverse Drug Reaction Reporting Systems explode all trees
#11MeSH descriptor Clinical Trials, Phase IV as Topic explode all trees
#12MeSH descriptor Poisoning explode all trees
#13MeSH descriptor Substance-Related Disorders explode all trees
#14MeSH descriptor Drug Toxicity explode all trees
#15MeSH descriptor Abnormalities, Drug-Induced explode all trees
#16MeSH descriptor Drug Monitoring explode all trees
#17MeSH descriptor Drug Hypersensitivity explode all trees
#18(toxicity or complication* or noxious or tolerability):ti,ab,kw
#19MeSH descriptor Case-Control Studies explode all trees
#20MeSH descriptor Cohort Studies explode all trees
#21(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22(#5 AND #21)
#23MeSH descriptor Oseltamivir explode all trees with qualifier: AE
#24MeSH descriptor Zanamivir explode all trees with qualifier: AE
#25(#22 OR #23 OR #24)
EMBASE (Ovid)
1 exp sialidase inhibitor/
2 exp oseltamivir/
3 exp zanamivir/
4 (oseltamivir or zanamivir or GS4071 or tamiflu or relenza).tw.
5 neuraminidase inhibitor*.tw.
6 or/1-5
7 (ae or si or to or co).fs.
8 side effect*.tw.
9 (safe or safety).tw.
10 ((adverse or undesirable or harms* or serious or toxic) adj3 (effect* or reaction* or event* or outcome*)).tw.
11 exp adverse drug reaction/
12 exp drug toxicity/
13 exp drug safety/
14 exp drug monitoring/
15 exp drug hypersensitivity/
16 exp postmarketing surveillance/
17 exp drug surveillance program/

18 exp phase iv clinical trial/
19 (toxicity or complication* or noxious or tolerability).tw.
20 exp case control study/
21 exp cohort analysis/
22 or/7-21
23 6 and 22

Appendix 5. Doshi's description of the exclusion of one study (Kaiser 2003)

The story behind the review

Peter Doshi
Program in History, Anthropology, Science, Technology and Society, E51-070, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.
Adapted from a BMJ analysis (Doshi 2009)
Since August, our Cochrane review team tried to do one simple thing: obtain the data necessary to verify claims that Tamiflu lowers serious complications of influenza such as pneumonia. We failed, but in failing, discovered that the public evidence base for this global public health drug is fragmented, inconsistent, and contradictory. We are no longer sure Tamiflu offers a therapeutic and public health policy advantage over aspirin. If the public is to trust in public health policies, the scientific basis informing knowledge of the harms and effects of those interventions must be public and open to independent analysis.

How a Cochrane review turned controversial

Systematic reviews are designed to synthesize the most reliable evidence on the effects of interventions. In retrospect, our Cochrane review of neuraminidase inhibitors began on a naïve but excited note. I had just received from the FDA a response to my Freedom of Information Act request, a CDROM containing thousands of postmarketing adverse event reports over the past decade for the two NI drugs Tamiflu (oseltamivir) and Relenza (zanamivir). The dataset was difficult to interpret, and analysis would require some time (1). Although the review had last been updated in 2008, our new task was to include a safety assessment component. Tom Jefferson, who led the review, wrote to the group then just being formed, "Dear Friends, I am writing to inform you that the NHS [National Institute of Health Research] has commissioned an update of our Cochrane review ... although it is always dangerous to pre-judge the issue, I expect no new effectiveness data but a lot of pharmacovigilance data." Two days later, a pediatrician from Japan submitted a comment to the Cochrane Collaboration that would end up bedevilling our analysis for months (See NI Review Web Extra: Hayashi criticism). Hayashi pointed out that while Jefferson et al's previous review (2) found Tamiflu effective in reducing important complications of influenza such as pneumonia, that conclusion was drawn from a single peer-reviewed study (Kaiser (3)) which itself had meta-analyzed 10 manufacturer-funded trials from the late 1990s, of which only 2 were published in peer reviewed journals (4,5). (The remaining eight were apparently either unpublished or published in abstract form.) The Hayashi comment exposed the fact that the conclusions of our review were based on taking the word of other papers on face value. Meeting Hayashi's challenge required we verify the data for ourselves.

A maze of inconsistencies

The Hayashi comment set off a series of perplexing discoveries. Despite funding the Kaiser meta-analysis which concluded that Tamiflu reduces complications, Tamiflu's manufacturer, Roche, apparently did not itself make any such claims about complications. A Tamiflu.com webpage reads, "Treatment with TAMIFLU has not been proven to have a positive impact on these outcomes," referring to pneumonia other respiratory diseases as well as influenza-related death (6).
Similarly, our Cochrane review of the literature also found both Tamiflu and competitor drug Relenza effective in reducing the duration of influenza-like illness symptoms. But here again, Roche's position is that Tamiflu is ineffective against influenza-like illnesses not caused by influenza (7). US, EU, and Japanese drug regulators agree: Tamiflu only works for true influenza virus infections. (Table)
These inconsistencies were pointing to the uncomfortable conclusion that the Cochrane Collaboration had promoted-by trusting the validity of other work in the scientific literature-efficacy claims more optimistic than even the drug manufacturer's.
Reality, however, proved more complex. Roche's statement that Tamiflu is not proven to reduce complications is apparently a message only meant for Americans. At the bottom of Tamiflu.com webpages is a bold-face note: "THIS [WEB]SITE IS INTENDED FOR U.S.

AUDIENCES ONLY." On Roche.com, the global website, the manufacturer boasts that Tamiflu provides a "67 percent reduction in secondary complications such as bronchitis, pneumonia and sinusitis in otherwise healthy individuals" (8). Statements from regulatory agencies in Tamiflu's three chief markets are similarly inconsistent: the EU EMEA mentions benefit, the US FDA denies benefit, and Japanese PMDA does not discuss complications (Table), raising the question of whether these agencies have evaluated the same datasets. (Jefferson emailed the EMEA asking for the raw data underlying the endorsement but after three weeks was asked what he meant by "the raw data".)

Data pertaining to Tamiflu's safety were equally confusing. We discovered that FDA's postmarketing drug safety database known as AERS (which collects reports of adverse events worldwide of FDA approved pharmaceuticals approved) had fewer total entries than Roche's own database held of just neuro-psychiatric classified adverse events (NPAEs). (Of 2466 NPAEs in the Roche Global Safety Database between 1999 and September 15, 2007, Roche researchers classified 562 "serious" (9). Over this period, the AERS database only holds 1805 adverse event reports of any kind.)

In publications we trust

Analyzing and learning from publications in the scientific literature is central to contemporary scientific practice. Essential to this practice is the act of trust. Trust that trials are carried out properly and that published reports are a genuine reflection of that research. Trust that policymakers accurately read and interpret those reports to make evidence based decisions. Trust, in other words, that claims about a drug's performance are backed by hard data. Hayashi's comment challenging our conclusions revealed the degree to which Cochrane reviews are fundamentally based on the premise that the published literature can be trusted.

The Cochrane Collaboration was not alone in trusting publications. The Kaiser paper has for several years been the sole citation offered in US CDC recommendations on influenza in support of the statement that Tamiflu reduces the risk of hospitalization and pneumonia (10-12). The claim also found its way into US national influenza preparedness documents. The United States HHS Pandemic Influenza Plan, for example, assumes that in a pandemic, neuraminidase inhibitors "will be effective in decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for interpandemic influenza), and will also decrease mortality."(13) These statements were made despite US regulators saying the opposite.

Or, in secrecy we trust?

Obtaining raw data from properly carried out trials on complications is the only way to resolve the inconsistencies surrounding Tamiflu's effect on reducing complications. On behalf of the review team, Jefferson wrote to the authors of the Kaiser paper, but was told that they no longer had the files and to contact Roche. Jefferson also wrote to authors of the two peer-reviewed published trials used in Kaiser's meta-analysis. One responded but once again directed us to the manufacturer.

Jefferson first contacted Roche in early September. On October 2, Roche indicated a willingness to share data, but not openly. It furnished Jefferson with a "confidentiality agreement," containing a clause that says that the signee (Jefferson) agrees "not to disclose ... the existence and terms of this Agreement...." (Web Extra: Roche confidentiality agreement). Roche apparently intended to not only keep its data concealed, but additionally intended to conceal the fact that it was quieting people through a secrecy clause.

Jefferson never signed the confidentiality agreement, but wrote the next day asking for clarification which he never received. On October 7 the company asked Jefferson to restate which data he was seeking. After Jefferson's answer, Roche said it was unable to provide data because it had already provided it for a similar meta-analysis being started by an independent expert influenza group. The Cochrane request, Roche said, might conflict with that review. In return, Jefferson challenged Roche to outline its concerns and explain why multiple groups of independent researchers should pose a problem and lead to data exclusivity. Roche did not answer these questions, but eight days later (October 21), unexpectedly emailed Jefferson excerpts of company reports from all clinical trials used in the Kaiser meta-analysis. Our team analyzed the data, and Jefferson wrote to Roche explaining that the files were insufficient to verify the effects on complications claims in Kaiser and the methods used in the trials. Roche responded on October 28, saying it would send more information the next week. Jefferson informed them that our deadline was now past, but we would accept any additional information for future updates. (As of November 15, we have heard nothing.)

The 2008 Cochrane review placed its trust in publications, and included Kaiser's analysis, consequently endorsing the conclusion that Tamiflu reduces complications such as pneumonia and bronchitis. Once again incorporating the Kaiser paper data into the updated review, despite our inability to obtain data sufficient to perform an independent analysis of the data, would have shifted our position from that of trust in publication to that of trust in secrecy. We dropped Kaiser's paper from our analysis.

Implications

After four months of seeking the data used to support the claims of Kaiser, we have come up empty-handed. If one is to trust in the performance of Tamiflu to reduce important complications of influenza such as pneumonia, they must do so trusting that data supporting those claims exist. Our experience has left us with a doubtful feeling towards placing our trust in drug companies.

We feel equally wary over our conclusion that Tamiflu and Relenza reduce the symptoms of influenza-like illness (ILI), but this is what our review concludes, incorporating the published trial data. Lack of effectiveness against ILI would be bad news: ILI is the clinical syndrome usually consisting of fever with cough or sore throat, well known as "the flu." Without laboratory testing, one cannot know whether influenza virus or some other agent is causing the patient's discomfort (14). In past influenza seasons, United States virologic surveillance data suggest that at peak "flu season" the proportion of respiratory specimens testing positive for influenza reaches 25-35%, but over the entire season, influenza viruses are found in only a small minority (14%) of tested patients. By contrast, of the patients with influenza-like illness recruited into the Tamiflu and Relenza trials we analyzed, an incredible 57-80% had influenza (Figure). The discrepancy appears the likely outcome of a special patient inclusion methodology, in which "Centers were activated to recruit subjects during an influenza outbreak in the locality, detected using standardized surveillance techniques," according to the company trial report excerpts we obtained. This crucial detail, however, was not mentioned in published Tamiflu trials (4,5). If Australia's winter experience with A/H1N1 is any guide, influenza is not a majority cause of ILI cases even during a pandemic, and thus NIs may be ineffective for most patients today (15).

If Tamiflu is no better than placebo in its ability to reduce the complications of influenza, and is also ineffective against non-influenza ILI, as US and Japanese regulatory documents indicate, Tamiflu's ability to treat the symptoms of influenza may be similar to that of an NSAID such as aspirin. This realization led us to call for a head-to-head trial of Tamiflu versus a NSAID.

With respect to safety concerns, FDA reporting rules turn out to have important limitations, namely that although manufacturers are under mandatory reporting requirements, adverse events occurring outside the United States judged to not meet the "both serious and unexpected" criteria are under no requirement to be reported. Thus the public AERS database relies on manufacturers to honestly and accurately judge whether adverse events reported in conjunction with their products are "serious" and therefore must be reported-or not. In the case of Tamiflu, considering that 75% of Tamiflu's market has been in Japan, this has important implications on our knowledge of its safety.

Public Health Drugs

In the ten years since Tamiflu was approved for use in 1999, neither American nor Japanese regulators have approved statements that the drug lowers rates of influenza-related complications, and one may have in fact even required Roche to declare "Tamiflu has not been proven to have a positive impact on the potential consequences (such as hospitalizations, mortality, or economic impact) of seasonal, avian, or pandemic influenza."(16) Despite the work of these regulators, public health officials trusted the published literature, said Tamiflu could, and spent billions of dollars building drug stockpiles, elevating Tamiflu to the status of a public health drug.

Public health drugs-like vaccines-get deployed on a population basis, directed by national or international level policy decisions. As witnessed in the UK, when the government declared that Tamiflu may be used to treat all symptomatic cases even without a physician consult or laboratory diagnosis, hundreds of thousands of courses of the drug were used in a fortnight (17). Mass prescription carries serious responsibilities. While the evidence base for all approved drugs should be sound, the evidence base for public health drugs must be of the highest quality, publicly available and open to independent scrutiny.

Trust is a noble human quality, but evidence based medicine should not hinge upon a singular trust in any one institution, particularly not in profit-driven companies to report information about their own products free of bias, let alone truthfully. As John Abraham once observed, there seems a tragic irony in that as pharmaceutical companies do not trust each other, that the public or government should be asked to trust them. (18) If governments have the authority to purchase and govern the use of multi-billion dollar drug stockpiles, they should have the interest, time, and money to transparently and independently first verify and evaluate the effects of that drug. The Box contains some ideas on where to start.

Acknowledgements: I would like to acknowledge the support of my Cochrane co-authors, and in particular thank Yuko Hara and Tom Jefferson for their helpful comments on the draft manuscript.

Competing Interest Statement: I am co-author of the Cochrane review about which this article is written.

Contributor: PD is sole author and guarantor of the paper.

Study funding: The authors' own resources.

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Table

Effect	For	Against
Complications of influenza	Roche (roche.com): "Tamiflu delivers ... [a] 67 percent reduction in secondary complications such as bronchitis, pneumonia and sinusitis in otherwise healthy individuals" (8) Kaiser: "Our analysis found that early treatment of influenza illness with the neuraminidase inhibitor oseltamivir significantly reduced influenza-related LRTCs, associated antibiotic use, and the risk of hospitalization. This effect was observed in both at-risk subjects and otherwise healthy individuals." (3) EU: "The proportion of subjects who developed specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics was reduced from 12.7 % (135/1063) in the placebo group to 8.6 % (116/1350) in the oseltamivir treated population (p = 0.0012)." (19) CDC: "In a study that combined data from 10 clinical trials, the risk for pneumonia among those participants with laboratory-confirmed influenza receiving oseltamivir 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) [(3)]." (12) HHS: "Treatment with a neuraminidase inhibitor (oseltamivir [Tamiflu®] or zanamivir [Relenza®]) will be effective in decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for interpandemic influenza), and will also decrease mortality." (13)	Roche (tamiflu.com): "Treatment with TAMIFLU has not been proven to have a positive impact on [asthma, emphysema, other chronic lower respiratory diseases, pneumonia, other respiratory diseases, pneumonitis, and influenza-related death]" (6). FDA: "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." (20) Japan PMDA: *no mention of complications on drug product information sheet* (21)
Influenza-like illness (ILI)	Nicholson: "The duration of illness was significantly lower in the intention-to-treat [ILI] population than in the other subgroups because of the high proportion of influenza-infected patients in this population." (5) Treanor: "As expected, the greatest benefit of therapy was seen in individuals with evidence of influenza virus infection. However, analysis of the entire population also demonstrated a significant	Roche: "We acknowledge that oseltamivir is ineffective against influenza-like illness caused by viruses other than influenza." (7) EU EMEA: "Oseltamivir is effective only against illness caused by influenza viruses. There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza viruses." (19) FDA: "There is no evidence for efficacy of TAM-

(*Continued*)

	benefit of treatment." (4) Previous Cochrane review: "Time to alleviation of symptoms [for ILI were] … in favour of the [neuraminidase inhibitor] treated group … (hazard ratio 1.20, 95% CI 1.06 to 1.35)." (22)	IFLU in any illness caused by agents other than 254 influenza viruses Types A and B." (20) Japan PMDA: "Tamiflu has no effect against infections except those caused by influenza A and B viruses." (21)

Table-Contradictory statements made about the potential benefits of Tamiflu

Box

Clarify expectations and provide evidence for them. Public health policies aiming to employ mass interventions should clearly state and identify (before approving the policy) the expected harms and benefits of that intervention. For every claim, raw data should be made available to aid independent analysis of the data. Clarity regarding the expectations of a drug can help reveal important inconsistencies, flagging them as areas of uncertainty that require better evidence.

Strengthen trial registration processes. All trials should be centrally registered (perhaps with the government in initiatives like ClinicalTrials.gov) with the names of all key study investigators and their affiliations to help reduce the potential for ghost authorship. A field for publications resulting from a given trial, as well as a field explaining why a study was not/never published one year past its completion would help third party investigators match clinical trial to publication, and bring more awareness of the importance of publishing "negative" results.

Make patient level data available. Individual patient data is often the only way to resolve questions about the effects of a drug. Publicly available anonymized patient level datasets on regulator websites would increase transparency and enable independent re-analyses of trial results.

Reduce the reliance on trust. Data collecting methodologies (such as adverse events reporting systems) that rely on companies to self-evaluate potential harms caused by their drug may lead to bias. Reduce this potential by making mandatory reporting requirement apply to all known adverse events, allowing the importance of a given adverse event to be determined by anybody who cares to analyze the publicly accessible post marketing surveillance database. Internet-only based reporting of adverse events would lessen the workload and help facilitate all known adverse events rapidly find their way into regulatory agency public databases.

Box-A short list of higher standards for evidence-based public health decision making

Figure

Figure-Proportion of respiratory specimens testing positive for influenza during influenza seasons (week 40 to week 20), 1997-98 to 2008-09, and comparison to proportion of intention-to-treat (ITT) population with influenza enrolled in ten Roche clinical trials reported by Nicholson, Treanor, and Kaiser. Peak weekly influenza positivity rate also shown. Seasonal data are from US CDC.

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FEEDBACK

Neuraminidase inhibitors for preventing and treating influenza in healthy adults, 16 July 2009

Summary

Dear Mr Jefferson

We have some questions on the conclusion in your Oseltamivir review especially about the prevention of complication. You described that Oseltamivir 150 mg daily prevented lower respiratory tract complications (OR 0.32, 95% CI 0.18 to 0.57).

However, we have found that this conclusion is based on the other review (Kaiser 2003) and not on your own data analysis. The authors of the review were four employees of F. Hoffman-La Roche Ltd, one paid consultant to F. Hoffman-La Roche Ltd and Kaiser. We cannot find any raw data about this conclusion from your review. Kaiser's review included 10 RCTs; two RCTs (Nicholson 2000 and Treanor 2003) were published as articles in the peer-reviewed medical journal (JAMA and Lancet), but other 8 RCTs were proceedings of congress (5 RCTs), abstracts of the congress (one RCT) and meeting (one RCT) and data on file, Hoffmann-La Roche, Inc, Nutley, NJ (one RCT). The lower respiratory tract complication rates of these articles were summarized on table: there was no significant difference between Oseltamivir and placebo, and their Odds Ratio's (ORs) were1.81. But ORs of other 8 RCTs were 4.37. We strongly

suppose that the reviewer's conclusion about the complications was mainly determined by these 8 RCTs, we should appraise the 8 trials rigidly. Without this process it's difficult to conclude that Osltamivir can prevent lower respiratory tract complications.

Table: All lower respiratory tract complications (influenza case only)

Nicholson 2000 + Treanor 2003

Complications	Placebo	Oseltamivir 150 mg
+	13	7
-	277	270

Other 8 RCTs

Complications	Placebo	Oseltamivir 150mg
+	22	10
-	350	695

Kaiser (Cochrane)

Complications	Placebo	Oseltamivir 150mg
+	35	17
-	627	965

Submitter agrees with default conflict of interest statement: 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

Response to Hayashi's Feedback comment: critical analysis of Kaiser et al (2003)

Kaiser et al (2003) combined 10 randomised control trials (RCTs) comparing oseltamivir with placebo in the treatment of influenza. They focused on risk of complications leading to antibiotic use. A limitation of their analysis was the combining of bronchitis, pneumonia and lower respiratory tract infections which they labelled as lower respiratory tract complications (LRTC). In the original trials complications studied also included sinusitis and otitis media however these were ignored in the Kaiser et al study. In addition bronchitis is a very general diagnosis whereas pneumonia is more specific and a much more serious condition. Combining of these two outcomes is questionable. Another limitation of the Kaiser et al study involves their choice of analysis strategy: Fishers exact test. This analysis does not stratify by trial but treats the whole 10 trials as one study. Therefore the benefit of randomisation is lost, resulting in a non-randomised comparison. To confirm that they did indeed use Fishers exact test two analyses where the actual P value is reported can be checked.

Hospitalisations:	18/1063 versus 9/1350 P = 0.019 (Kaiser et al report P = 0.02)
LRTC in high risk patients:	74/401 versus 45/368 P = 0.021 (Kaiser et al report P = 0.02)

The resulting P values are the same (to two decimal places) therefore it is highly likely that they did indeed use Fishers exact test to compare the overall groups (without stratification). Normally in a meta-analysis of individual RCTs, separate comparisons by trial are made and then combined in an appropriate way to obtain the overall effect of treatment. A "correct" analysis is especially important in this case because of the following facts reported in Kaiser et al:

1. The populations studied in each trial are different: healthy adults in four studies; elderly patients in four studies, and adults with chronic obstructive airways disease (COAD) in two studies.
2. Overall there are more oseltamivir patients compared to placebo patients (2023 versus 1541) hence at least one trial did not have a 1:1 allocation ratio.
3. The trials had different proportions of influenza infected patients (ranging from 50% to 73%).
4. Overall there were more high risk patients in the placebo group compared to the oseltamivir group (38% versus 27%) hence (overall) groups are not comparable.

The Kaiser et al study did not report the numbers of patients randomised to the two groups for each of the 10 trials; they just reported overall numbers. The following hypothetical meta-analysis of two trials illustrates why a correct analysis is critical.

Table of proportions of adverse events by (hypothetical) trial

Trial number	Adverse Events		
	Treatment	Placebo	Total
Trial 1 (high risk patients)	50/100 (50%)	50/100 (50%)	100/200 (50%)
Trial 2 (low risk patients)	10/200 (5%)	4/80 (5%)	14/280 (5%)
Total	60/300 (20%)	54/180 (30%)	

This meta-analysis shows two trials with no effect. However, the two trials have recruited much different patient groups (e.g. elderly patients in trial 1 and the general population in trial 2). Also trial 2 has not allocated with a ratio of 1:1 (as in at least one of the Kaiser et al trials). Like the Kaiser et al study there is a higher proportion of high risk patients overall in the placebo group (56% versus 33%). A naïve analysis that does not stratify by trial (Fishers exact test) shows a significant difference between treatment (20% events) and placebo (30% events) with P = 0.01 (odds ratio = 0.58). Conversely an analysis that stratifies for trial (logistic regression) shows no difference (P = 1.0, odds ratio = 1.0). In the case of the Kaiser et al data, a random-effects meta-analysis that takes into account heterogeneity between trials may be most appropriate.

Note that the hypothetical example shown above is "extreme". However, it does illustrate what could happen with a naïve analysis that does not stratify by trial. The important point is that with a naïve analysis there is no guarantee of an unbiased estimate of treatment effect or a realistic 95% confidence interval and P value.

Tom Jefferson, Mark Jones, Peter Doshi, Chris Del Mar, Liz Dooley

Date of inclusion: 10 November 2009

Contributors

Keiji Hayashi

Date of inclusion: 16 July 2009

Neuraminidase inhibitors for preventing and treating influenza in healthy adults, 30 July 2009

Summary

The last sentence under Results, preceding Discussion is: 'Finally, use of relief medications and antibiotics is unaffected by assumption of NIs (OR 0.81, 95% CI 0.59 to 1.12).' Here 'assumption' makes no sense, so should the words in bold be 'consumption of an NI'? Submitter agrees with default conflict of interest statement: 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

Thanks you, we have re-written this part of the review to make it clearer.

Tom Jefferson, Mark Jones, Peter Doshi, Chris Del Mar, Liz Dooley

Date of inclusion: 15 November 2009

Contributors

Andrew Herxheimer

Date of inclusion: 30 July 2009

WHAT'S NEW

Last assessed as up-to-date: 6 August 2009.

Date	Event	Description
29 September 2010	Amended	Published notes section updated to explain to readers why this review will not be updated.

HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 1999

Date	Event	Description
12 November 2009	New citation required and conclusions have changed	1. We excluded two new studies (Blumentals 2007 and Toovey 2008). 2. We now study pharmacovigilance data. 3. We excluded a previously included study (Kaiser 2003) as we could not answer the Hayashi comment by reconstructing the Kaiser 2003 data set. Hayashi prompted us to more carefully evaluate the Kaiser 2003 study. More critical evaluation of it leads essentially to a retraction of our 2006 and 2009 updates of this review. It results in changed conclusions: excluding the Kaiser 2003 data, and failing to identify sufficient toxicity data from pharmacovigilance sources, we conclude that there is insufficient evidence to describe the effects of oseltamivir on complications of influenza and its toxicity. 4. There is a change in authors of the review team. 5. The review was published in a print journal in a shortened form, December 2009 (Jefferson 2009e).
7 August 2009	New search has been performed	Safety/adverse effects searches conducted.
30 July 2009	Feedback has been incorporated	Feedback added to review.
16 July 2009	Feedback has been incorporated	Feedback added to review.
14 July 2009	New search has been performed	Effectivess searches conducted.
20 May 2008	New search has been performed	Searches conducted in May 2008. For this update we assessed 688 possible studies, retrieved 17 and excluded all of them. Our conclusion did not change but we found non-comparative phase IV evidence from a

(*Continued*)

		thorough review of the evidence on harms by Hama which we mentioned in the Discussion section. Updated review published in issue 2, 2009.
29 April 2008	Amended	Converted to new review format.
19 May 2006	New citation required and conclusions have changed	Substantive amendment published in Issue 3, 2006.
13 October 2005	New search has been performed	Searches conducted in October 2005. We completely revised the text and added a section on evidence from an avian influenza epidemic that took place in the Netherlands in 2003 and claimed one life. We also added a section on post-exposure prophylaxis (PEP) . We dropped studies looking at the effects of neuraminidase inhibitors (NIs) on experimental influenza cases (that is to say, on subjects who had been deliberately infected as part of an experiment) and concentrated on the now numerous studies of naturally-acquired influenza cases. The terms "laboratory-confirmed influenza" and "clinically confirmed influenza" have been changed for the more correct terms "influenza" and "influenza-like-illness" (ILI). We believe these words to reflect the difference between real influenza (caused by influenza A and B viruses) and what is colloquially known as "the flu". The two are rarely clinically distinguishable in real-time unless a very good surveillance apparatus is in place, as in most of the trials in our review. Updated review published in Issue 3, 2006.
24 February 1999	New search has been performed	Review first published in Issue 2, 1999.

CONTRIBUTIONS OF AUTHORS

For the 2009 update Tom Jfferson (TOJ) applied inclusion criteria.

Liz Dooley (ED) and TOJ independently read all titles and studies retrieved in the search and applied inclusion criteria. All authors except Ruth Foxlee (RF) reappraised and investigated extracted data while Chris Del Mar (CDM) supervised the process and arbitrated when necessary.

Mark Jones (MJ) and Peter Doshi (PD) checked and transformed data and supervised the revised meta-analysis.

TOJ and CDM edited the text and together with ED, MJ and PD, contributed to the final draft.

RF developed and conducted the searches for adverse effects studies.

DECLARATIONS OF INTEREST

In 1998 to 1999 Tom Jefferson was an ad hoc consultant for Hoffman LaRoche Ltd. In 2008 to 2009 Chris Del Mar provided expert advice to Glaxo Smith Kline about vaccination against acute otitis media.

SOURCES OF SUPPORT

Internal sources

- The authors' own institutions (2005 update), Italy.
- The author's own institutions (2005 update), Australia.

External sources

- National Instiutue of Health Research (NIHR), UK.

Competitive grant awarded through the Cochrane Collaboration

- National Health and Medical Research Council (NHMRC), Australia.

Competitive grant awarded to Chris Del Mar and Tom Jefferson, 2009

NOTES

This review will not be updated as the review authors are working with the authors of the Cochrane Review 'Neuraminidase inhibitors for preventing and treating influenza in children' to write an amalgamated review 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children'. This new protocol is expected to be published on *The Cochrane Library* by the end of 2010.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [adverse effects; *therapeutic use]; Enzyme Inhibitors [adverse effects; *therapeutic use]; Influenza, Human [*drug therapy; *prevention & control]; Neuraminidase [*antagonists & inhibitors]; Oseltamivir [adverse effects; therapeutic use]; Post-Exposure Prophylaxis; Randomized Controlled Trials as Topic; Zanamivir [adverse effects; therapeutic use]

MeSH check words

Adult; Humans