

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

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[Intervention Review]

Neuraminidase inhibitors for preventing and treating influenza in healthy adults

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ABSTRACT

Background

Neuraminidase inhibitors (NI) are recommended for use against influenza and its complications in interpandemic years and in a pandemic.

Objectives

To assess the effects of NIs in preventing or ameliorating influenza, its transmission and its complications in 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* 2008, issue 2) which contains the Acute Respiratory Infections Group's Specialized Register, MEDLINE (2005 to May, Week 4 2005), and EMBASE (2005 to May 2008).

Selection criteria

Randomised or quasi-randomised placebo-controlled studies of NIs in healthy adults exposed to naturally occurring influenza.

Data collection and analysis

Two review authors 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, 13 treatment and four post-exposure prophylaxis (PEP) trials. In prophylaxis compared to placebo, NIs have no effect against influenza-like illnesses (ILI) (relative risk (RR) 1.28, 95% confidence interval (CI) 0.45 to 3.66 for oral

oseltamivir 75 mg daily; RR 1.51, 95% CI 0.77 to 2.95 for inhaled zanamivir 10 mg daily). The efficacy of oral oseltamivir 75 mg daily against symptomatic influenza is 61% (RR 0.39, 95% CI 0.18 to 0.85), or 73% (RR 0.27, 95% CI 0.11 to 0.67) at 150 mg daily. Inhaled zanamivir 10 mg daily is 62% efficacious (RR 0.38, 95% CI 0.17 to 0.85). Neither NI has a significant effect on asymptomatic influenza. Oseltamivir induces nausea (odds ratio (OR) 1.79, 95% CI 1.10 to 2.93). Oseltamivir for PEP has an efficacy of 58.5% (15.6% to 79.6) for households and of 68% (34.9 to 84.2%) to 89% in contacts of index cases. Zanamivir has similar performance. The hazard ratios for time to alleviation of influenza symptoms were in favour of the treated group 1.33 (1.29 to 1.37) for zanamivir and 1.30 (1.13 to 1.50) for oseltamivir. Viral nasal titres were significantly diminished by both NIs. Oseltamivir 150 mg daily prevented lower respiratory tract complications (OR 0.32, 95% CI 0.18 to 0.57). We could find no comparative data on the effects of oseltamivir on avian influenza.

Authors' conclusions

Because of their low effectiveness, NIs should not be used in routine seasonal influenza control. In a serious epidemic or pandemic, NIs should be used with other public health measures. We are unsure of the generalisability of our conclusions from seasonal to pandemic or avian influenza.

PLAIN LANGUAGE SUMMARY

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

Symptoms include fever, headache and cough. Serious complications such as pneumonia can also occur. This review of trials found that neuraminidase inhibitors (NIs) such as zanamivir and oseltamivir are effective in preventing ("prophylaxis") and treating ("treatment") the symptoms and complications of influenza but do not prevent infection or interrupt voidance of viruses from the nose. Oseltamivir causes nausea, vomiting and retching while zanamivir causes diarrhoea. There is no evidence that NIs may be effective against bird flu. Because of their performance, NI should not be used on their own, but alongside barrier (masks, gloves), personal hygiene and quarantine measures.

BACKGROUND

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 (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).

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. Recently, the World Health Organisation 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 familiarity 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 took a different line, identifying NIs (especially oseltamivir) as compounds with a complementary effect to vaccines to be used in a influenza pandemic (EMA 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

Although several systematic reviews of the effects of NIs are available (Burls 2002; Cooper 2003; Jefferson 2000; Turner 2003), none are up to date and none evaluated the potential role of NIs in an influenza pandemic, where high viral load and high transmission appear to be the norm. 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).

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 randomised or quasi-randomised studies 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

Clinical

Numbers, temporal distribution and/or severity of influenza cases (defined as participants with clinical signs and symptoms of influenza with a positive laboratory diagnosis based on either on antibody titre rises or viral isolation or both) or influenza-like illness cases (ILI, defined as participants with clinical signs and symptoms of influenza) and their complications.

Laboratory

Measures of viral load (such as concentration of influenza viruses excreted by nasal mucous).

Adverse effects

Number and seriousness of adverse effects.

Search methods for identification of studies

Electronic 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.

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.

For this 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).

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.

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

See Appendix 1 for the EMBASE search strategy.

Searching other resources

We also checked the bibliographies of other systematic reviews of the topic (Burls 2002; Cooper 2003; Turner 2003). No language or publication restrictions were applied.

Data collection and analysis

Data analysis

Selection of studies

Two review authors (VD, TOJ) read all trials retrieved in the search and applied inclusion criteria.

Data extraction and management

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

Characteristics of participants

- Number of participants.
- Age, gender, ethnic group, risk category.

Characteristics of interventions

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

Characteristics of outcome measures

- Number and severity of influenza cases in NI and placebo groups.
- Concentration of influenza viruses excreted by nasal mucus.
- Adverse effects: presence and type.
- Date of trial.
- Location of trial.
- Funder of trial (specified, known or unknown).
- Publication status.

Assessment of risk of bias in included studies

Assessment of methodological quality for RCTs was carried out using criteria from the *Cochrane Handbook of Reviews of Interventions* (Higgins 2008). 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.

Data synthesis

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

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 (relative risk) 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).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Prophylaxis trials

We identified four prophylaxis trials, two assessing zanamivir ([Kaiser 2000](#); [Monto 1999a](#)) and two assessing oseltamivir ([Hayden 1999a](#); [Kashiwagi 2000a](#)).

The mean and median zanamivir arm size was 492 individuals (25th percentile 461, 75th percentile 522) and the mean length of follow up was 22 days. The mean oseltamivir arm size was 598 (median 597, 25th percentile 376 and 75th percentile 818 individuals) and the mean length of follow up was 49 days.

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](#)) and five of oseltamivir ([Kaiser 2003](#); [Kashiwagi 2000b](#); [Li 2003](#); [Nicholson 2000](#); [Treanor 2000](#)) fulfilling our inclusion criteria. Two zanamivir trials ([Aoki 2000](#); [Boivin 2000](#)) were linked publications of the [Monto 1999b](#) and [MIST 1998](#) trials. One oseltamivir study included supplementary outcome data from all treatment trials ([Kaiser 2003](#)). One oseltamivir trial ([Li 2003](#)) was linked to two redundant publications ([Li 2001](#); [Longuyn 2004](#)).

The mean zanamivir arm size was 297 individuals (median 250, 25th percentile 149, 75th percentile 340), the mean oseltamivir arm size was 383.8 individuals (median 245, 25th percentile 216, 75th percentile 314) and the mean length of follow up was 26 days for zanamivir and 21 days for oseltamivir.

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 446.54 (25th percentile 422 and the 75th percentile 470). Two further PEP trials assessed zanamivir ([Hayden 2000a](#); [Monto 2002](#)). In both trials, household contacts of an index case with ILI were randomised to either placebo or zanamivir.

A full description of all trials is available in the 'Characteristics of included studies' table.

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, four trials ([Aoki 2000](#); [Boivin 2000](#); [Kaiser 2003](#); [Kashiwagi 2000b](#)) has unclearly described processes, although three ([Aoki 2000](#); [Boivin 2000](#); [Kaiser 2003](#)) 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.

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 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, RR 1.51, 95% CI 0.77 to 2.95 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 61% (RR 0.39, 95% CI 0.18 to 0.85), 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 62% efficacious (RR 0.38, 95% CI 0.17 to 0.85). The addition of an intranasal dose does not seem to significantly enhance its prophylactic activity (RR 0.22, 95% CI 0.08 to 0.58), although again this last observation is based on a single study.

Oseltamivir confers 64% protection against symptomatic and a symptomatic 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 1.63, 95% CI 0.99 to 2.67). 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 intention to treat population) was assessed by 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 ($I^2 = 0\%$). 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). 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 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 intention to treat 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 ($I^2 = 0$). 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 (1.22, 95% CI 1.07 to 1.39) although this observation is based on a single study (Treanor 2000). There was no evidence of heterogeneity ($I^2 = 0\%$). 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 ($I^2 = 34.6\%$) 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. Treatment did not, however, 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.

Oseltamivir 150 mg daily is effective in preventing lower respiratory tract complications in influenza cases (OR 0.32, 95% CI 0.18 to 0.57), especially bronchitis (OR 0.40, 95% CI 0.21 to 0.76) and pneumonia (OR 0.15, 95% CI 0.03 to 0.69), but not in ILI cases (OR 0.21, 95% CI 0.02 to 2.04). Both NIs are effective in preventing complications of all types in the intention-to-treat (ITT) population (OR 0.49, 95% CI 0.38 to 0.62), although these observations are based on single studies (Kaiser 2003; Makela 2000) the combined denominator is fairly substantial (2991).

NIs are not associated with any adverse event in a treatment role, although this may be due to the difficulty in separating adverse events from the symptoms of influenza and to the relatively small denominators in the analysis. Finally, use of relief medications and antibiotics is unaffected by assumption of NIs (OR 0.81, 95% CI 0.59 to 1.12).

DISCUSSION

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.

Role of NIs in avian influenza

We identified no comparative evidence of the role of NIs in avian influenza. 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 symptoms onset (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 8 to 35 (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. Finally, the inability of the NIs to prevent infection and to sup-

press viral nasal excretion raise 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 association with 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 of serious neuropathic cases received since the 2001 launch of the drug. However it is estimated that 9 million doses had been sold since 2001, making such harms (even if proven) rare.

AUTHORS' CONCLUSIONS

Implications for practice

NIs are not recommended for routine use in seasonal influenza.

In exceptional circumstances they could be used as an adjunct to 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.

Implications for research

Larger trials are required to assess the effects of NIs in epidemic influenza, especially their impact on complications and deaths. Further research on the possible effects of NIs on avian influenza subtypes is also required. We recommend that any recipient should be followed up with prospective surveillance. As Hama suggests (Hama 2008) the burden of causality be further clarified by a well-conducted and adequately powered case-control study.

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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. The Monto 99c
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 (e.g., 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	<p>Serological: Serum samples were collected on days 1 and 21, and assayed for the presence of anti-influenza antibodies by haemagglutination inhibition</p> <p>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</p> <p>The clinical efficacy of Zanamivir and was reported is the Monto 99c trial. Safety outcomes are not reported</p>
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
<i>Risk of bias</i>	
Item	Authors' judgement Description

Aoki 2000 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Boivin 2000

Methods	Double-blind, randomised, placebo controlled, multicentre 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 multicentre 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 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 attend 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 (Table 3)
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

Hayden 1999a (Continued)

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 37.2C or more with at least one respiratory (cough, sore throat, coryza) or one constitutional symptom (aches, fatigue, headache, chills, sweats) Safety: study withdrawals: 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

Hayden 2000a (Continued)

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
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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 randomized 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)

Hayden 2004 (Continued)

	<p>Percentage of households with at least 1 secondary case of ILI during the 10-day period after the start of treatment in the ICs</p> <p>Both outcomes were also calculated for individual contacts and for children aged 1 to 12 years.</p> <p>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)</p> <p>Efficacy analyses were carried out for:</p> <p>intention-to-treat index-infected (ITTII) population defined as those households and contacts of laboratory-confirmed, influenza-infected ICs.</p> <p>Subpopulation of contacts who were virus-negative at baseline (ITTIINAB)</p> <p>Overall intention-to-treat (ITT) population (all randomized households and contacts, regardless of infection status in the IC).</p> <p>Safety:</p> <p>withdrawals</p> <p>nausea</p> <p>vomiting</p> <p>The data for children aged 1 to 12 were not extracted</p>
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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
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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	<p>Participants were randomised to four treatment groups:</p> <ol style="list-style-type: none"> 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

Kaiser 2000 (Continued)

	All were self administered for 5 days	
Outcomes	<p>Serological/laboratory: serum samples (days 1 and 21) and viral upper airways samples were taken</p> <p>Effectiveness: six point scale of influenza like symptoms ILI, including: - headache sore throat feverishness, muscle aches, cough, nasal congestion, weakness loss of appetite</p> <p>Observations were recorded twice daily for 10 days</p> <p>Safety: no detailed outcome data are reported</p>	
Notes	<p>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.</p> <p>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</p>	
Risk of bias		
Item	Authors’ judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kaiser 2003

Methods	Report of complications outcomes from ten placebo controlled RCTs of oseltamivir from the Roche clinical studies database. Only three are from healthy adult populations and are included in this review. Methods are those of the relevant studies. The studies were conducted in 1997-1998 in northern and southern hemispheres. 68% of the participants had influenza, predominantly H3N2, while 12% had influenza B. For further information see Treanor 2000 and Nicholson 2000
Participants	
Interventions	
Outcomes	
Notes	

Kaiser 2003 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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	<p>Serological: viral antibody titres</p> <p>Effectiveness: Group 1: participants with fever of 37.5C or more and at least two other influenza symptoms with laboratory confirmed influenza Group 2: participants without fever of 37.5C 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</p> <p>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 adv 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</p>	
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

Kashiwagi 2000a (Continued)

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 intention to treat infected (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	<p>Serological: viral antibody titres</p> <p>Effectiveness: time to resolution of illness (ITTI) time to resolution of symptoms (ITTI) cases of influenza (ITTI) influenza viral titre severity (symptom scores)</p> <p>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.</p> <p>An extensive list of laboratory and diagnostic tests is reported</p>
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

Kashiwagi 2000b (Continued)

<i>Risk of bias</i>		
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 37.8C 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 intention- to- treat population (ITT) (216 oseltamivir and 235 placebo) with 273 individuals were identified as influenza infected through laboratory test and were regarded as the intention- to- treat infected population (ITTI) (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	<p>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)</p> <p>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</p> <p>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)</p>

Li 2003 (Continued)

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
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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	<p>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</p> <p>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</p> <p>Safety: bronchitis sinusitis diarrhoea pharyngitis nausea and vomiting pneumonia</p>

Makela 2000 (Continued)

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	
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	<p>Serological: serology and virological samples were taken and influenza viruses identified with PCR.</p> <p>Effectiveness: participants were instructed in the use of diaries to record symptoms.</p> <p>- 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).</p> <p>- Time to resumption of normal activities</p> <p>Safety: possible adverse events hoarse voice, headache, diarrhoea</p>	

Matsumoto 1999 (Continued)

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-Meier plots (time to resumption of normal activities). Average reporting quality but randomisation and double blinding are not described
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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 37.8C or feverishness or both and at least two of the following myalgia, sore throat, cough, headache). There were 76 participants (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

MIST 1998 (Continued)

	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 C with a rise in antibody titres and/or viral isolation febrile illness if only temp of at least 37.8 C Safety is not mentioned in detail, only as any adverse event	

Monto 1999a (Continued)

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 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	<p>Serological: serum assays at days 1 and 21 and viral isolation from airways</p> <p>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</p> <p>Safety Diarrhoea</p>

Monto 1999b (Continued)

	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 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	
<i>Risk of bias</i>		
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)
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 (e.g. general well-being, use of relief medication etc) for which data were apparently collected

Risk of bias

Puhakka 2003 (Continued)

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 38C 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. Convuluted reporting and extensive use of medians may lead to loss of important data

Risk of bias

Item	Authors' judgement	Description
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 37.2C 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

d = day

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

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 97-99 registration studies already in review
Bijl 2007	No data presented
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
Kawai 2005	Prospective cohort study non comparative with all oseltamivir exposure
Kawai 2006	Non comparative cohort study
Kawai 2007a	Prospective cohort study all treated with zanamivir
Kawai 2007b	Retrospective cohort
Kawai 2007c	Non comparative study with sole exposure to oseltamivir
Kawai 2008	Prospective cohort study with oseltamivir vs nothing
LaForce 2007	Placebo controlled RCT in elderly
Li 2001	Same data set as Li 2003
Lin 2006	V small RCT high risk oselt vs do-nothing
Longuyn 2004	Redundant publication of Li 2003

(Continued)

Macfarlane 2005	Editorial
Massarella 2000	Phase 2a study with no safety outcomes reported
Monto 1999	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 Os, Zaamavir do nothing
Sato 2008	Prospective cohort study in children

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)	1.20 [0.77, 1.87]
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)	1.51 [0.77, 2.95]
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)	0.41 [0.25, 0.65]
2.1 Oral oseltamivir 75 mg daily	2	1087	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.18, 0.85]
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)	0.38 [0.17, 0.85]
2.4 Intranasal zanamivir 0.32 mg daily	1	189	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.54, 2.08]
2.5 Inhaled and intranasal zanamivir 10 mg and 0.32 daily	1	194	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.08, 0.58]
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)	0.93 [0.57, 1.51]
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)	1.63 [0.99, 2.67]
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 - bronchitis (ILI cases only)	1	714	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.35, 2.20]
5.1 Oseltamivir 150 mg daily	1	714	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.35, 2.20]

6	Complications - bronchitis (influenza cases only)	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.76]
6.1	Oseltamivir 150 mg daily	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.76]
7	Complications - all lower respiratory tract complications (ILI cases only)	1	714	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.30, 1.58]
7.1	Oseltamivir 150 mg daily	1	714	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.30, 1.58]
8	Complications - all lower respiratory tract complications (influenza cases only)	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.18, 0.57]
8.1	Oseltamivir 150 mg daily	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.18, 0.57]
9	Complications - pneumonia (ILI cases only)	1	714	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.02, 2.04]
9.1	Oseltamivir 150 mg daily	1	714	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.02, 2.04]
10	Complications - pneumonia (influenza cases only)	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.15 [0.03, 0.69]
10.1	Oseltamivir 150 mg daily	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.15 [0.03, 0.69]
11	Complications - all hospitalisations (ILI cases only)	1	714	Odds Ratio (M-H, Random, 95% CI)	2.25 [0.46, 10.92]
11.1	Oseltamivir 150 mg daily	1	714	Odds Ratio (M-H, Random, 95% CI)	2.25 [0.46, 10.92]
12	Complications - all hospitalisations (influenza cases only)	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.10, 1.69]
12.1	Oseltamivir 150 mg daily	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.10, 1.69]
13	Complications - hospitalisations possibly caused by influenza (ILI cases only)	1	714	Odds Ratio (M-H, Random, 95% CI)	4.50 [0.23, 87.40]
13.1	Oseltamivir 150 mg daily	1	714	Odds Ratio (M-H, Random, 95% CI)	4.50 [0.23, 87.40]
14	Complications - hospitalisations possibly caused by influenza (influenza cases only)	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.02, 2.16]
14.1	Oseltamivir 150 mg daily	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.02, 2.16]
15	Complications - all types (ILI cases only)	2	1070	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.43, 0.90]
15.1	Oseltamivir 150 mg daily	1	714	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.37, 1.23]
15.2	Zanamivir	1	356	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.95]
16	Complications - all types (influenza cases only)	2	1921	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.21, 0.90]
16.1	Oseltamivir 150 mg daily	1	1644	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.20, 0.46]
16.2	Zanamivir	1	277	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.38, 1.08]
17	Complications - all types (ITT)	2	2714	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.56]
17.1	Oseltamivir 150 mg daily	1	2358	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.28, 0.55]
17.2	Zanamivir	1	356	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.32, 0.76]
18	Adverse events - cough	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
18.1	Zanamivir	2	1043	Odds Ratio (M-H, Random, 95% CI)	1.40 [0.14, 13.49]
18.2	Oral oseltamivir 150 mg daily	1	273	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.53, 3.22]
19	Adverse events - headache	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
19.1	Zanamivir	2	1352	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.39, 1.97]
19.2	Oral oseltamivir 150 mg daily	1	273	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.45, 2.05]
20	Adverse events - diarrhoea	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

20.1 Zanamivir	4	2415	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.37, 1.63]
20.2 Oral oseltamivir 150 mg daily	1	313	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.28, 1.13]
21 Adverse events - nasal symptoms (congestion, rhinitis, dry or sore throat)	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 Zanamivir	3	2299	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.47, 2.06]
21.2 Oral oseltamivir 150 mg daily	1	273	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.51, 1.44]
22 Adverse events - nausea	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 Zanamivir	3	2067	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.10]
22.2 Oral oseltamivir 150 to 300 mg daily	2	928	Odds Ratio (M-H, Random, 95% CI)	1.80 [0.73, 4.41]
23 Adverse events - bronchitis or pneumonia	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
23.1 Zanamivir	3	2299	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.24, 2.26]
24 Adverse events - all types	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 Zanamivir	3	1159	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.69, 1.14]
24.2 Oral oseltamivir 150 mg daily	1	313	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.43, 1.05]
25 Use of relief medications and antibiotics	4	1830	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.60, 1.11]
25.1 Zanamivir	2	838	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.41, 1.01]
25.2 Oseltamivir	2	992	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.67, 1.52]
26 Mean nasal viral titres (at 24 hours since randomisation)	4	1002	Mean Difference (IV, Random, 95% CI)	-0.62 [-0.82, -0.41]
26.1 Zanamivir 10 to 20 mg daily	2	441	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.75, -0.06]
26.2 Oseltamivir 75 to 150 mg daily	2	561	Mean Difference (IV, Random, 95% CI)	-0.73 [-0.99, -0.47]
27 Mean nasal viral titres (at 48 hours since randomisation)	3	659	Mean Difference (IV, Random, 95% CI)	-0.63 [-1.13, -0.13]
27.1 Zanamivir 10 to 20 mg daily	2	441	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.58, 0.16]
27.2 Oseltamivir 150 mg daily	1	218	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.74, -0.14]

WHAT'S NEW

Last assessed as up-to-date: 19 May 2008.

22 May 2008	New search has been performed	For the 2008 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 thorough review of the evidence on harms by Hama which we mentioned in the Discussion
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HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 2, 1999

29 April 2008	Amended	Converted to new review format.
15 May 2006	New citation required and conclusions have changed	Substantive amendment
12 October 2005	New search has been performed	In the 2005 update 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.
23 February 1999	New search has been performed	Review first published Issue 2, 1999

CONTRIBUTIONS OF AUTHORS

For the 2006 update TOJ and DR applied inclusion criteria and extracted data while VD supervised extraction and arbitrated when necessary.

MJ and CD checked and transformed data and supervised the revised meta-analysis.

TOJ edited the text and all authors contributed.

DECLARATIONS OF INTEREST

In 1998 to 1999 Dr Jefferson was an ad hoc consultant for Hoffman LaRoche Ltd.

Please refer to Appendix 2 for a glossary of terms.

SOURCES OF SUPPORT

Internal sources

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

External sources

- Ministry of Defence (1999 review), UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetamides [therapeutic use]; Amines [therapeutic use]; Antiviral Agents [*therapeutic use]; Enzyme Inhibitors [*therapeutic use]; Guanidines [therapeutic use]; Influenza, Human [*drug therapy; *prevention & control]; Neuraminidase [*antagonists & inhibitors]; Oseltamivir; Pyrans [therapeutic use]; Sialic Acids [therapeutic use]; Zanamivir

MeSH check words

Humans