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Neuraminidase inhibitors for preventing and treating influenza in children (published trials only) (Review)

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[Intervention Review]

Neuraminidase inhibitors for preventing and treating influenza in children (published trials only)

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ABSTRACT

Background

During epidemics, influenza attack rates in children may exceed 40%. Options for prevention and treatment currently include the neuraminidase inhibitors zanamivir and oseltamivir. Laninamivir octanoate, the prodrug of laninamivir, is currently being developed.

Objectives

To assess the efficacy, safety and tolerability of neuraminidase inhibitors in the treatment and prevention of influenza in children.

Search methods

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 1) which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to January week 2, 2011) and EMBASE (January 2010 to January 2011).

Selection criteria

Double-blind, randomised controlled trials (RCTs) comparing neuraminidase inhibitors with placebo or other antiviral drugs in children aged up to and including 12 years. We also included safety and tolerability data from other types of studies.

Data collection and analysis

Four review authors selected studies, assessed study quality and extracted data for the current and previous versions of this review. We analysed data separately for oseltamivir versus placebo, zanamivir versus placebo and laninamivir octanoate versus oseltamivir.

Main results

Six treatment trials involving 1906 children with clinical influenza and 450 children with influenza diagnosed on rapid near-patient influenza testing were included. Of these 2356 children, 1255 had laboratory-confirmed influenza. Three prophylaxis trials involving 863 children exposed to influenza were also included. In children with laboratory-confirmed influenza oseltamivir reduced median duration of illness by 36 hours (26%, P < 0.001). One trial of oseltamivir in children with asthma who had laboratory-confirmed influenza showed only a small reduction in illness duration (10.4 hours, 8%), which was not statistically significant (P = 0.542). Laninamivir octanoate 20 mg reduced symptom duration by 2.8 days (60%, P < 0.001) in children with oseltamivir-resistant influenza A/H1N1. Zanamivir reduced median duration of illness by 1.3 days (24%, P < 0.001). Oseltamivir significantly reduced acute otitis media in children aged one to five years with laboratory-confirmed influenza (risk difference (RD) -0.14, 95% confidence interval (CI) -0.24 to -0.04). Prophylaxis with either zanamivir or oseltamivir was associated with an 8% absolute reduction in developing influenza after the introduction of a case into a household (RD -0.08, 95% CI

-0.12 to -0.05, P < 0.001). The adverse event profile of zanamivir was no worse than placebo but vomiting was more commonly associated with oseltamivir (number needed to harm = 17, 95% CI 10 to 34). The adverse event profiles of laninamivir octanoate and oseltamivir were similar.

Authors' conclusions

Oseltamivir and zanamivir appear to have modest benefit in reducing duration of illness in children with influenza. However, our analysis was limited by small sample sizes and an inability to pool data from different studies. In addition, the inclusion of data from published trials only may have resulted in significant publication bias. Based on published trial data, oseltamivir reduces the incidence of acute otitis media in children aged one to five years but is associated with a significantly increased risk of vomiting. One study demonstrated that laninamivir octanoate was more effective than oseltamivir in shortening duration of illness in children with oseltamivir-resistant influenza A/H1N1. The benefit of oseltamivir and zanamivir in preventing the transmission of influenza in households is modest and based on weak evidence. However, the clinical efficacy of neuraminidase inhibitors in 'at risk' children is still uncertain. Larger high-quality trials are needed with sufficient power to determine the efficacy of neuraminidase inhibitors in preventing serious complications of influenza (such as pneumonia or hospital admission), particularly in 'at risk' groups.

PLAIN LANGUAGE SUMMARY

Neuraminidase inhibitors for preventing and treating influenza in children

Influenza (true 'flu) is an infection of the airways caused by the Influenza group of viruses. Influenza occurs most commonly during winter months and can result in symptoms such as fever, cough, sore throat, headache, muscle aches and fatigue. These are usually self limiting but may persist for one to two weeks. The most common complications of influenza are secondary bacterial infections including otitis media (ear infections) and pneumonia. Influenza infection is also highly contagious and is spread from person-to-person by droplets produced when an infected individual coughs or sneezes.

This update reviews the randomised controlled trial evidence of a class of drugs called the neuraminidase inhibitors in treating and preventing influenza in children. Neuraminidase inhibitors work against influenza by preventing viruses from being released from infected cells and subsequently infecting further cells. Oseltamivir (Tamiflu), an oral medication, and zanamivir (Relenza), an inhaled medication, are currently licensed, whilst laninamivir is undergoing Phase III clinical trials. Neuraminidase inhibitors are usually prescribed to patients presenting with flu-like symptoms during epidemic periods to reduce symptoms or prevent spread of the virus.

We included six treatment trials involving 1906 children with clinically suspected influenza and 450 children with influenza diagnosed on rapid influenza testing. Of these 2356 children, 1255 had proven influenza infection confirmed on laboratory testing. We also included three trials of neuraminidase inhibitors for the prevention of influenza, which involved 863 children who had been exposed to influenza.

This review found that treatment with neuraminidase inhibitors was only associated with modest clinical benefit in children with proven influenza. Treatment with oseltamivir or zanamivir shortened the duration of illness in healthy children by about one day. One trial demonstrated that the new neuraminidase inhibitor drug laninamivir reduces duration of illness by almost three days in children with oseltamivir-resistant influenza. The effect of neuraminidase inhibitors in preventing transmission of influenza was also modest; 13 children would need to be treated to prevent one additional case. Neuraminidase inhibitors are generally well tolerated but there will be one extra case of vomiting for every 17 children treated with oseltamivir. Other side effects such as diarrhoea and nausea were no more common in children treated with neuraminidase inhibitors compared to placebo. There is currently no high-quality evidence to support targeted treatment of 'at risk' children (with underlying chronic medical conditions) with neuraminidase inhibitors.

BACKGROUND

Description of the condition

Influenza virus is an important cause of illness among children and during seasonal epidemics, influenza attack rates often exceed 40% in preschool children (Glezen 1978). Influenza viruses are transmitted primarily through droplet transmission and contact with infected respiratory secretions. School age children are the main source of introducing influenza into the household (Longini 1982).

The unique epidemiology of influenza is due to the ability of the virus to change its antigenic coat either slowly by mutation driven drift or suddenly by re-assortment driven antigenic shift (usually within duck and pig reservoirs in Southern China). It is the latter phenomenon that may give rise to a pandemic such as the recent H1N1.

In some epidemic years, up to a quarter of emergency department admissions will be children with fever or respiratory symptoms with laboratory evidence of influenza (Poehling 2006). Although hospitalisation rates attributable to influenza are important, outpatient visits associated with influenza are some five to 250 times as common. For instance, in the 2003 to 2004 season, the estimated burden of USA outpatient visits associated with influenza was 95 clinic visits and 27 emergency department visits per 1000 children under the age of five (Poehling 2006).

Complications of influenza are common in children and include upper respiratory tract infections (otitis media, sinusitis, bronchitis, bronchiolitis, croup), febrile convulsions and exacerbations of asthma. For example, acute otitis media occurs after influenza in 20% to 50% of children under six, with the highest incidence in children less than two years of age (Belshe 1998; Neuzil 2002). In the 2009 H1N1 pandemic, almost one in three cases of influenza in the UK were in children aged under 10 (HPA 2009). In addition, children with certain chronic medical conditions are at greater risk of developing complications of influenza and children born prematurely are considerably more likely to be hospitalised with respiratory complications than healthy children during influenza seasons (Izurieta 2000). Influenza causes substantial burden on health care and socioeconomic resources. Nationally in the US, the total number of workdays missed yearly by caregivers of children who attended Emergency Department for influenza infections approaches quarter of a million days (Bourgeois 2009). Influenza vaccination is recommended in individuals considered to be at increased risk of serious illness as a result of influenza infection (DoH 2007). However, vaccine coverage may be low, especially during the early stages of an influenza pandemic. In children with asthma, vaccine coverage has been reported to be as low as 15% to 30% (Esposito 2008).

Many simple and low-cost interventions, such as handwashing and wearing masks, reduce the transmission of epidemic respiratory viruses (Jefferson 2009b). Antiviral medications have been used to reduce transmission and treat infected individuals. Neuraminidase inhibitors are recommended for the treatment and prophylaxis of influenza because the efficacy of other antivirals, such as amantadine and rimantadine, are limited by drug resistance (Jefferson 2009a). Oseltamivir (Tamiflu®) is administered orally and is licensed for the treatment and post-exposure prophylaxis of influenza in children aged over one and who have been symptomatic for no more than two days. Zanamivir (Relenza®) is inhaled as a dry powder and is licensed for treatment and post-exposure prophylaxis of influenza in children aged five and over within 36 hours of onset of symptoms (NICE 2009). Laninamivir octanoate (CS-8958) is currently being developed by Daiichi Sankyo Co Ltd. (Tokyo, Japan). It is the pro-drug of laninamivir, a long-acting neuraminidase inhibitor, which has been shown to have in vitro neuraminidase-inhibitory activity against various influenza A and B viruses, including subtypes of N1 to N9 and oseltamivir resistant viruses (Yamashita 2009). Laninamivir octanoate is administered as a single inhaled dose.

Description of the intervention

Zanamivir (GlaxoSmithKline), administered by inhalation via a Diskhaler(R), is indicated in the UK for the treatment of influenza in children aged five years and older who present with symptoms of influenza when influenza is known to be circulating in the community. It is also indicated for post-exposure prophylaxis in the same age group and for seasonal prophylaxis in children aged over 12 years.

Oseltamivir (Roche), administered orally, is indicated in the UK for the treatment of influenza in children aged one year and older who present with influenza-like symptoms when influenza is known to be circulating. It is also indicated for post-exposure prophylaxis and seasonal prophylaxis in the same age group.

Development of peramivir (BioCryst) was discontinued following initial findings from a phase III clinical trial in adults which demonstrated no statistical difference in relief of influenza symptoms between peramivir (BioCryst 2002). No paediatric patients were enrolled in trials of the drug (A.K. Schleusner, BioCryst, personal communication, 2002).

Recently, a newer drug, laninamivir octanoate (CS-8958, Daiichi Sankyo Co. Ltd. Tokyo, Japan) has undergone studies for the treatment and prophylaxis of influenza A and B in children (Sugaya 2010; Yamashita 2009). Laninamivir octanoate is administered as a single inhaled dose, after which it is converted to laninamivir, a potent and long-acting neuraminidase inhibitor.

How the intervention might work

Drug inhibition of the enzyme neuraminidase interrupts the propagation of both influenza A and B viruses within the respiratory tract. Neuraminidase inhibitors have been used for prophylaxis and therapeutic treatment of influenza A and B.

Why it is important to do this review

The last update of this Cochrane review was in 2005 and included three treatment trials and one prophylaxis trial (Matheson 2007a). In addition to this we published an update in 2009 in the BMJ (Shun-Shin 2009), including four randomised controlled trials (RCTs) of treatment of influenza (two with oseltamivir, two with zanamivir) involving 1766 children (1243 with confirmed influenza, of whom 55% to 69% had influenza A) and three RCTs for prophylaxis (one with oseltamivir, two with zanamivir) involving 863 children. None of these trials tested efficacy with the H1N1 pandemic and at the time of the BMJ review we were aware of seven RCTs currently underway, six being treatment trials and one a prophylaxis trial.

As children have a differing burden of disease and a number of trials of neuraminidase inhibitors are due to report with potentially differing efficacy, safety and tolerability profile, this review will appraise trials of zanamivir, oseltamivir and laninamivir in children aged 12 years and under.

OBJECTIVES

To assess the efficacy, safety and tolerability of neuraminidase inhibitors in the treatment and prevention of symptomatic influenza in children aged 12 years and under.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind randomised controlled trials (RCTs) comparing neuraminidase inhibitors with placebo or other antiviral drugs for preventing and treating influenza in children aged 12 years and younger.

Types of participants

Children aged 12 years and under. For studies examining the efficacy of influenza treatment, we stipulated that the participants must have: a clinical diagnosis of influenza (temperature above 37.8 °C; at least two of the following symptoms: cough, headache, myalgia, sore throat or fatigue; absence of another confirmed viral or bacterial infection) made by a healthcare professional in a community in which there was an influenza outbreak with or without laboratory or near-patient test confirmation of influenza.

For studies examining efficacy of prophylaxis, we stipulated that participants must meet all the following criteria: residence in a community in which there is an influenza outbreak; prophylaxis administered before the onset of influenza-like illness; laboratory or near-patient test confirmation of influenza.

We excluded studies involving participants recruited from inpatient settings.

Types of interventions

Neuraminidase inhibitors (oseltamivir, zanamivir, peramivir and laninamivir) for treatment and prophylaxis of influenza.

Types of outcome measures

We assessed outcomes in all eligible participants recruited to the studies, as well as those participants in whom influenza infection was later confirmed by laboratory testing of microbiological samples or serology.

Primary outcomes

The primary outcome measures for treatment were:

1. time to resolution of illness. We defined resolution of illness as the resolution of symptoms (cough, headache, myalgia, sore throat, fatigue, fever) together with return to usual activities;
2. return to normal activity or school;
3. time to resolution of symptoms; and
4. the incidence of complications (e.g. acute otitis media, pneumonia, death).

The primary outcome measure for prophylaxis was the attack rate of symptomatic influenza infection in participants in a community in which influenza was known to be circulating.

Outcome measures for adverse events were:

1. incidences of treatment discontinuation/study withdrawal; and
2. local and systemic events recorded in clinical trials.

Secondary outcomes

Secondary outcome measures for treatment were:

1. symptom scores;
2. highest daily temperature;
3. sleep disturbance;
4. rescue medication (e.g. paracetamol or other antipyretic);
5. antibiotic use; and
6. admission to hospital.

For children with asthma, subjective and objective data on associated symptoms (such as reported exacerbations and lung function tests) were reported.

Search methods for identification of studies

We updated our electronic search from the previous update in 2005 to January 2011. In this review update, we have only added data reported in published studies. We did not apply any language restrictions to our search.

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 1, part of *The Cochrane Library* (www.thecochranelibrary.com (accessed 25 January 2011)) which includes the Acute Respiratory Infections Group's Specialised Register, DARE and HEED, MEDLINE (April 2005 to January week 2, 2011) and EMBASE (January 2010 to January 2011). Details of the previous searches are in Appendix 1.

We used the following search strategy to search MEDLINE, CENTRAL, DARE and HEED. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). The search was adapted to search EMBASE (see Appendix 2).

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 (influenza* or flu).tw.
5 or/1-4
6 Oseltamivir/
7 Zanamivir/
8 neuraminidase inhibitor*.tw.
9 (oseltamivir or zanamivir or tamiflu or relenza or peramivir or laninamivir or gs4071).tw,nm.
10 or/6-9
11 5 and 10

Searching other resources

The following only applies to the previous update of this Cochrane review. Other resources were searched as outlined below. We

searched the online GlaxoSmithKline Clinical Trials Register for studies relating to "Zanamivir or Relenza", and the online Roche Clinical Trial Protocol Registry and Clinical Trial Results Database for studies relating to "Oseltamivir or Tamiflu".

We also searched the following databases for completed trials or trials in progress: the International Standard Randomised Controlled Trial Number Registry, the National Health Service Research and Development Health Technology Assessment Programme, the National Institutes of Health Randomized Controlled Trial Records, and the Current Controlled Trials register (http://www.controlled-trials.com/).

We also searched the web sites of the UK Medicine and Healthcare Regulatory Authority (UK MHRA), and the US Food and Drug Administration (FDA) (http://www.fda.gov), and associated "MedWatch" safety advisories (http://www.fda.gov/medwatch), and the European Medicines Agency (EMEA) (http://www.emea.europa.eu) for references to additional trials, data and post-marketing reports of adverse events (accessed 30 June 2010).

In addition we searched the bibliographies of all included trials, and other systematic reviews (Burch 2008; Tappenden 2009).

Data collection and analysis

Selection of studies

Two previous review authors performed the initial searches and screened the titles and abstracts to generate a broad list of studies for possible inclusion, obtained the full article and translation of appropriate passages if needed. They assessed the quality of the studies and made a decision on inclusion or exclusion. Two review authors (KW, PG) repeated this process for additional studies found in the updated search performed in January 2011.

Data extraction and management

Two previous review authors independently extracted data using standardised data extraction forms. They included articles and resolved disagreements by discussion if unsolved after contacting authors or manufacturers. Two review other authors (KW, PG) repeated this process for additional studies found by the updated search performed in January 2011.

Assessment of risk of bias in included studies

Two previous review authors initially assessed the quality of the controlled trials using the Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011). Two other review authors (KW, PG) repeated this process for additional studies found by the updated search performed in January 2011. They assessed studies for: adequate sequence generation, allocation concealment, blinding, how incomplete outcome data were addressed, if they were free of selective reporting and if there were any other potential sources of bias.

We documented the methodological quality of studies by the following criteria: baseline differences between experimental groups, diagnostic criteria used, length of follow-up and prevalence of vaccination. We also identified and documented deviations from an intention-to-treat (ITT) analysis.

Measures of treatment effect

Our primary outcome measure (time to resolution of influenza illness) does not follow a normal distribution: the majority of people get better within a certain time frame and few have persisting symptoms for many more days. Therefore, the median provides a better assessment of clinical effect (a specified percentage will be better within a certain number of days). However, the mean may be more useful in assessing the economic cost of lost days over populations. Secondary outcomes such as secondary complications and adverse events are reported as dichotomous outcomes.

Unit of analysis issues

Prophylaxis studies of influenza were randomised by household after the introduction of an index case. As this review focuses on the treatment of children, we obtained individual attack rate data where possible.

Dealing with missing data

Our primary analysis was by ITT. Where statistics such as the standard deviation (SD) or confidence intervals (CIs) were not available, we contacted trial authors or manufacturers for further information.

Assessment of reporting biases

We did not undertake a formal method of assessing reporting bias such as a funnel plot as only a small number of high-quality trials were found for treatment and post-exposure prophylaxis.

Data synthesis

Primary endpoints for all treatment studies (time to resolution of illness, time to resolution of symptoms) were reported as medians with 95% CI if available. We calculated risk differences (RD) and 95% CIs for dichotomous outcomes and used the I^2 statistic to measure the level of statistical heterogeneity for each outcome. We performed a random-effects meta-analysis when no heterogeneity was detected. We considered possible explanations for substantial heterogeneity (I^2 statistic > 50%) and considered not combining results. We used sensitivity analysis when necessary to investigate the contribution of individual trials to any heterogeneity. Subgroup analyses included type of neuraminidase inhibitor and children with clinical or confirmed influenza. We used Review Manager version 5.1 (RevMan 2011) for statistical analysis.

RESULTS

Description of studies

Results of the search

Our electronic search retrieved 3716 articles excluding duplicates. A search of the GlaxoSmithKline Clinical Trial Register and Roche Clinical Trial Results Database identified two further unpublished trials (NAI30028; NV16871) and one in progress trial of neuraminidase in the treatment of influenza infection in children (NV20234).

Roche has previously supplied eight conference presentations providing data from trials WV15758 (Hayden 2000; Reisinger 2000a; Whitley 2000a; Whitley 2000b; Winther 2000), WV15759/WV15871 (Whitley 2000a) and WV16193 (Belshe 2001; Hayden 2002) and a

conference presentation reporting a pooled analysis of safety data from controlled trials of oseltamivir in children and adults (Waskett 2001).

GlaxoSmithKline has previously supplied a conference presentation providing data from trial NAI30010 (Hayden 1999). In addition, subgroup data for children aged 12 years and under, allowing for the inclusion of two new trials (NAI30031 (Monto 2002), NAI30010) in this review.

In total we independently reviewed 54 full-text articles, including eight RCTs of neuraminidase inhibitors compared to placebo. Of these five were treatment trials and three were post-exposure prophylaxis trials. In addition we found one trial of laninamivir octanoate compared to oseltamivir (Sugaya 2010). In total, we included nine studies in our systematic review.

Limitations of the available literature

We were unable to find any RCTs that compared the intervention against current practice or best management, such as use of antipyretics or analgesics. We were also unable to find any studies where neuraminidase inhibitors were compared in the context of acute asthma exacerbations to optimisation of their asthma medications.

Oseltamivir is not licensed for use in children under 12 months of age (FDA 2006). We were unable to find any trials in this age group but two case series we found which were excluded from the analysis (Okamoto 2005; Tamura 2005). We were unable to find any completed trials of neuraminidase inhibitors in pandemic influenza. One study comparing a low and high dose of oseltamivir in the treatment of severe influenza and avian influenza had been completed (ISRCTN43083885) but no publications were available for this trial apart from one case report (de Jong 2005).

Details of all included and excluded studies can be found in the Characteristics of included studies and Characteristics of excluded studies tables.

Included studies

RCTs of the treatment of influenza in children with zanamivir

NAI30009 assessed the efficacy, safety and tolerability of a five-day course of zanamivir 10 mg inhaled twice daily via Diskhaler(R) (total daily dose 20 mg) compared to placebo for five days in 471 children aged between five and 12 years old with influenza-like symptoms. It was an international multi centre trial, conducted between January and April 1999 (Table 1).

NAI30028 assessed the efficacy, safety and tolerability of a five-day course of zanamivir 10 mg inhaled twice daily via Diskhaler(R) (total daily dose 20 mg) compared to placebo for five days. Included participants were required to have a positive influenza result on near-patient testing ("Influenza-Quick-Test"). The study recruited 266 children aged five to 12 years between January 2000 and April 2001 across 45 centres in Germany. This study has not been published in a peer-reviewed journal; GlaxoSmithKline did not provide any additional methodology information to that supplied in the online trial registry. However, they did supply additional subgroup data (Table 2).

RCTs of the treatment of influenza in children with oseltamivir

WV15758 assessed the efficacy, safety and tolerability of a twice-daily oral course of 2 mg/kg/dose of oseltamivir or placebo for five days in children with influenza-like symptoms. They recruited 695 children between the ages of one and 12 years presenting within 48 hours of the onset of influenza-like symptoms during the 1998/99 influenza season (Table 3). Winther 2010 was a retrospective analysis of the 452 trial participants with laboratory-confirmed influenza to compare the incidence and course of acute otitis media in children treated with oseltamivir compared to placebo.

WV15759/WV15871 (two codes were assigned as the study was rolled over for a second influenza season due to low recruitment) assessed the efficacy, safety and tolerability of a twice-daily oral course of 2 mg/kg/dose of oseltamivir or placebo in a multinational study of 234 children in the Northern and Southern hemispheres with asthma who presented with influenza-like symptoms. The primary endpoint (time to resolution of illness) and conduct of the trial were the same as in WV15758. However, there were additional asthma-related secondary endpoints (Table 4).

Heinonen 2010 was a double-blind, randomised, placebo-controlled trial conducted in Turku, Finland, assessing the efficacy of oseltamivir treatment started within 24 hours of symptom onset in children aged one to three years with laboratory-confirmed influenza (n = 98) (Table 5). The trial also assessed the safety and tolerability of early oseltamivir treatment in children with < 24 hours of a fever (oral, rectal or axillary temperature >= 38 °C) and >= one sign of respiratory infection (cough, rhinitis or sore throat) or positive rapid influenza test result (n = 406). Children were given oseltamivir suspension (30 mg if <= 15 kg or 45 mg if 15.1 to 23.0 kg) twice daily for five days. The primary outcome was the development of acute otitis media in children with laboratory-confirmed influenza in whom treatment was started within 24 hours of symptom onset. A subgroup analysis for the primary outcome was also performed in children with laboratory-confirmed influenza in whom treatment was started within 12 hours of symptom onset.

RCTs of the prophylaxis of influenza in children with zanamivir

NAI30010 assessed the efficacy and safety of two 5 mg inhalations of zanamivir twice daily for 10 days (total daily dose 20 mg) to prevent influenza in household members after the introduction of an index case. The study was conducted between October 1998 and May 1999 across 15 centres in the USA, UK, Canada and Finland. Participants were randomised by household to receive either active drug or placebo within 36 hours of the onset of an influenza-like illness in one member. In both groups, the index case was also randomised with the family to either active drug or placebo for five days (no separate analysis by age was available). Two hundred and seventy-seven of the 837 contact cases randomised were children aged between five and 12 (Table 6).

NAI30031 (Monto 2002) had a similar methodology to NAI30010, but in order to address concerns that treatment of the index case may have confounded the prophylactic efficacy they did not randomise the index case to treatment (either active or placebo). The study was conducted between June 2000 and April 2001 in 59 sites across 11 countries including the UK and USA. Unpublished subgroup data on 371 of 1291 contact cases on children aged five to 12 years were supplied by the manufacturer (Table 7).

RCTs of the prophylaxis of influenza in children with oseltamivir

WV16193 assessed the efficacy, safety and tolerability of a 10-day course of oral oseltamivir 2 mg/kg once daily versus expectant management for the prophylaxis of influenza infection in household contacts of index cases with influenza-like illness. The study included 222 contacts aged one to 12 years, for whom a separate subgroup analysis of prophylactic efficacy was conducted. As well as randomising contacts to receive oseltamivir prophylaxis or expectant management, all index cases (including 134 children aged one to 12 years) were treated with a five-day course of twice-daily oral oseltamivir and contacts randomised to the control arm were given a standard treatment course if illness subsequently developed. Limited safety data were available for this population. This was an open-label study, which raises the possibility of bias in outcomes. However, the composite primary endpoint was based on objective measures (laboratory confirmation of infection; temperature greater than or equal to 37.8 °C) as well as subjective (clinical symptoms of influenza). Overall, it was felt that the data were likely to be reliable. Therefore, although not meeting one of our pre-specified inclusion criteria (double-blinding), it was felt that the study should nonetheless be included in the review (Table 8).

RCTs of the treatment of influenza in children with laninamivir

Sugaya 2010 conducted a multi centre, double-blind, randomised trial in Japan comparing the efficacy, safety and tolerability of laninamivir octanoate 40 mg (single inhaled dose) versus laninamivir octanoate 20 mg (single inhaled dose) versus oseltamivir (2 mg/kg orally twice daily for five days in children weighing < 37.5 kg, 75 mg orally twice daily for five days in children weighing >= 37.5 kg) in children aged nine years or younger with influenza diagnosed using rapid diagnostic testing (Table 9). Outcomes were reported for the 184 participants in the full analysis set: 61 in the laninamivir 40 mg group, 61 in the laninamivir 20 mg group and 62 in the oseltamivir group. All participants in the laninamivir octanoate groups and 58/62 participants in the oseltamivir group had laboratory-confirmed influenza. The primary outcome was time to alleviation of influenza illness, defined in this study as the interval between the start of the trial treatment and the start of the first 21.5-hour period in which the nasal symptoms and cough had improved to “absent” or “mild” and axillary temperature had returned to 37.4 °C or below. Based on this definition, we analysed this outcome as 'time to resolution of symptoms' in this review.

Excluded studies

We identified 54 studies in the initial screening and excluded 45 of them. Twenty-nine studies were excluded because they were not double-blind RCTs, nine because they did not include paediatric participants <= 12 years, three due to issues with quality (Imamura 2003; Sato 2005; Sato 2008) and four as whilst they included paediatric patients, we were unable to obtain these subgroup data (NV16871; Nordstrom 2004; Shapira 2010; Waskett 2001).

Risk of bias in included studies

Data for this review were drawn from a range of primary and secondary sources. We assessed the risk of bias using the Cochrane 'Risk of bias' tool (Higgins 2011). As some of the studies used were unpublished, with the results and methods published on a trial registry, a low score may reflect the limitation of the available data rather than that of the study. The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

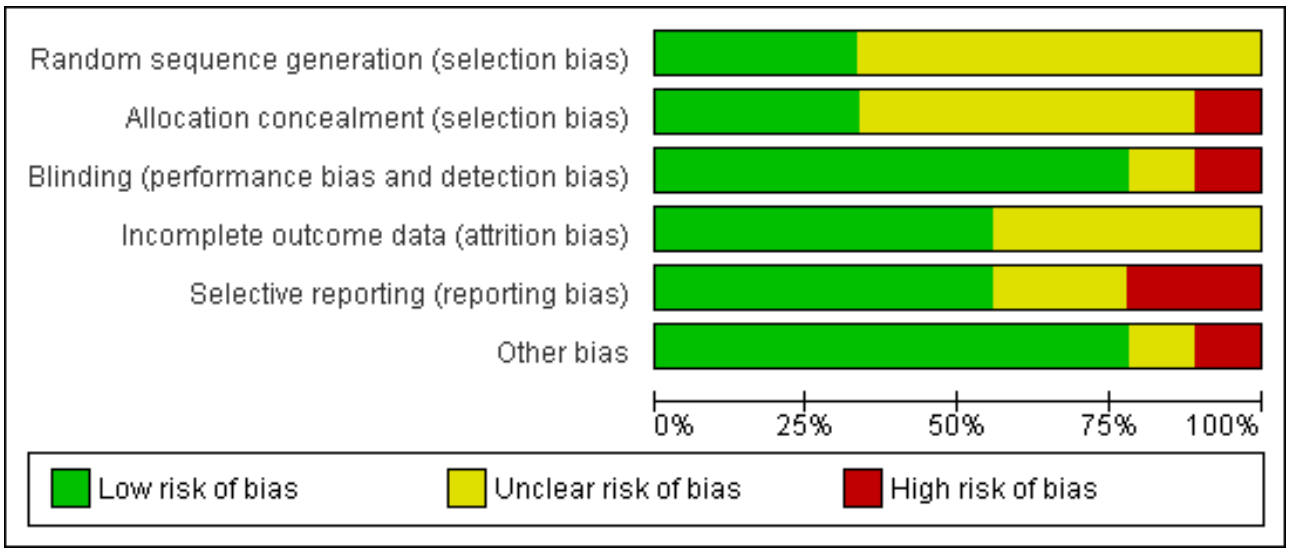
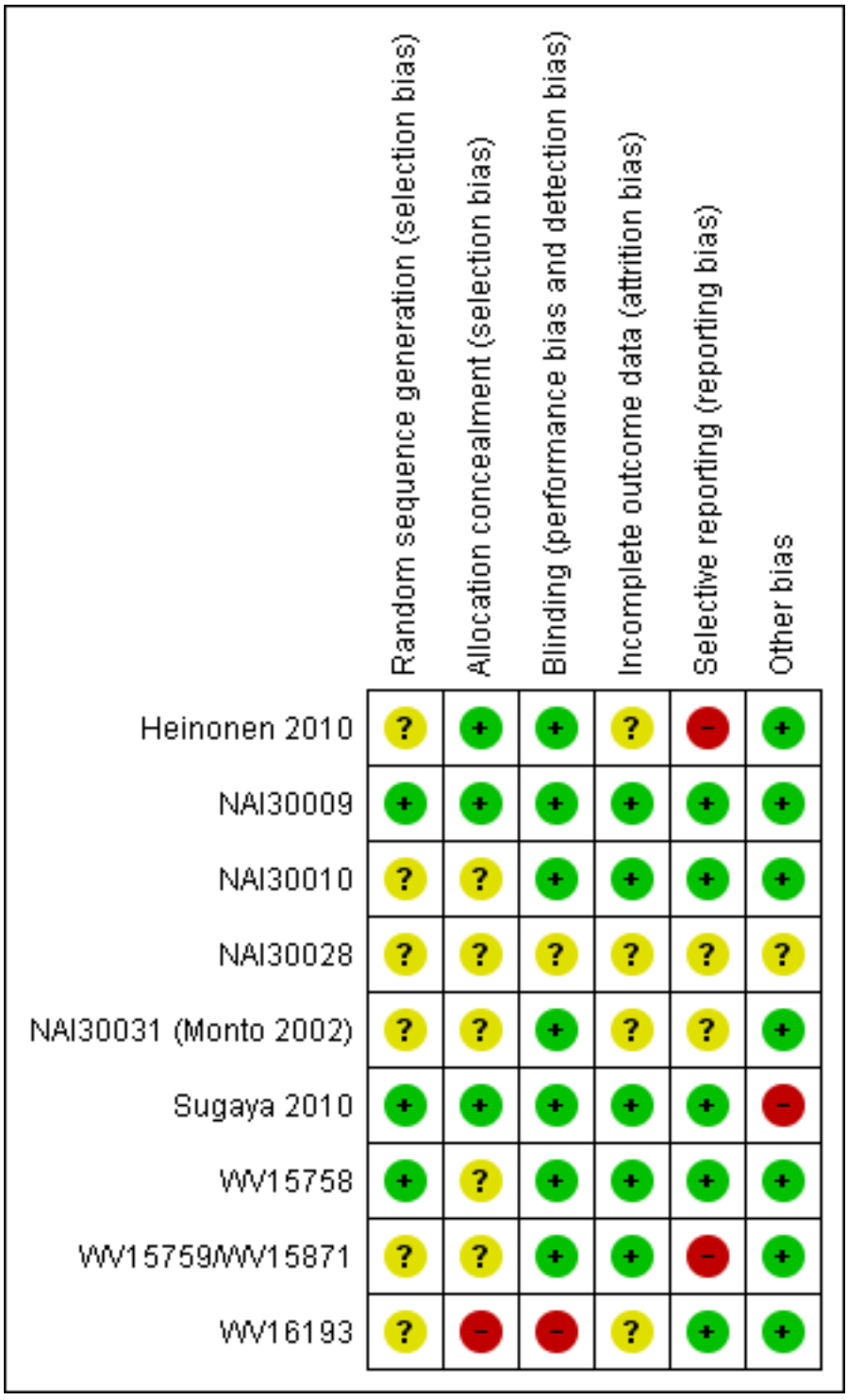


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Treatment trials

Both NAI30028 and WV15759/WV15871 were described as "randomised", but no further methodological details were given. NAI30009 used computer-generated randomisation with no stratification between centres and WV15758 used block randomisation by site stratified for the presence of otitis media at enrolment. Heinonen 2010 randomised treatments in blocks of four with an allocation ratio of 1:1 to children with clinical evidence of influenza or a positive rapid influenza test result. However, the study only reported efficacy outcomes in the subgroup with laboratory-confirmed influenza. Despite randomisation, participants with laboratory-confirmed influenza were not evenly distributed between the two treatment arms (oseltamivir 18% (37/204), placebo 30% (61/204), RR 0.6 P =<

0.007). Sugaya 2010 randomly assigned participants to one of the three treatment groups in a 1:1:1 ratio. The allocation sequence was generated by a computer and was stratified according to the institution and type of influenza virus based on the results of testing with a rapid diagnostic kit.

Prophylaxis trials

Randomisation by household occurred in the three trials of post-exposure prophylaxis. In two trials, NAI30010 and WV16193, randomisation included treatment of the index case, whereas in NAI30031 (Monto 2002) the index case was not treated. Treatment of the index case may lead to overestimation of prophylactic efficacy in family contact members.

In WV16193 randomisation was stratified by the presence of an infant (age < one year) and by the presence of a second index case in the household. Descriptions of the mechanism of randomisation in all three trials was unclear.

Blinding

Treatment trials

All six trials of neuraminidase inhibitors (Heinonen 2010; NAI30028; NAI30009; Sugaya 2010; WV15758; WV15759/WV15871) in the treatment of influenza were double-blinded.

Prophylaxis trials

Since WV16193 was an open-label trial, participants who knew they were receiving the inactive drug (placebo) might have reported symptoms more readily than participants receiving oseltamivir because they considered themselves to be unprotected against influenza. However, the composite primary endpoint of this study was objective (laboratory confirmation of influenza infection; temperature >= 37.8 °C) and so is less likely to have been affected by this potential source of bias.

In NAI30010 the index case received treatment and the diagnosis of influenza in the contacts was based on objective criteria similar to WV16193. We did not identify any problems with the blinding of the zanamivir prophylaxis trial NAI30031 (Monto 2002).

Incomplete outcome data

Treatment trials

In NAI30009 an intention-to-treat (ITT) analysis was used and the primary analysis included participants with incomplete or missing data. In WV15758, appropriate censoring and statistical tests were used. Three children who were randomised but withdrew before taking any medication were excluded from all analyses. In the children with confirmed influenza, there was no efficacy data on 18 and missing data in 28; these participants were censored. Median time to alleviation of all symptoms was presented in both the ITT and confirmed-influenza populations. In WV15759/WV15871 one child who was randomised to receive oseltamivir withdrew before taking any medication and was excluded from all analyses. The trial also only reported the primary outcome measures for the intention-to-treat infected population (i.e. participants with laboratory-confirmed influenza and the per-protocol population (i.e. participants with laboratory-confirmed influenza who had no major protocol violations or deviations). As NAI30028 has not been published in a peer-reviewed journal, the description of the methodology is less detailed compared to that in the other trials included in this review. However, the number of withdrawals from the trial was minimal: only 6/266 participants withdrew (five in the zanamivir group and one in the placebo group). We therefore assessed the risk of bias from incomplete outcome data in this trial to be low.

The numbers of participants who withdrew from or were lost to follow-up in the Heinonen 2010 trial were also low. Of the 202 participants in the oseltamivir group, one was lost to follow-up, two discontinued treatment early due to refusal to take study medication and nine discontinued treatment early due to adverse events including vomiting (five children), diarrhoea (two children), vomiting and diarrhoea (one child) and streptococcal tonsillitis (one child). In the placebo group (n = 204), one participant was lost to follow-up and five discontinued treatment early due to adverse events including vomiting (one child), diarrhoea (two children), vomiting and diarrhoea (one child) and insomnia (one child). It is therefore likely that the risk of bias from incomplete outcome data on adverse events in the trial safety (ITT) population was low. However, the study only reported data in the subgroup of children with laboratory-confirmed influenza detected by any laboratory method on any nasal swabs taken during any clinic visits occurring during the course of the study (n = 91). We therefore assessed the overall risk of bias from incomplete outcome data to be unclear.

Sugaya 2010 reported outcomes in the study's full analysis set, which included all randomised participants who met the major eligibility criteria, had received at least one dose of the trial treatment and had undergone at least one assessment for influenza symptoms and axillary temperature (laninamivir octanoate 40 mg n = 61, laninamivir octanoate 20 mg n = 61, oseltamivir n = 62). The full analysis set was analysed according to the ITT principle. We therefore assessed the risk of bias from incomplete outcome data to be low in this study.

Prophylaxis trials

All three trials (NAI30010; NAI30031 (Monto 2002); WV16193) reported outcomes using ITT analyses and had low rates of discontinuation.

Selective reporting

Based on the data available to us, we assessed the risk of reporting bias to be low in five studies (NAI30009; NAI30010; Sugaya 2010; WV15758; WV16193), unclear in two studies (NAI30028; NAI30031 (Monto 2002)) and high in two studies (Heinonen 2010; WV15759/WV15871). WV15759/WV15871 only reported efficacy outcomes in participants with laboratory-confirmed influenza and in the per-protocol population. Similarly, although Heinonen 2010 randomised all children with clinical evidence of influenza or a positive rapid influenza test result, the study also only reported efficacy outcomes in the subgroup of patients with laboratory-confirmed influenza. Three nasal swabs were taken from each child on study entry as well as on subsequent visits if the child was symptomatic. Children were considered to have laboratory-confirmed influenza if any of their swabs tested positive for influenza A or B viruses by any laboratory method (culture, immunoperoxidase staining with monoclonal antibodies, antigen detection by means of time-resolved fluoroimmunoassay or reverse transcriptase polymerase chain reaction). No data were reported on the number of children with laboratory-confirmed influenza detected on swabs taken on study entry versus swabs

taken on subsequent visits. The study also did not report data on the number of children in whom influenza was detected using different laboratory methods. Participants who were lost to follow-up or who discontinued treatment early were included in the ITT safety population but not in the efficacy analysis.

Other potential sources of bias

Treatment trials

Five studies reported that there were no significant differences between participants in different treatment groups at baseline (Heinonen 2010; NAI30009; Sugaya 2010; WV15758; WV15759/WV15871). NAI30028 did not report whether or not there were any significant differences between participants in the two treatment arms at baseline.

However, there was significant variation between different trials in terms of the proportion of children who had been vaccinated against influenza at baseline. In Sugaya 2010 47% (86/184) of children had been vaccinated compared to only 19% (65/334) in WV15759/WV15871, 13% (13/98) in Heinonen 2010, 5% (34/695) in WV15758 and 2% (11/471) in NAI30009.

There were also differences between trial populations in the baseline incidence of otitis media. The two trials reporting the highest proportions of children with otitis media at baseline were WV15758 (15% to 16%) and Heinonen 2010 (11%). In NAI30028 otitis media was only reported in 7/266 children (3%) during the five-day treatment course. Only WV15758 stratified for the presence of otitis media at baseline when randomising participants. Although Heinonen 2010 did not do this, the proportions of participants with otitis media were not significantly different between the oseltamivir and placebo groups at baseline.

Trials varied in their provision of and instructions for utilisation of relief medications. Use of relief medications may have confounded participants' reporting of illness and symptom duration in these trials. WV15758 offered participants paracetamol while WV15759/WV15871 provided all participants with paracetamol. NAI30028 provided all participants with paracetamol and cough syrup. Participants in NAI30009 were provided with paracetamol and dextromethorphan/pholcodeine, although the latter was not provided in four recruitment centres which did not routinely prescribe it. Participants were advised to refrain from taking relief medications unless their symptoms were severe. In contrast, Heinonen 2010 did not provide participants with relief medications but advised parents to give children analgesics and antipyretics as needed. Sugaya 2010 did not report whether or not participants were permitted or advised to use relief medications. Only NAI30009 reported relief medication use as an outcome.

Variations in the duration of participant follow-up between different trials may have affected detection rates of secondary complications and adverse events. NAI30028 only presented data on secondary complications and adverse events occurring during the five days on treatment. However, Sugaya 2010 followed participants up for 15 days, Heinonen 2010 for 21 days, WV15758 and WV15759/WV15871 for 28 days and NAI30009 for 14 to 28 days depending on persistence of symptoms.

No adjustment was made in statistical analyses for multiple comparisons in WV15758. The other five treatment trials included (Heinonen 2010; NAI30009; NAI30028; Sugaya 2010; WV15759/WV15871) did not specifically state whether or not statistical analyses were adjusted for multiple comparisons. In NAI30009 and WV15759/WV15871 it was not clear whether many of the secondary endpoints were specified a priori in the trial design or calculated post hoc.

Prophylaxis trials

Baseline data for the child subgroup were unavailable for NAI30010, NAI30031 (Monto 2002) and WV16193. The rates of vaccination in the prophylaxis trials were similar in the all ages population of NAI30010, NAI30031 (Monto 2002) and WV16193; we did not have subgroup data on children aged 12 years and younger.

Effects of interventions

Time to resolution of illness (i.e. resolution of symptoms and return to usual activities)

WV15758: oseltamivir reduced the median duration of illness by 1.5 days (26%, P < 0.0001), from 5.7 (95% confidence interval (CI) 5.2 to 6.25 days) to 4.2 days (95% CI 3.7 to 4.9 days) in the intention-to-treat-infected (ITTI) population. A significant but smaller reduction of 0.88 days was seen in the ITT population (a 17% reduction, from 5.3 to 4.4 days, P = 0.0002). An analysis stratified by age showed similar results (Table 10).

WV15759/WV15871: a trend to a reduction in the median duration of illness by 0.43 days (from 5.60 days to 5.16 days, P = 0.54) in the ITTI population was seen in this trial of oseltamivir in children with asthma. The trial failed to reach its recruitment target of 500, achieving only 334; of which 46% had influenza (sample size calculations were based on an infection rate of 50%); and 14% (25/176) were vaccinated in the ITTI group. The magnitude of the reduction in time to recovery was increased when they looked at participants who had received oseltamivir within < 24 hours of the first symptom; 39.8 hours (P = 0.078). Primary outcome data were not reported on an ITT ('safety') population.

NAI30009 and NAI30028 did not report the composite of the time to resolution of all symptoms and return to work.

Heinonen 2010 reported that oseltamivir reduced the median duration of illness by 1.4 days (P = 0.004), from 5.7 (interquartile range (IQR): 4.2 to 10.3) to 4.3 days (IQR: 2.2 to 5.9) in children with laboratory-confirmed influenza A or B.

Time to resolution of influenza symptoms

NAI30009 and NAI30028 defined the resolution of symptoms as: no fever (temperature less than 37.8 °C), cough as "none" or "mild" and muscle/joint aches and pains, sore throat, chills/feverishness and headache as "absent/minimal" for three consecutive assessments. WV15758 and WV15759/WV15871 defined the symptoms based on the Canadian Acute Respiratory Infection and Flu Scale (CARIFS) (Table 11). Heinonen 2010 defined time to resolution of symptoms as the total absence of cough and rhinitis although did not state how long this absence had to last for. In Sugaya 2010 time to alleviation of influenza illness was defined as the interval between the start of the trial treatment and the start of the first 21.5-hour period in which the nasal symptoms and cough had improved to “absent” or “mild” and axillary temperature had returned to 37.4 °C or below. Since this definition did not include whether or not the participant had returned to normal activities, we analysed this outcome as 'time to resolution of symptoms' in this review.

NAI30009: zanamivir reduced the median time to the resolution of symptoms by 1.25 days (from 5.25 to 4 days, P < 0.001) in the ITTI population, with a smaller decrease of 0.5 days (from 5.0 to 4.5 days, P = 0.001) in the ITT population.
NAI30028: zanamivir reduced the median time to the resolution of symptoms by 0.5 days, from 5.5 to 5 days in the ITT population (who were positive for influenza at recruitment based on near-patient testing). No CI was supplied; though in referring to the mean difference the trial summary reports a P value less than 0.0377.
WV15758: treatment with oseltamivir showed a significant reduction in the median time to the resolution of all symptoms of 36 hours (from 100 to 63 hours, P < 0.0001) in the ITTI population.
WV15759/WV15871: treatment with oseltamivir showed a trend to a reduction in the median time to alleviation of all symptoms by 25.3 hours (115.6 to 90.4 hours, P = 0.1197) in the ITTI population.
Heinonen 2010: reported that oseltamivir reduced the median duration of symptoms by 2.8 days (P < 0.001), from 13.3 (IQR: 10.3 to 17.1) to 10.4 days (IQR: 4.6 to 12.4) in children with laboratory-confirmed influenza A or B.

Analysis 1.1 summarises pooled data on the proportion of children with cough on day 2 (NAI30009) and day 5 (NAI30028). Treatment with zanamivir was associated with a 13% reduction in the proportion of children with cough up to five days after commencing treatment (risk difference (RD) -0.13, 95% CI -0.21 to -0.05).

Sugaya 2010 reported that treatment with laninamivir octanoate 20 mg reduced duration of influenza symptoms by 31 hours compared to treatment with oseltamivir in children with influenza diagnosed on rapid near-patient testing (36%, P = 0.009). Treatment with laninamivir octanoate 40 mg was associated with a very similar reduction in symptom duration in these children (31.9 hours, 36.5%) but this reduction was not statistically significant (P = 0.059) (Table 12). However, in children with influenza A/H1N1 (of whom 96.4% had the oseltamivir-resistant H274Y mutation) laninamivir octanoate significantly shortened duration of symptoms at both 20 mg (66.2 hours, 60%, P = 0.001) and 40 mg (60.9 hours, 55%, P = 0.007) doses. These observations are unlikely to be due to laninamivir octanoate 40 mg having a toxic effect, since laninamivir octanoate was well tolerated at both doses and no clinically meaningful laboratory changes were observed in any treatment groups.

Time to return to normal activities

NAI30009: zanamivir reduced the median time to return to normal activity by one day in both the ITTI (P = 0.022) and the ITT populations (P = 0.019).
NAI30028: after the five-day observation period 62/172 (36.0%) participants who received zanamivir and 25/89 (28.1%) of the placebo recipients had returned to school in the ITT population (risk difference (RD) 0.08, 95% CI -0.04 to 0.20, P = 0.19).
WV15758: oseltamivir reduced the median time to return to normal activity by 1.9 days (40%, P < 0.0001) in the ITTI population; no data were available for the ITT population.
WV15759/WV15871: a trend to benefit was observed for oseltamivir in asthmatic children with laboratory-confirmed influenza, with a reduction in median time to return to normal activity of 12.6 hours (11%, P = 0.46); no data were available for the ITT population.
Heinonen 2010: reported that children treated with oseltamivir returned to daycare two days earlier than children in the placebo group (duration of absence from daycare: oseltamivir - median two days, IQR: 1 to 4; placebo - median four days, IQR: 3 to 5, P = 0.01).

Asthma-related symptoms

Only WV15759/WV15871 explicitly reported asthma-related symptoms; WV15758 and NAI30028 did not report the baseline incidence of asthma or related complications. In the ITT population of NAI30009 36/471 (8%) participants had an unspecified "concurrent chronic respiratory condition". This study also reported a very low incidence of asthma exacerbations; 2/224 (< 1%) in the zanamivir group and 5/247 (2%) in the placebo group.
WV15759/WV15871 reported that oseltamivir resulted greater improvement in forced expiratory volume at 1 second (FEV_1) between study entry and Day 6 in the ITTI population (median improvement of 10.8% and 4.7% in the oseltamivir and placebo groups respectively). There was a similar improvement in peak expiratory flow (PEF) (14.3% and 3.7%). Based on PEF measurements, the frequency of asthma exacerbations was significantly lower in the oseltamivir group than in the placebo group; 68% of participants in the placebo group remained within 20% of the highest peak flow at Day 7 compared to 51% of participants in the placebo group (P = 0.031). However, the difference between the frequency of medical reports of asthma exacerbations in the two groups was not statistically significant (Analysis 1.2).

Other secondary outcome measures

NAI30009: zanamivir reduced time to resolution of illness including no further use of relief medication by 1.5 days in the ITTI population (from 6.5 to 5.0 days, P < 0.001) and 1.0 days in the ITT population (from 6.0 to 5.0 days, P = 0.002).
NAI30028: there was a trend to reduction in the time to resolution of cough of 1.5 days, from 5.0 days in the placebo ITT population to 3.5 days with zanamivir (P = 0.1960).
WV15758: oseltamivir reduced the median time to resolution of fever by 1.0 days (from 2.8 days to 1.8 days, P < 0.0001). The median time resolution of the CARIFS symptoms score was shorter in the oseltamivir treated ITTI group by 1.5 days (from 4.17 to 2.75 days, P < 0.0001). A subgroup analysis of children infected with influenza B (n = 144, 32% of the ITTI population) found that the median duration of fever, cough and coryza was reduced by 1.1 days (from 4.2 to 3.0 days, P = 0.01). Median total acetaminophen consumption was reduced by 31% in participants treated with oseltamivir compared to placebo (P = 0.002).

WV15759/WV15871: the primary efficacy outcome (time to freedom from illness) required, for a period of at least 21.5 hours: absence of fever (< 37.2 °C), return to normal activities and a symptom score of 0 or 1. Focusing on only one of these parameters showed similar but statistically non-significant decreases in the median time to resolution with oseltamivir. Time to return to normal health and activity decreased by 0.53 days (from 4.75 to 4.23 days, P = 0.4555). Time to alleviation of all symptoms decreased by 1.05 days (from 4.82 to 3.77 days, P = 0.1197). Three participants with laboratory-confirmed influenza were hospitalised during the trial, two of whom were in the oseltamivir group (one with vomiting and one with abdominal pain) and one of whom was in the placebo group (viral encephalitis).

Heinonen 2010: the mean number of doses of antipyretics and/or analgesics was decreased by 1.5 (5.9 to 4.4, P = 0.03) in children with laboratory-confirmed influenza who were treated with oseltamivir and by 1.8 (6.1 to 4.3, P = -0.01) in children with influenza A. However, no difference was observed in children with influenza

B (oseltamivir: 4.8, placebo: 5.1, P = 0.88). No children in the ITTI population were diagnosed with pneumonia or hospitalised. One child in the safety population who received oseltamivir was hospitalised with bronchiolitis on Day 3 of the study. This child did not have a laboratory-diagnosis of influenza.

Three trials also reported secondary outcomes in relation to viral shedding and/or titres (Sugaya 2010; WV15758, WV15759/WV15871) but we did not pre-specify these as secondary outcomes in this review.

Otitis media

NAI30009: the incidence of otitis media was not reported.
NAI30028: a low incidence of otitis media in the ITT population was reported in both the placebo (3/90, 3%) and zanamivir groups (4/176, 2%). These results did not demonstrate a statistically significant reduction in otitis media with zanamivir treatment (RD -0.01, 95% CI -0.05 to 0.03, Analysis 1.3).
WV15758: Whitley 2001 reported a 44% relative risk reduction (P = 0.01) in the incidence of otitis media developing after study day 2 in children treated with oseltamivir (26/217) compared to placebo (50/235) in the ITTI population. Winther 2010 was a retrospective analysis of the same ITTI population. However, Winther 2010 reported that 27/217 children treated with oseltamivir developed acute otitis media on or after study day 3 (12.4%) compared to 51/235 children treated with placebo (12.4%). The benefit of oseltamivir was most evident in children aged one to two years, who were also most likely to develop new acute otitis media infections. In this group, 17.5% of children treated with oseltamivir developed acute otitis media compared to 41.4% of children treated with placebo (RR 0.42, 95% CI 0.20 to 0.89). In children aged two to five years, 10% of those treated with oseltamivir developed acute otitis media compared to 22.4% of those treated with placebo (RR 0.45, 95% CI 0.19 to 1.04). In children aged six to 12 years there was no difference in the incidence of new otitis media infections between the oseltamivir and placebo groups (RR 1.03, 95% CI 0.51 to 2.10). We were unable to present age stratified data from Winther 2010 as RD with 95% CI in Analysis 1.4 because the study only presented these data as summary statistics.
WV15759/WV15871: a low incidence of otitis media in the ITT population was reported in both the placebo (7/164, 4.3%) and oseltamivir groups (6/170, 3.5%). These results did not demonstrate a statistically significant reduction in otitis media with oseltamivir treatment (RD -0.01, 95% CI -0.05 to 0.03, Analysis 1.3).
Heinonen 2010: in children with laboratory-confirmed influenza, treatment with oseltamivir within 24 hours of symptom onset reduced the incidence of otitis media by 10% (RD -0.10, 95% CI -0.27 to 0.08). The trial authors reported that this reduction was not statistically significant (RR 0.69, 95% CI 0.34 to 1.37, P = 0.31). However, the trial authors did report a statistically significant reduction in the incidence of otitis media in children who commenced treatment within 12 hours of symptom onset (RR 0.15, 95% CI 0.03 to 0.75, P = 0.02).

Analysis 1.3 summarises data from included trials of oseltamivir and zanamivir on the incidence of acute otitis media in children with clinical influenza. Analysis 1.4 summarises data from included trials of oseltamivir on the incidence of acute otitis media in children with laboratory-confirmed influenza. Data from WV15758 demonstrated statistically significant absolute risk reductions in otitis media with oseltamivir treatment in children aged one to five years (RD -0.16, 95% CI -0.29 to -0.04) and one to 12 years (RD -0.09, 95% CI -0.16 to -0.02). Although we considered the risk of reporting bias in Heinonen 2010 to be high, pooling data from this study together with that from WV15758 still resulted in statistically significant reductions in otitis media with oseltamivir treatment in children aged one to five years (RD -0.14, 95% CI -0.24 to -0.04) and one to 12 years (RD -0.09, 95% CI -0.16 to -0.03).

Antibiotic usage

NAI30009: in the ITTI population fewer participants received antibiotics in the zanamivir group (12%) than in the placebo group (15%). Although this represented a 20% relative reduction in antibiotic use, this difference was not statistically significant.

WV15758: the overall proportion of participants prescribed antibiotics was significantly lower in the oseltamivir group (68/217, 31%) than in the placebo group (97/235, 41%; P = 0.03). The incidence of physician-diagnosed complications requiring antibiotic treatment developing after the day of recruitment was reduced by 40% in the oseltamivir treatment group (36/217, 17% compared to the placebo group 65/235, 28%); this difference was statistically significant (P = 0.005).

Overall, treatment with neuraminidase inhibitors did not significantly reduce antibiotic use (RD -0.07, 95% CI -0.15 to 0.01) (Analysis 1.5).

Influenza A and B

WV15758: a trend to benefit was reported for oseltamivir in children with influenza B, with a reduction in median time to return to normal activity of 19% (111.7 hours in the control group compared with 90.1 hours in the treatment group) but this did not reach statistical significance (WV15758 - EMEA 2005). In children aged one to five years, oseltamivir shortened the median time to return to normal activity from 121.3 hours in the control group to 63.5 hours in the treatment group, a reduction of 48% (P = 0.003; WV15758 - Reisinger 2004). Oseltamivir produced a reduction in the incidence of acute otitis media in children aged one to 12 years with influenza A (incidence of acute otitis media - oseltamivir group: 18/150, placebo group: 38/153, Chi^2 test P value 0.06) but not influenza B (WV15758 - Winther 2010).

Heinonen 2010: oseltamivir did not significantly reduce the incidence of acute otitis media in children with influenza A (relative risk reduction 31%, 95% CI -50% to 70%, P = 0.37) or influenza B (relative risk reduction 31%, 95% CI -148% to 83%, P = 0.99) who received treatment within 24 hours of symptom onset. Oseltamivir also did not significantly reduce the incidence of acute otitis media in children with influenza A who started treatment within 12 hours of symptom onset (relative risk reduction 79%, 95% CI -1% to 96%, P = 0.08).

Oseltamivir significantly reduced the median time to resolution of illness from 6.5 days (IQR 4.3 to 11.1) to 3.0 days (IQR 2.2 to 5.9) in children with influenza A (P = 0.002). However, this difference was not significant in children with influenza B (median time to resolution of illness - oseltamivir 4.4 days, IQR 4.1 to 6.9; placebo 4.7 days, IQR 3.4 to 8.3, P = 0.93). Oseltamivir also significantly reduced the median time to resolution of symptoms in children with influenza A (median time to resolution of illness - oseltamivir 9.4 days, IQR 4.4 to 12.4; placebo 14.0 days, IQR 11.3 to 18.0, P = 0.001) but not influenza B (median time to resolution of illness -

oseltamivir 11.3 days, IQR 5.2 to 12.8; placebo 13.2 days, IQR 7.2 to 13.3, P = 0.41).

Sugaya 2010: both dosages of laninamivir octanoate (40 mg and 20 mg) produced a significantly greater reduction in median time to symptom resolution than oseltamivir in children with oseltamivir-resistant influenza A/H1N1. Laninamivir octanoate 40 mg reduced median time to symptom resolution by 60.9 hours (95% CI -71.0 to -10.2, P = 0.007) and laninamivir 20 mg by 66.2 hours (95% CI -81.2 to -18.5, P = 0.001) compared to oseltamivir. Differences in median time to symptom resolution between the three treatment groups were not statistically significant in children with influenza A/H3N2 or influenza B. Duration of fever was significantly shorter in children with influenza A/H1N1 who were treated with laninamivir octanoate 40 mg (median difference: -18.8 hours, 95% CI -27.7 to -0.5, P = 0.034) or 20 mg (median difference -25.5 hours, 95% CI -30.4 to -4.4, P = 0.006) compared to oseltamivir. However, duration of fever was significantly longer in participants infected with influenza A/H3N2 who were treated with laninamivir 40 mg (median difference 21.6 hours, 95% CI 1.3 to 25.8, P = 0.018) compared to oseltamivir.

NAI30009: zanamivir produced a significant reduction in time to alleviation of clinically significant symptoms in children with influenza A (median difference in alleviation 1.0 day, 95% CI 0.0 to 1.5, P = 0.049) and influenza B (median difference in alleviation 2.0 days, 95% CI 1.0 to 3.5, P < 0.001).

No data were available by serotype or age group for NAI30028 or WV15759/WV15871.

Prophylaxis of influenza

NAI30010: in this open-label study, prophylaxis with zanamivir within 1.5 days of introducing a case of influenza-like illness to the household (who was also randomised with the household) resulted in a decrease in the incidence of symptomatic influenza in household contacts from 7.0% (10/142) to 2.2% (3/135), though the P value was 0.086. We do not have subgroup data for those in whom the index case had laboratory-confirmed influenza.

NAI30031 (Monto 2002): prophylaxis with zanamivir within 1.5 days of the introduction of an index case to a household reduced the incidence of symptomatic, laboratory-confirmed influenza in contacts from 12.0% (22/183) to 3.7% (7/188) (RD -0.08, 95% CI -0.14 to -0.03, P = 0.003). The relative risk of symptomatic influenza after the introduction of an index case of influenza-like illness into a household with prophylactic inhaled zanamivir as compared to placebo was 0.31 (95% CI 0.16 to 0.62, P = 0.001). Analysis 1.6 contains a summary of the prophylactic efficacy of zanamivir.

WV16193: post-exposure prophylaxis with oseltamivir reduced the incidence of symptomatic influenza in household contacts to varying degrees in different subgroups. Among all participants who received oseltamivir prophylaxis, the attack rate was significantly reduced from 19% (21/111) to 7% (7/104) (P = 0.0188). Oseltamivir prophylaxis reduced the attack rate in contacts of influenza-positive index cases from 24% (18/74) to 11% (6/55) but this was not statistically significant (P = 0.089).

Safety and tolerability data

NAI30009: in the ITT population no significant difference in the rate of adverse events was observed between children treated with zanamivir (21%) and those treated with placebo (26%). Less than 1% of participants allocated to zanamivir reported nausea, compared with 2% in the control group; 3% in each group reported vomiting and 1% allocated to zanamivir reported diarrhoea compared with 2% in the control group. More than 97% of children completed eight to 10 drug doses. Only one severe adverse event was recorded (worsening of symptoms), which occurred in the zanamivir group.

NAI30010: whilst subgroup data for children under the age of 12 were not available, Hayden 2000 reported that the frequency of adverse events was similar in the overall zanamivir and placebo groups, as well as among children who were five to 11 years old. Most adverse events were of mild or moderate intensity. The majority of adverse events were considered to be associated with influenza rather than drug-related. Only one serious adverse event occurred: a participant with an index case of laboratory-confirmed influenza developed pneumonia four days after the start of treatment with zanamivir but this resolved approximately one week later.

NAI30028: reported adverse event rates were similar in both the zanamivir (30/176, 17.0%) and placebo (15/90, 16.7%) groups. There was a low incidence of vomiting in both groups (zanamivir 2/176; placebo 1/90). There was only one participant with a severe adverse event (*Mycoplasma* pneumonia and otitis media) which occurred in the zanamivir group. There were no fatal events in either group.

NAI30031 (Monto 2002): age-stratified adverse event data were not available for this study. However, the associated paper, Monto 2002, notes that "The incidence of adverse events was similar across all age groups, and no notable differences in the nature of the adverse events could be discerned between the children and adults." Overall, there was no significant difference in the rate of reported adverse events in participants of all ages between the placebo group (276/661, 42%) and the zanamivir group (325/629, 52%). The most common reported adverse advents were symptoms compatible with influenza; no severe adverse events thought to be related to treatment were noted.

WV15758: oseltamivir treatment was generally well tolerated. The adverse event profile in the oseltamivir group was comparable to that in the placebo group. The most common adverse events were gastrointestinal. Vomiting was reported more commonly in participants receiving oseltamivir than placebo (oseltamivir 49/344, 14.3%; placebo 30/351, 8.5%, P = 0.02). However, only 1% of the study population discontinued their study drug because of vomiting. Diarrhoea was reported in a higher proportion of participants in the placebo group (10.5%) than in the oseltamivir group (8.8%). Five participants (0.7%) reported serious adverse events during treatment. Pneumonia was reported in one patient in the placebo group and two in the oseltamivir group. Dehydration was reported in one participant in each treatment group. No participants in the oseltamivir group and only two participants in the placebo group required hospitalisation during this study (one child for dehydration and one for ingestion of a caustic substance).

WV15759/WV15871: adverse events were monitored for up to four weeks after the last dose of the study drug. No deaths were reported. Adverse events occurring with an incidence of greater than 1% were reported. Vomiting was the most commonly reported adverse event with a higher incidence in the oseltamivir group

(27/170, 15.9%) than in the placebo group (18/164, 11%). The incidences of diarrhoea (oseltamivir 5.9%; placebo 7.3%) and nausea (oseltamivir 2.4%; placebo 4.9%) were also low.

WV16193: oseltamivir was generally well tolerated for both treatment and prophylaxis by 257 children who received the drug as index cases, contacts in the prophylaxis arm or contacts in the control arm who subsequently developed influenza. No children withdrew because of problems tolerating the study medication. Vomiting occurred in 31/158 children who received twice-daily treatment (21%) compared with 10/99 children who received once-daily prophylaxis (10%) (though the report does not make it clear if there were corrections for the different durations of exposure to the drug (five days for treatment versus 10 days for prevention).

Heinonen 2010: in the safety population of 406 children, vomiting was the only adverse event reported more frequently in oseltamivir recipients (59/202, 29.2%) than in children receiving placebo (38/204, 18.6%, P = 0.01). One child receiving oseltamivir was hospitalised with bronchiolitis on Day 3. No other serious adverse events were recorded in either group. The proportions of children with diarrhoea were similar between the two groups (oseltamivir 35.1%; placebo 35.8%, P = 0.89). No significant differences were observed with respect to abdominal pain, exanthema, irritability, fatigue, headache or decreased appetite between the two groups.

Analysis 1.7 summarises adverse event rates in included RCTs comparing neuraminidase inhibitors with placebo.

Sugaya 2010: the most common adverse events were gastrointestinal events. Diarrhoea occurred in 3.2% (2/62), 6.6% (4/61) and 1.6% (1/62) of children in the laninamivir 40 mg, laninamivir 20 mg and oseltamivir groups respectively. Vomiting occurred in 3.2% (2/62), 4.9% (3/61) and 6.5% (4/62) respectively and nausea occurred in 1.6% (1/62), 1.6% (1/61) and 0.0% (0/62) respectively. Psychiatric disturbances occurred in 3/123 participants treated with laninamivir but they were mild and did not require any treatment. Adverse event rates in this study are summarised in Analysis 2.1.

DISCUSSION

Efficacy of neuraminidase inhibitors

Time to resolution of illness and symptoms

Treatment with oseltamivir or zanamivir was only associated with modest benefit in reducing illness duration and duration of symptoms in children with influenza diagnosed on laboratory or near-patient testing. Treatment with neuraminidase inhibitors reduced time to resolution of illness by between 0.4 and 1.5 days and time to resolution of symptoms by 0.5 to 2.8 days compared to placebo. Both NAI30009 and WV15758 demonstrated a statistically significant decrease in both the intention-to-treat (ITT) and intention-to-treat-infected (ITTI) populations. NAI30028 and WV15759/WV15871 showed a trend to improvement but did not achieve statistical significance. In Heinonen 2010, oseltamivir produced statistically significant reductions in both resolution of illness and resolution of symptoms.

We were unable to pool data on time to resolution of illness and were only able to summarise data on time to resolution of symptoms across two studies. The pooled estimates of time to alleviation of symptoms and time to return to normal activities provided in the Health Technology Assessment (HTA) report by Turner 2002 was based on an approximation using mean and median data to account for censoring and assuming an exponential distribution for the survival function.

Otitis media

Treatment with oseltamivir was associated with a small reduction in the incidence of otitis media in children aged one to five years with laboratory-confirmed influenza (risk difference (RD) -0.14, 95% confidence interval (CI) -0.24 to -0.04). One placebo-controlled trial of zanamivir (NAI30028) did not demonstrate any difference in the incidence of otitis media between children treated with zanamivir or placebo. This may be explained by the low incidence of otitis media among participants in this trial, the lower prevalence of otitis media in children over the age of five years, the trial's relatively short follow-up period (five days) compared to those of WV15758 (28 days) and Heinonen 2010 (21 days) and difficulties with administration of inhaled zanamivir. In children, less than 8% of inhaled zanamivir is systemically absorbed (10% to 20% in adults), with the highest concentrations occurring in lung tissue (Peng 2000). In contrast, oseltamivir provides 80% systemic bioavailability of its active metabolite, oseltamivir carboxylate, after oral dosing in adults, with good penetration to middle ear and sinus secretions (Bardsley-Elliot 1999; Hayden 2001). The benefits of the two drugs in treating extra-pulmonary complications may therefore not be equivalent, owing to the markedly different levels of drug exposure in extra-pulmonary tissues.

Based on data from Heinonen 2010 and WV15758 (Winther 2010), 12 children with laboratory-confirmed influenza would need to be treated with oseltamivir to prevent one case of otitis media, regardless of whether or not acute otitis media was present at enrolment (95% CI 7 to 34). Amongst children aged one to five years, in whom acute otitis media is more common, the number needed to benefit (NNTB) is only eight (95% CI 5 to 25). Benefits may be maximised further by targeting children at high risk of developing acute otitis media, such as the very young (less than two years old) or children with a history of recurrent acute otitis media (Lindbaek 1999). WV15759/WV15871 reported a non-significant reduction in acute otitis media in children with clinical influenza treated with oseltamivir (RD -0.01, 95% CI -0.05 to 0.03).

Children with asthma

Only one study directly investigated the efficacy of oseltamivir in reducing the time to recovery from illness and asthma-related symptoms (WV15759/WV15871). Whilst the study reported a trend to benefit in the primary endpoint of median time to freedom from illness this was not statistically significant and of a small magnitude (10 hours). Furthermore, whilst the median improvement in FEV_1 by Day 6 (secondary endpoint) showed a statistically significant benefit with oseltamivir, its magnitude was also small at 6.1% (10.8% versus 4.7% improvement with placebo); similar results were found when measuring the incidence of asthma exacerbations.

A study of oseltamivir for the treatment of influenza in 329 children and adolescents aged six to 17 years with asthma (NV16871; not eligible for this review as no data were separately reported for children aged up to and including 12 years) also observed no difference in time to resolution of symptoms in children with laboratory-confirmed influenza. Furthermore, the clinical

significance of the reduction in asthma endpoints is unknown. Studies with a better control of the "step-up" therapy for the illness are required.

In children with asthma who experience a viral-induced exacerbation, the clinical scenario which is most likely to present and concern the primary care physician, the probability of it being caused by an influenza virus is actually less than in the general population of children who present with a fever. Consequently, under such circumstances and prescribing on a clinical case definition, the overall average efficacy (or number needed to treat to benefit) will be lower. Therefore, we found no evidence of benefit in the median time to resolution of illness and a small benefit in a FEV_1 and number of asthma exacerbations at Day 7 with oseltamivir in treating children with influenza.

Based on guidelines from the Food and Drug Administration (FDA), the Medicine and Healthcare Regulatory Authority (MHRA) and the European Medicines Agency (EMEA), zanamivir is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease (COPD)) due to risk of serious bronchospasm (EMEA 2007; FDA 2008; MHRA 2009).

Children 'at risk'

There is a higher rate of complications of influenza in children with underlying chronic medical conditions than in healthy children (Meier 2000). However, with the exception of WV15759/WV15871 (which involved children with asthma) our included studies either did not report 'at risk' conditions in participating children (NAI30028) or excluded children with 'at risk' conditions (Heinonen 2010; NAI30009; Sugaya 2010; WV15758). Consequently, current evidence for the efficacy and safety of neuraminidase inhibitors in 'at risk' children is based on a combination of case reports or series and inference from healthy populations, assuming a fixed-effect for benefit and a constant risk of adverse effects. We found four trials in 'at risk' populations which are still awaiting classification. Two trials have been completed but only summary results have been made available for one (NCT00412737) and no results have yet been published for the other (NCT00298233). One trial is reported as ongoing but not recruiting participants (NCT00867139) and another as still recruiting participants (NV20234).

Prophylaxis of influenza

Based on data from 648 children in trials treated with either zanamivir or placebo, prophylaxis with zanamivir caused a significant reduction in risk ratio of developing symptomatic influenza in children after the introduction of and index case to the household (RR 0.31, 95% CI 0.16 to 0.62, P = 0.001).

This efficacy is based on initiating prophylaxis in the rest of the household and, in NAI30009, also in the index case. The latter in theory should reduce secondary exposure, thereby improving the protective efficacy but the individual effect is unknown.

Only one (open-label) trial of oseltamivir for the prevention of influenza transmission in households reported data for paediatric contacts. Where index cases had laboratory-confirmed influenza, a protective efficacy for oseltamivir prophylaxis of 55% was observed, although this did not reach statistical significance (P = 0.089). One reason for this relatively modest effect appeared to be that some contacts were already positive for sub-clinical influenza infection (diagnosed by viral culture of throat and nose swabs) when prophylaxis was commenced - in a retrospective analysis of paediatric contacts who were confirmed to be influenza negative at baseline, protective efficacy rose to 80% (P = 0.021). In clinical practice, it is not possible to make this distinction. On the other hand, in the ITT group (which was not the trial's primary population of analysis) a statistically significant protective efficacy of 64% was seen. As influenza was circulating in the community, there is a high likelihood of a secondary contact source. Consequently, the modest effect in the ITTI population may relate to the low numbers (129 children in total) and the results from the ITT population may be more representative. Therefore, at present, the evidence supporting the use of oseltamivir for the post-exposure prophylaxis of influenza in children remains weak.

Serotype of influenza

Although public health surveillance is able to specify the serotype of influenza circulating at a given time many currently available near-patient tests are unable to distinguish between different influenza serotypes. There is considerable variation between the findings of different studies in terms of the efficacy of neuraminidase inhibitors against different influenza serotypes. Zanamivir produced significant reductions in time to resolution of symptoms in children with influenza A and children with influenza B (NAI30009). Oseltamivir produced a significant reduction in time to resolution of illness and time to resolution of symptoms in children aged one to three years with influenza A but not in children with influenza B (Heinonen 2010). WV15758 reported a non-significant benefit in children with influenza B treated with oseltamivir. Oseltamivir did not produce a significant reduction in incidence of acute otitis media in children with influenza A or children with influenza B when treatment was commenced within 24 hours of symptom onset, although a trend to reduction in children with influenza A was observed when treatment was commenced within 12 hours of symptom onset (Heinonen 2010). Laninamivir octanoate significantly reduced time to resolution of symptoms in children with influenza A/H1N1 (but not influenza A/H3N2 or influenza B) compared to oseltamivir, but this was only based on a small sample of 184 children. Current evidence therefore does not conclusively support targeting neuraminidase inhibitor treatment at specific influenza serotypes. In smaller studies there may have been too few children with influenza B to detect a significant treatment effect.

Safety and tolerability

Adverse events related to study medication can be difficult to separate from symptoms and complications of influenza infection itself when these events are assessed in treatment trials. The markedly different incidences of adverse events reported in the control arms of WV15758 and WV15759/WV15871, as compared with NAI30009 and NAI30028 may relate to systematic differences in study design, reporting methods and duration of follow-up, resulting in different sensitivities for detection and reporting of mild events. The adverse event profile of zanamivir was no worse than placebo but vomiting was more common in children treated with oseltamivir than with placebo (number needed to harm = 17). The adverse event profile of laninamivir octanoate was similar to that of oseltamivir. Even so, WV15758 reported that only 1% of the study population discontinued their study drug because of vomiting.

The adverse event profile of zanamivir was similar to that of placebo. This may relate to the different methods of drug administration and the consequent low absorption of zanamivir into the systemic circulation. Administration via inhalation may also underlie rare reports of bronchospasm in adults treated with zanamivir (but not oseltamivir), many but not all of whom had underlying chronic respiratory conditions (NAI30009 - FDA 2003; Williamson 2000). However, we did not identify any reports of zanamivir-related bronchospasm in children, and nor was bronchospasm reported in a meta-analysis (Lalezari 2001) and RCT (Murphy 2000) examining the use of zanamivir in high-risk patients.

Limitations of the review

Limitation of the evidence

In the only trial we found involving children with asthma (WV15759/WV15871), children had asthma severe enough to require regular medical follow-up monitoring or hospital care. We did not find any trials conducted in children with less severe or better-controlled asthma. We also did not find any trials in children in other 'at risk' groups, which met the eligibility criteria for this review. We found one abstract of a randomised placebo-controlled trial studying the safety and tolerability of a 12-week course of oseltamivir prophylaxis in solid organ transplant and haemopoietic stem cell transplant recipients, including children (Shapira 2010). However, we were unable to include this study because data on paediatric cases aged up to and including 12 years were not reported separately.

We found one trial comparing laninamivir octanoate with oseltamivir (Sugaya 2010) but no trials comparing laninamivir octanoate with placebo or comparing zanamivir with oseltamivir. We also did not find any trials conducted in children with pandemic influenza or which reported the effect of neuraminidase inhibitors on the incidence of serious complications of influenza, such as pneumonia or hospitalisation.

Missing data

Two studies (Heinonen 2010; WV15759/WV15871) only reported efficacy outcomes in children with laboratory-confirmed influenza (i.e. ITTI populations). In two studies, children had to test positive for influenza based on rapid near-patient testing to enter the trial (NAI30028; Sugaya 2010). Two treatment trials (WV15758; NAI30028) reported outcomes in both the ITT and ITTI populations. Both NAI30028 and WV15759/WV15871 were described as "randomised" but no further methodological details were given.

Studies varied both in the outcomes measured and in the consistency of reporting of results, particularly time to resolution of illness and time to resolution of symptoms. We were unable to pool these data from different studies because we did not have access to individual patient data. WV15758 - Winther 2010 only reported summary data (risk ratios and 95% CIs) on the development of new acute otitis media infections in three age subgroups (one to two years, three to five years and six to 12 years).

Availability of data

We identified several negative results reported by regulatory bodies as part of drug licensing and approval assessments that had, at least initially, not been published in peer-reviewed journal articles or conference presentations (Symmonds 2004). For example, non-significant primary endpoint data for children with influenza B were only available from the EMEA (WV15758 - EMEA 2005).

Whether these omissions represent true publication bias (failure to publish negative or null results) or time-lag bias (trials with positive results are published more quickly than trials with negative or null results) is not clear, although the latter is well known to exaggerate treatment effects in early meta-analyses (Hopewell 2006). In general, both Roche and GlaxoSmithKline were willing to supply conference abstracts/posters and references to published data but, with the exception of the children subgroup in NAI30010 and NAI30031 (Monto 2002) and a number of clarifications by Roche, would not provide re-analyses or additional data.

Implementation

Diagnosis of influenza

Diagnosing influenza based on clinical features has high sensitivity but limited specificity. In the clinical trials included in this review, this specificity ranged from 24% (Heinonen 2010) to 73% (NAI30009). However, influenza is usually diagnosed based on clinical symptoms and signs in clinical practice outside of a research trial setting. Amongst children aged 14 years or less attending UK general practices with influenza-like illness (fever, cough and respiratory tract illness) during three successive winter seasons, influenza was detected in only 30% to 39% of nasopharyngeal swabs submitted for virological surveillance (Zambon 2001a).

Treating children with neuraminidase inhibitors based on a clinical diagnosis of influenza may decrease their overall benefit. Rapid near-patient influenza tests may improve the accuracy with which children with influenza virus infection can be identified. However, some variation in the performance of different tests has previously been demonstrated. In a direct comparison of four rapid diagnostic tests for influenza amongst a predominantly paediatric population, using viral culture and direct immunofluorescence as a gold standard, sensitivity and specificity ranged from 72% to 95% and 76% to 84%, respectively (Rodriguez 2002).

The predictive value of clinical features and near-patient influenza tests improves during periods of high influenza activity. During an influenza epidemic (number of consultations for influenza-like illness > 100 per 100,000 population), the presence of previous influenza-like contacts, cough, expectoration on the first day of illness and fever (> 37.8 °C) increases the likelihood for influenza threefold (Michiels 2011). A review evaluating the performance of the QuickVue(R) near-patient influenza test found no consistent relationship between the diagnostic performance of QuickVue(R) and the broadness of clinical diagnostic criteria, although the positive predictive value of QuickVue(R) was higher during influenza seasons and epidemics (Petrozzino 2010). Surveillance data on influenza activity in the community should therefore be considered alongside clinical features and near-patient test results when assessing the likelihood of influenza virus infection and potential benefit from prescribing neuraminidase inhibitors in a clinical setting.

Timing of treatment

Successful treatment with neuraminidase inhibitors in adults requires commencement of therapy as soon as possible, when influenza virus replication in the respiratory tract is maximal (Moscona 2005). Data reported in this review are for patients treated

within 24 (Heinonen 2010) to 48 (NAI30028; WV15758; WV15759/WV15871) hours of symptoms onset. Amongst children aged 14 years or younger attending UK General Practices during a winter influenza season who received a clinical diagnosis of influenza infection, 64% presented within two days of becoming ill (Ross 2000). Commencement of therapy is not generally recommended outside this period, although it may be considered for critically ill, hospitalised patients.

WV15759/WV15871 performed subgroup analyses on participants treated < 24 hours and >= 24 hours after the development of symptoms. Differences in time to return to normal health and activity and time to alleviation of symptoms between children treated with oseltamivir or placebo were not statistically significant in either of these subgroups. Participants who received treatment < 24 hours after symptom onset experienced a larger reduction in time to return to normal health and activity than participants treated >= 24 hours after symptom onset. However, the study did not report whether or not this difference was statistically significant. Heinonen 2010 performed a pre-defined subgroup analysis in children treated with oseltamivir within 12 hours of symptom onset. Oseltamivir prevented the development of acute otitis media in this subgroup but no significant reduction in the incidence of acute otitis media in children treated with oseltamivir within 24 hours of symptom onset was observed.

Age-related issues

This review includes treatment trials whose participants were children up to and including 12 years of age. One trial was conducted in preschool children aged one to three years (Heinonen 2010), one in children aged nine years and under (Sugaya 2010) and three in children aged five to 12 years (NAI30009; NAI30028; WV15759/WV15871). WV15758 was conducted in children aged one to 12 years, but Whitley 2001 presented data stratified according to three age groups (up to and including two years, two to five years, older than five years) and Winther 2010 presented summary statistics for the incidence of acute otitis media in children aged one to two years, three to five years and six to 12 years.

Young preschool children with laboratory-confirmed influenza gain the greatest benefit from oseltamivir treatment in terms of reducing the incidence of acute otitis media. WV15758 (Winther 2010) reported that the benefit of oseltamivir treatment in preventing the development of acute otitis media was most evident in children aged one to two years. In Heinonen 2010 oseltamivir treatment within 12 hours of symptom onset significantly reduced the incidence of acute otitis media in children aged one to three years.

WV15758 (Whitley 2001) found that oseltamivir significantly reduced median duration of illness in children aged one to 12 years. However, oseltamivir did not significantly reduce duration of illness in any of the three age subgroups (up to and including two years, two to five years, older than five years). The study also did not report whether differences in shortening of illness duration between these subgroups were statistically significant.

Oseltamivir is an oral medication and suitable for children aged one to 12 years. Zanamivir is delivered by inhalation and is only suitable for children aged five years or older. Laninamivir octanoate (CS-8958) is the prodrug of laninamivir, a long-acting neuraminidase inhibitor being developed by Daiichi Sankyo, which is also delivered by inhalation. In Sugaya 2010, the age range of participants was three to nine years. It may be difficult to administer inhaled antiviral medications successfully to children because of problems generating adequate peak inspiratory flow rates. These problems may still occur in older children. Peng 2000 described 16 children aged five to 12 years who received zanamivir by Diskhaler, of whom five had either no detectable serum zanamivir concentrations at any time during the eight hours after dosing or had zanamivir concentrations below quantifiable limits at later time points in the study. Furthermore, FDA 2003 (NAI30009) states that zanamivir "is indicated only for children seven years of age or older". This evaluation is based on the combination of lower estimates of treatment effect in five and six year olds compared with the overall study population and evidence of "inadequate inhalation through the Diskhaler". Since we do not have access to efficacy data for zanamivir by age group, it is reasonable to agree with the FDA's opinion that zanamivir be limited to children aged seven years or older. Laninamivir octanoate may be easier to administer effectively in younger children than zanamivir because it can be given as a single inhaled dose whereas the treatment regimen of zanamivir involves twice-daily inhaled doses over a five-day period.

Development of resistance

The emergence of strains of influenza resistant to amantadine and rimantadine, with no decrease in virulence, has been well documented. However, resistance to neuraminidase inhibitors can also arise through mutations in haemagglutinin or neuraminidase (Zambon 2001b). Increasing oseltamivir resistance has been reported internationally and may be associated with an increased risk of influenza-related complications. During the 2008/2009 influenza season, a total of 30 countries from all WHO regions reported oseltamivir resistance for 1291 of 1362 A(H1N1) viruses analysed. The prevalence of oseltamivir resistance was very high in Canada, Hong Kong Special Administrative Region (SAR), Japan, the Republic of Korea, USA, France, Germany, Ireland, Italy, Sweden and the UK (WHO 2009). A recent meta-analysis (Thorlund 2011) reported a pooled incidence rate for oseltamivir resistance of 2.6% (95% CI 0.7% to 5.5%) and found that oseltamivir resistance was significantly associated with pneumonia. However, the pooled incidence rate for zanamivir resistance was 0% and the incidence of peramivir resistance was 0% in one included study. The documented rates of oseltamivir resistance following treatment have been higher in children than in adults, perhaps because children shed virus particles for longer or have a less effective initial immune response to infection (Moscona 2005). In NAI30009 no evidence of zanamivir resistance was reported (although this was investigated in a sample of only nine children) and in Gubareva 1998 the treatment regimen and clinical circumstances under which emerged a zanamivir-resistant strain of influenza B were both highly atypical.

Summary of main results

Treatment with oseltamivir or zanamivir is only associated with modest reductions in duration of illness (range 0.4 to 1.5 days) and time to resolution of influenza symptoms (mean difference (MD) 1.36 days, 95% CI 0.76 to 1.95). Based on the findings of one trial, laninamivir octanoate 20 mg produces significantly more rapid alleviation of symptoms than oseltamivir by 2.76 days in children with oseltamivir-resistant influenza.

One trial found that oseltamivir produced a small improvement in FEV_1 in the first six days of illness in children with asthma. Oseltamivir treatment also produces a small reduction in the development of acute otitis media in children aged one to five years with laboratory-confirmed influenza (RD -0.14, 95% CI -0.24 to -0.04), particularly if treatment is commenced within 12 hours of symptom onset. No benefit has been demonstrated for zanamivir.

A household prophylaxis strategy reduces the absolute risk of developing influenza by 8%. This means that 13 children would have to be treated with a 10-day course of zanamivir or oseltamivir to prevent one additional child from developing influenza.

The adverse event profile of zanamivir was no worse than placebo but vomiting was more common in children treated with oseltamivir than with placebo. Oseltamivir was associated with an additional one in 17 children treated developing vomiting. The adverse event profile of laninamivir octanoate was similar to that of oseltamivir.

Overall completeness and applicability of evidence

Attrition rates were low among participants in our included studies. However, there was wide variation in the duration of follow-up between different studies, ranging from five days (NAI30028) to 28 days (WV15758; WV15759/WV15871). The completeness of data collected on clinical efficacy outcomes and adverse events may have been restricted in studies with shorter follow-up periods. WV15758 (Winther 2010) reported age-stratified data on the development of new acute otitis media infections as risk ratios and 95% CIs. Since no raw data were reported, we were unable to include these participants in Analysis 1.4.

The findings of this review are mainly applicable to healthy children who are not in 'at risk' groups. We only found one trial (WV15759/WV15871) which was conducted in an 'at risk' group of children (children with asthma) even though, as previously mentioned, children in 'at risk' groups with underlying chronic medical conditions are at greater risk of developing complications of influenza (Meier 2000).

Levels of influenza activity also need to be considered carefully when estimating the likely effect of treatment with neuraminidase inhibitors in a clinical setting. Our findings were based mainly on data from children with either laboratory-confirmed influenza (Heinonen 2010; WV15758; WV15759/WV15871) or influenza diagnosed on rapid near-patient testing (NAI30028; Sugaya 2010). However, rapid near-patient influenza tests are not currently used on a routine basis in clinical settings and influenza is therefore diagnosed on initial presentation based on the presence of clinical features of influenza-like illness. The treatment effect of neuraminidase inhibitors is likely to be less pronounced in patients with influenza-like illness, since only a proportion will have influenza virus infection.

In populations where a high proportion of children are vaccinated against influenza, the apparent efficacy of neuraminidase inhibitors may be reduced as the severity of influenza illness is often milder in vaccinated than in unvaccinated children. There was significant variation in the rates of influenza vaccination between trials comparing oseltamivir or zanamivir with placebo, ranging from 2% (NAI30009) to 19% (WV15759/WV15871). In studies involving a high proportion of vaccinated children, the apparent efficacy of neuraminidase inhibitors may be reduced as the severity of influenza illness is often milder in vaccinated than in unvaccinated children. In Sugaya 2010, 47% of children had been vaccinated against influenza. Vaccination rates varied between 35.5% in the oseltamivir group and 55.7% in the laninamivir 40 mg group. However, the authors report that the differences in vaccination rates between the three arms of their trial were not statistically significant. No baseline data on other vaccinations against infections which might lead to complications in children with influenza, including *Haemophilus influenzae* b (Hib), Meningococcus group C (MenC) and pneumococcal conjugate vaccine (PCV) were presented in any of the included trials.

Since all our included trials were conducted in the context of seasonal influenza, the applicability of their findings in an influenza pandemic is uncertain.

Quality of the evidence

The methodological quality of our included studies was generally moderate. The risk of bias was rated as low in only one of the nine included studies (NAI30009). In four studies the risk of selection bias was unclear, as insufficient details were given about how the randomisation sequence was generated and how allocation concealment was performed (NAI30010; NAI30028; NAI30031 (Monto 2002); WV15759/WV15871). One study provided details of the randomisation method used but not of the method used for allocation concealment (WV15758). One study (WV16193) was open-label but was still included as we deemed the overall risk of bias to be low. The risk of reporting bias was assessed to be high in two studies (Heinonen 2010; WV15759/WV15871), which only reported efficacy outcome findings in participants with laboratory-confirmed influenza. In one study comparing laninamivir octanoate against oseltamivir all but four patients in with influenza A H1N1 2008-2009 were found to have the oseltamivir-resistant H274Y mutation (Sugaya 2010).

Potential biases in the review process

Although we used a comprehensive search strategy for this 2011 update, we only added new published data to this review. As a result, our findings may have been subject to significant publication bias. We added peramivir to our search strategy but did not find any studies involving peramivir which met the eligibility criteria for this review. We found one trial comparing laninamivir octanoate with oseltamivir (Sugaya 2010) but no trials comparing laninamivir octanoate with placebo.

Studies varied both in the outcomes measured and in the consistency of reporting of results, particularly time to resolution of illness and time to resolution of symptoms. Results were not always reported in sufficient detail for children in preschool and school age groups (WV15758 - Winther 2010). These factors severely hampered our ability to pool results from different studies. We pooled together results from placebo-controlled trials of zanamivir and oseltamivir because there were few data available for analysis from our included studies.

None of our included studies was sufficiently powered to determine the effects of neuraminidase inhibitors on serious complications of influenza (such as pneumonia or admission to hospital) and we found no evidence from these trials on efficacy and safety in children aged under one year.

All nine of our included studies received financial support from pharmaceutical companies. These companies included GlaxoSmithKline (NAI30010; NAI30009; NAI30028; NAI30031 (Monto 2002)), Roche Pharmaceuticals (WV16193; WV15758; WV15759/WV15871; Heinonen 2010) and Daiichi Sankyo Co. Ltd (Sugaya 2010).

Agreements and disagreements with other studies or reviews

Comparison to other systematic review

Two Canadian Coordinating Office for Health Technology Assessment (CCOHTA) Reports (Brady 2001; Husereau 2001) and the first UK NHS HTA Report (Burls 2002) comprise reviews of clinical trials of neuraminidase inhibitors in adults but not children. However, the second UK NHS HTA Report included a systematic review and meta-analysis of the use of neuraminidase inhibitors for the prevention and treatment of influenza A and B in both adults and children (Turner 2002). For paediatric trials, there is broad agreement between the evidence bases on which Turner 2002 and this review are based. However, the only treatment trials included in Turner 2002 were WV15758 and NAI30009, whereas this review also included important data on the use of oseltamivir in 'at risk' children from WV15759/WV15871 as well as data from two other placebo-controlled trials of zanamivir (NAI30028) and oseltamivir (Heinonen 2010) and one trial comparing laninamivir octanoate with oseltamivir (Sugaya 2010). Endpoints in Turner 2002 are reported separately for WV15758 and NAI30009, with no pooling of data across the trials and were commensurate with those stated in this review. For NAI30009, data were stratified for 'at risk' and healthy children (data provided on request by GlaxoSmithKline, including re-analysis of time-to-endpoint data allowing for censored observations, consistent with WV15758). No data were reported by influenza serotype; no isolated paediatric data were reported from prevention studies; and no details of adverse events were reported for treatment or prevention trials.

AUTHORS' CONCLUSIONS

Implications for practice

If near-patient testing is available and economic resources permit, oseltamivir may be considered for the treatment of children aged one to 12 years with influenza infection provided that therapy can be commenced within 48 hours of the start of the illness. However, the benefits of oseltamivir treatment are likely to be relatively modest. Oseltamivir reduces duration of illness by about a day and is associated with a slight reduction in the incidence of acute otitis media, particularly in younger children (children aged one to 12 years number needed to treat to benefit (NNTB) = 12 (95% confidence interval (CI) 7 to 34) to prevent one case; children aged one to five years NNTB = 8 (95% CI 5 to 25) to prevent one case). Oseltamivir is the preferred treatment because a reduction in secondary complications, in particular acute otitis media, has not been demonstrated for zanamivir.

If near-patient testing is not available, the case for oseltamivir is less compelling. Benefits will be reduced on a proportionate basis, corresponding to the specificity of clinical diagnosis for influenza infection. Assuming a specificity of 50%, the NNTB to prevent one case of acute otitis media would be doubled to 24.

Oseltamivir may be considered for use in children aged one to 12 years for post-exposure prophylaxis of influenza in the household (when another family member is affected), although the evidence supporting this intervention is weak.

There is currently no high-quality evidence to support targeted treatment of 'at risk' children (with underlying chronic medical conditions) with neuraminidase inhibitors, as benefit has not been shown in this population (oseltamivir and zanamivir) and bronchospasm remains a theoretical risk (zanamivir) (EMEA 2007; FDA 2008; MHRA 2009).

A further Cochrane review on neuraminidase inhibitors in the treatment and prevention of influenza in healthy adults and children was published in December 2011 (Jefferson 2012). This subsequent review includes unpublished study data and may therefore result in different conclusions to those reported in our review, the 2011 update of which only included published data.

Implications for research

More data are needed to clarify the benefits of neuraminidase inhibitors for the treatment of influenza in 'at risk' children (including addressing the potential confounder of prior vaccination) and children with influenza B. In the treatment trials included in this review, children with influenza were identified on a retrospective laboratory basis. Prospective trials are required that use near-patient testing to identify influenza positive children. Greater selectivity in reporting a limited number of clinically relevant outcome measures is also needed to avoid the problems of multiple comparisons. In particular, larger trials are needed to determine the effect of neuraminidase inhibitors on the incidence of serious complications of influenza (such as pneumonia or hospital admission).

Further information on the use of neuraminidase inhibitors for the prevention of influenza in children could be provided directly by future trials, or by re-analysis of data from studies of influenza prophylaxis in households, which included children but did not break-out data for the paediatric population.

Head-to-head comparison of oseltamivir versus zanamivir would allow clarification of the efficacy of these drugs in relation to each other in treating secondary complications and the frequency of drug-related adverse events. Comparing laninamivir against placebo and against oseltamivir in children with oseltamivir-sensitive influenza infection would also help further characterise its efficacy.

Cost-effectiveness studies may help define the role of neuraminidase inhibitors in clinical practice and further data from clinical use in large populations are required to determine the implications of viral resistance in practice.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by year of study]

WV15758

Methods	Double-blind, randomised, placebo-controlled trial Multicentre trial in USA (70 sites) and Canada (10 sites) Recruitment period during northern hemisphere influenza season 1998/1999
Participants	Children aged 1 to 12 years with influenza like illness < 48 hours duration (temperature >= 37.8 °C and at least 1 of cough or coryza) Children were stratified for the presence of otitis media at enrolment Nose and throat swabs obtained for detection of influenza virus at enrolment and on days 6 and 10

WV15758 *(Continued)*

	Children excluded if they had respiratory syncytial virus infection (rapid antigen), hospitalised > 24 h, evidence of poorly controlled systemic illness, immunosuppressed (drugs, transplant recipient, HIV infection), or history of acetaminophen allergy
Interventions	5-day course of twice-daily oral oseltamivir 2 mg/kg to max 100 mg dose (or placebo) All participants were offered acetaminophen for symptomatic relief. Diary cards also recorded the administration of analgesics/antipyretics and compliance with the daily regimen of study medication
Outcomes	Caregiver diary cards were used to record response to therapy. These were measured twice daily and included a) temperature, b) Canadian Acute Respiratory Infection and Flu Scale (CARIFS) which includes 18 different influenza symptoms, rated on a scale of 0 to 3, and c) ability to return to day care/school and/or resumption of their normal "pre-illness" daily activity. Tympanometry was performed at enrolment and on days 6, 10 and 28 Time to resolution of illness from start of treatment: defined as first time at which the following were resolved simultaneously and remained so for at least 24 hours: (1) cough and nasal congestion none or minor problem and (2) return to day care/school or resumption of pre-illness daily activity and (3) temperature < 37.2 °C. Follow-up 28 days Other endpoints: 1) time to return to normal health and activity, 2) incidence of secondary illnesses (i.e. otitis media etc), 3) time to alleviation of all CARIFS symptoms, and the severity of illness for the total CARIFS scores, 4) effects on individual symptoms, 5) acetaminophen and antibiotic use, 6) viral shedding, 7) hospitalisation rates
Notes	There was an updated study looking at acute otitis media specifically and completing a secondary analysis (Winther 2010)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation by site, stratified by presence of otitis media
Allocation concealment (selection bias)	Unclear risk	Insufficient detail
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind placebo or liquid oseltamivir
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis, appropriate censoring and statistical tests
Selective reporting (reporting bias)	Low risk	Reported outcomes in ITT and ITTI populations
Other bias	Low risk	Yes

NAI30010

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study 15 centres in the USA, Canada, Finland and UK

NAI30010 *(Continued)*

	1998 to 1999
Participants	Families in which at least 1 member (index case) developed influenza-like illness (defined as presence of at least 2 of the following: temperature >= 37.8 °C, feverishness, cough, headache, sore throat and myalgia), were randomised to zanamivir or placebo. Eligible family members (contact cases) were >= 5 years of age
Interventions	Contact cases received inhaled zanamivir 5 mg, 2 puffs twice a day for 10 days or inhaled placebo Index cases received inhaled zanamivir 5 mg, 2 puffs twice a day for 5 days or inhaled placebo
Outcomes	Proportion of families with at least 1 initially healthy member in whom symptomatic, laboratory-confirmed influenza A or B developed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised by household. Insufficient description
Allocation concealment (selection bias)	Unclear risk	Insufficient description
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind. Participants were blinded to the drug via a placebo inhaler device
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT Low discontinuation rate
Selective reporting (reporting bias)	Low risk	Full reporting of data
Other bias	Low risk	Index cases were randomised with the household to treatment or placebo

WV15759/WV15871

Methods	Double-blind, randomised, placebo-controlled trial Multicentre trial in Northern and Southern hemispheres Recruitment period during Northern hemisphere influenza season 1998 to 1999 and Southern hemisphere influenza season 1999 Study performed in accordance with declaration of Helsinki. Written informed consent obtained from parent/legal guardian of each participant, and from child if old enough to understand risks/benefits
Participants	Children aged 6 to 12 years with asthma severe enough to require regular medical follow-up monitoring or hospital care, presenting with influenza symptoms (temperature >= 37.8 °C plus cough or coryza) within 48 hours of onset of symptoms Main exclusion criteria were tested positive for respiratory syncytial virus, taking immunosuppressive medications (excluding inhaler or oral steroids for asthma), known HIV infection, uncontrolled re-

WV15759/WV15871 *(Continued)*

	nal/vascular/neurologic/metabolic/pulmonary (excluding asthma) disease, transplant recipients, allergic to test medications or acetaminophen
Interventions	5-day course of twice-daily oral liquid oseltamivir 2 mg/kg or placebo
Outcomes	Primary outcome: time to freedom from illness, defined as time when all of the following were met for a period of 21.5 hours (24 hours =/- 10%): (1) symptoms alleviated (no or minor problem on symptom questionnaire), (2) return to normal health and activity (return to school or normal style of play behaviour), and (3) temperature </= 37.2 °C Secondary outcomes: 1) return to normal health and activity defined as time taken to return to pre-influenza health and activity for a minimum of 21.5 hours, 2) duration of symptoms defined as time to alleviation of all 18 symptoms, 3) asthma exacerbation defined as > 20% reduction from the highest peak flow reading recorded up to day 28 Outcomes evaluated using caregiver held symptom questionnaire which evaluated the Canadian Acute Respiratory Infection and Flu Scale (CARIFS), oral thermometer and peak flow meter Follow-up for 28 days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but no further details
Allocation concealment (selection bias)	Unclear risk	Insufficient detail
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, use of a placebo inhaler
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appropriate censoring and statistical tests
Selective reporting (reporting bias)	High risk	Only reported outcomes in confirmed influenza and per-protocol populations
Other bias	Low risk	

NAI30009

Methods	Double-blind, randomised, placebo-controlled trial Multicentre trial: 67 sites in USA, Canada, Europe/Israel Recruitment period during northern hemisphere winter season 1998/1999
Participants	Outpatient children aged 5 to 12 years with influenza-like illness <= 36 hours duration defined as temperature >= 37.8 °C and no clinical evidence of bacterial infection Patients who had received influenza vaccine for current season were recruited if they demonstrated a positive rapid influenza A or B antigen test

NAI30009 *(Continued)*

	Children excluded if they were hypersensitive to any study medications, recent use of influenza antiviral or investigational drug, immunosuppressed, cystic fibrosis
Interventions	5-day course of twice-daily inhaled zanamivir 10 mg or matched inhaled placebo Relief medications (acetaminophen and dextromethorphan/pholcodeine) were provided to participants, who were advised to refrain from taking them unless necessitated by the severity of their symptoms. Dextromethorphan/pholcodeine was not used in 4 centres
Outcomes	Primary: time to alleviation of clinically significant symptoms of influenza defined as cough none or mild, and arthralgia/myalgia + sore throat + chills/feverishness + headache absent or minimal, and temperature </= 37.8 °C for 3 consecutive assessments Secondary: 1) time to alleviation of clinically significant symptoms with no use of relief medication, 2) use of relief medications, 3) time until the patient returned to normal activities, 4) number of days of Days 2 to 5 of moderate or severe cough, 5) rate of complications, and 6) associated use of antibiotics Follow-up 14 to 28 days (depending on persistence of symptoms)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blindly assigned to zanamivir or placebo in a 1:1 ratio by a computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Yes
Blinding (performance bias and detection bias) All outcomes	Low risk	Randomisation code broken after the study was complete and all the data had been entered and verified in the database
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, "The primary analysis included subjects with incomplete or missing data"
Selective reporting (reporting bias)	Low risk	All stated primary and secondary outcomes were reported
Other bias	Low risk	

NAI30028

Methods	Double-blind, randomised, placebo-controlled trial Multicentre study in Germany (45 centres) 2000 to 2001
Participants	Children age 5 to 12 years with influenza-like illness < 48 hours duration defined as temperature >= 37.8 °C and no clinical evidence of bacterial infection AND rapid influenza test positive. Children must have been able to use the study medication within 48 hours and be able to use a diskholder Exclusion criteria not reported

NAI30028 *(Continued)*

Interventions	Zanamivir 10 mg twice-daily for 5 days (Diskhaler) Placebo (Diskhaler) All participants received paracetamol liquid and cough syrup
Outcomes	Primary: time to alleviation of symptoms defined as temperature consistently < 37.8 °C, at most slight cough, absence of headache, sore throat, feverishness and aching muscles or joints Secondary: 1) time to return to normal activities (school, play school); 2) incidence of complications
Notes	Trial completed and published on the GSK web site; terminated as poor recruitment of influenza-positive children. Not published in a peer-reviewed journal

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but no further details given
Allocation concealment (selection bias)	Unclear risk	Insufficient evidence to permit judgement
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis, insufficient details. Few withdrawals
Selective reporting (reporting bias)	Unclear risk	Data on 95% CIs missing
Other bias	Unclear risk	No full publication; insufficient evidence in available report

NAI30031 (Monto 2002)

Methods	Double-blind, randomised, placebo-controlled trial 59 sites in 11 countries Australia, Canada, Czech Republic, Finland, France, Latvia, New Zealand, South Africa, Sweden, UK and USA 2000 to 2001
Participants	Households were entered into the study if a member had an influenza-like illness defined as at least 2 of the following: fever (temperature >= 37.8 °C) or feverishness, headache, sore throat and myalgia Eligible households were composed of 2 to 5 members, including one child 5 to 17 years of age
Interventions	All household contacts received either inhaled zanamivir 10 mg twice-daily for 10 days or inhaled placebo within 36 hours of symptom onset in the index case Members of the same household received the same study medication Index cases were not treated with influenza antiviral therapy but were given symptomatic medications (acetaminophen, dextromethorphan)

NAI30031 (Monto 2002) *(Continued)*

Outcomes	Primary: development of symptomatic, laboratory-confirmed influenza infection during the period of the prophylaxis, 1 to 11 days Secondary: 1) development of laboratory-confirmed symptomatic or asymptomatic influenza; 2) symptomatic, laboratory-confirmed influenza A; 3) symptomatic, laboratory-confirmed influenza B; 4) laboratory-confirmed influenza and a complication; 5) secondary complications of influenza; 6) symptomatic, laboratory-confirmed influenza in index case matched to that of the contact case who developed influenza; and 7) time to use relief medication
Notes	Data for household contacts < 12 years obtained from GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised by household, did not describe sequence generation
Allocation concealment (selection bias)	Unclear risk	Insufficient detail
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo inhaler
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis, low discontinuation
Selective reporting (reporting bias)	Unclear risk	Data for household contacts < 12 years not available in published study but obtained from GSK
Other bias	Low risk	

WV16193

Methods	Prospective, open-label, parallel-group trial Europe and North America (number of sites not specified) 2000 to 2001
Participants	Household contacts of index cases presenting with influenza-like illness defined as temperature >= 37.8 °C plus cough and/or coryza Eligible households had 3 to 8 members, including at least 1 index case and at least 2 contacts age 1 to 12 years Excluded: children <= 1 year and any household where 1 member was pregnant, breastfeeding, immunosuppressed, cancer, HIV infection, chronic liver or renal disease, significant cardiac failure. Households were not eligible if they had > 1 member of household who met exclusion criteria (eligible if 1 member)
Interventions	Households were randomised by cluster, so that all contacts in the same household received the same treatment. Stratified by the presence/absence of an infant < 1 and by the presence/absence of a second index case in the household

WV16193 *(Continued)*

	Index cases received 5-day course of twice-daily oral oseltamivir 30 to 75 mg (depending on age) within 48 hours of onset of symptoms Household contacts received 10-day course of once-daily oral oseltamivir 30 to 75 mg (depending on age), or placebo, within 48 hours of the onset of symptoms in the index case
Outcomes	Primary: percentage of households with at least one secondary case of laboratory-confirmed influenza within 10 days after starting treatment in the index case Secondary: 1) percentages of households with at least one secondary case of laboratory-confirmed influenza within 10 days of starting treatment where: a) the index case did not have proven influenza in the index case; b) households with introduction of influenza A or B virus; c) individual contacts; and d) children aged 1 to 12 years. 2) Time to alleviation of symptoms (defined as 24-hour period after influenza symptoms scored as mild or none) for: a) treated index case; and b) those who developed illness Follow-up 30 days
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised by household, no further details
Allocation concealment (selection bias)	High risk	Open-label
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT, low discontinuation
Selective reporting (reporting bias)	Low risk	Yes
Other bias	Low risk	This trial was included despite the open-label design as we deemed the overall risk of bias as low

Sugaya 2010

Methods	Double-blind, randomised, placebo-controlled trial Multicentre trial involving 43 institutions in Japan December 2008 to March 2009
Participants	Inclusion criteria: children 9 years of age and under who presented within 36 hours of the onset of any influenza symptom, had an axillary temperature of >= 38.0°C, and could inhale the test drug successfully. Influenza virus infection was diagnosed by the investigator based on the results obtained with a rapid diagnostic kit Exclusion criteria: suspected of having an infection by bacteria or a non influenza virus within 1 week before enrolment, reported any influenza-like symptoms within 1 week before the onset of influen-

Sugaya 2010 *(Continued)*

	za, had any chronic respiratory disease, cardiovascular disease, central nervous disorder, renal dysfunction, metabolic disorder, immune dysfunction or other severe disorder, had a history of abnormal behaviour while infected with influenza virus, or had been treated with amantadine, zanamivir or oseltamivir within the previous 4 weeks
Interventions	Laninamivir octanoate 40 mg inhaled single dose on day 1 of trial calendar Laninamivir octanoate 20 mg inhaled single dose on day 1 of trial calendar Oseltamivir 2 mg/kg body weight twice-daily for 5 days to participants whose body weight was < 37.5 kg or 75 mg twice-daily for 5 days to participants whose body weight was >= 37.5 kg (oral) Patients were allowed to use acetaminophen as a rescue medication for symptom relief
Outcomes	Primary outcome: time to alleviation of influenza illness, defined as the interval between the start of the trial treatment and the start of the first 21.5-hour period in which the nasal symptoms and cough had improved to “absent” or “mild” and axillary temperature had returned to 37.4 °C or below Secondary outcomes: 1) median time to return to normal axillary temperature, and 2) the proportion of participants shedding virus at each time point
Notes	1 patient received laninamivir 20 mg and oseltamivir. This patient was analysed as a member of the original treatment group (laninamivir 20 mg) in full analysis set and safety analysis set but excluded from per-protocol set

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned to 1 of the 3 treatment groups in a 1:1:1 ratio
Allocation concealment (selection bias)	Low risk	The allocation sequence was generated by a computer and stratified according to the institution and type of influenza virus based on the results of testing with a rapid diagnostic kit capable of detecting influenza A and B viruses separately
Blinding (performance bias and detection bias) All outcomes	Low risk	The participants, their legally acceptable representatives, the investigators and the trial personnel were blinded to the allocation sequence throughout the trial by using a double-dummy method
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate
Selective reporting (reporting bias)	Low risk	Reported findings for ITT (full analysis set) and per protocol analysis set
Other bias	High risk	Among the 112 participants infected with influenza A/H1N1 2008-2009, all but 4 had the oseltamivir resistant H274Y mutation

Heinonen 2010

Methods	Double-blind, randomised, placebo-controlled trial Single primary care study clinic in Turku, Finland

Heinonen 2010 *(Continued)*

	January to April 2008, January to March 2009
Participants	Children age 1 to 3 years with < 24-hour history of fever (oral, rectal or axillary temperature >= 38 °C) and >= 1 sign or symptom or respiratory infection (cough, rhinitis or sore throat) or positive rapid Influenza test Exclusion criteria: virologically confirmed infection other than influenza, suspicion of serious invasive bacterial infection requiring immediate hospitalisation, poorly controlled underlying medical condition, known immunosuppression, allergy to oseltamivir, oseltamivir treatment within the preceding 4 weeks, participation in another clinical trial with an investigational drug
Interventions	Oseltamivir suspension 30 mg twice daily (children <= 15 kg) for 5 days Oseltamivir suspension 45 mg twice daily (children 15.1 to 23.0 kg) for 5 days Placebo All participants' parents were advised to give children relief medication (antipyretics and/or analgesics) as needed
Outcomes	Primary outcome: development of acute otitis media in children with laboratory-confirmed influenza in whom the treatment was started within 24 hours of the onset of symptoms Secondary outcome: 1) time to resolution of illness, defined as the interval from the administration of the first dose of the study medication to the first time when the following conditions were met simultaneously and lasted so for 24 hours: temperature 37.5 °C, rhinitis and cough either absent or mild, a healthy appearance and a return of the child to normal activities; 2) time to resolution of all symptoms (requiring total absence of cough and rhinitis); 3) resolution of fever (37.5 °C); 4) parental absence from work; 5) child's absence from day care; 6) use of relief medications or antibiotics; 7) incidence of complications other than acute otitis media; and 8) hospitalisation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Treatments randomised in blocks of 4 with an allocation ratio of 1:1. Despite randomisation, participants with laboratory-confirmed influenza were not evenly distributed between the 2 treatment arms (oseltamivir 18% (37/204), placebo 30% (61/204), RR 0.6, P < 0.007)
Allocation concealment (selection bias)	Low risk	Study drugs were forwarded to investigators in individually sealed and consecutively numbered packages. In consecutive order of study entry, children were given the next available package of medication that contained oseltamivir or matching placebo
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was a low attrition rate in the safety (intention-to-treat) safety population in whom data on adverse events were reported. Of the 202 participants in the oseltamivir group, 1 was lost to follow-up and 2 discontinued treatment early due to refusal to take study medication and 9 discontinued treatment early due to adverse events. Of the 204 participants in the placebo group, 1 participant was lost to follow-up and 5 discontinued treatment early due to adverse events. However, the study only reported data on efficacy outcomes in the subgroup of children with laboratory-confirmed influenza.

Heinonen 2010 *(Continued)*

Selective reporting (reporting bias)	High risk	The study only reported data on efficacy outcomes in the subgroup of children with laboratory-confirmed influenza (n = 91). Children were considered to have laboratory-confirmed influenza if any nasal swab taken on any clinic visit tested positive for influenza by any laboratory method.
Other bias	Low risk	

See references to included studies for details of all sources of data. Additional safety and tolerability data, for which Study IDs are not explicitly stated, are reported from FDA 2003 (NAI30009) and FDA 2004 (WV15758).
bid: twice a day
CIs: confidence intervals
GSK: GlaxoSmithKline
h: hour
ITT: intention-to-treat
ITTI: intention-to-treat-infected
RR: risk ratio
RD: risk difference

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

Study	Reason for exclusion
Chik 2004	Prospective, observational study of the treatment of paediatric haematology inpatients with oseltamivir
Cole 2002	Retrospective study of health insurance claims data examining the effect of zanamivir on complications of influenza in 4674 patients, including 22 children aged 5 to 11 years. Not eligible for analysis of treatment efficacy; no paediatric safety data provided
Deng 2004	Did not include paediatric cases aged <= 12 years
Dutkowski 2010	A double-blind, randomised, placebo-controlled trial to assess the safety and pharmacokinetics of oseltamivir at standard and high dosages (5, 225 or 450 mg twice daily (every 12 h) for 5 days). Did not include paediatric cases aged <= 12 years
Goldstein 2010	An observational study of oseltamivir for the treatment and prevention of pandemic influenza A/H1N1 virus infections in households. Comparisons made between oseltamivir administered at different time intervals after symptom onset. Oseltamivir was not compared to either placebo or other antivirals
Gubareva 1998	Case report of zanamivir-resistant influenza B emerging in an immunocompromised girl aged 18 months treated for 2 weeks with nebulised zanamivir
Gums 2008	A retrospective cohort study to assess influenza-related secondary complications, hospitalisation and healthcare expenditure in healthy adults and children. Patients treated with oseltamivir were matched in a 1:1 ratio with patients with no evidence of antiviral therapy using the nearest neighbour approach
Hata 2004	Uncontrolled, observational study examining the reliability of a rapid diagnostic test in the diagnosis of influenza in 887 paediatric patients, including 337 treated with amantadine or oseltamivir. Not eligible for analysis of treatment efficacy; full report in Japanese, not translated
Holodniy 2008	An open-label, randomised, 3-arm pharmacokinetic drug interaction study. Participants in group 1 received a single dose of 75 mg of oseltamivir taken orally every 24 h for 15 days. Participants in group 2 received a single dose of 75 mg of oseltamivir taken orally every 48 hours plus probenecid at 500 mg taken orally 4 times daily for 15 days. Participants in group 3 received a single dose of 75

Study	Reason for exclusion
	mg of oseltamivir taken orally every 48 hours plus probenecid 500 mg taken orally twice daily for 15 days. Did not include paediatric cases aged <= 12 years
Hu 2004	Cost-effectiveness analysis
Imamura 2003	Inpatient study, controls from a different cohort
Ishizuka 2010	Double-blind, randomised, placebo-controlled trials of laninamivir to assess its safety, tolerability and pharmacokinetics after inhaled administration of its prodrug, CS-8958. Did not include paediatric cases aged <= 12 years
Kano 2007	An observational study comparing the proportions of children previously treated with oseltamivir who had persistent influenza A infection based on rapid influenza testing at different time intervals after resolution of fever
Kashiwagi 2000	A randomised controlled trial, but no paediatric cases
Kawai 2003	Open-label study comparing age, time to administration and type of influenza against length and magnitude of fever. No placebo-controlled group
Kawai 2005	An observational study of factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza
Kawai 2006	An observational study comparing the effectiveness of oseltamivir for the treatment of influenza A and influenza B
Kawai 2007	An observational study of viral shedding
Kawai 2008	An observational study which reported the duration of fever in patients with influenza A or B and who were treated with oseltamivir
Kiso 2004	Uncontrolled, observational study examining the emergence of oseltamivir-resistant influenza virus isolates in 50 patients aged 2 months to 14 years during and after treatment with oseltamivir. No clinical endpoint data
Kohno 2010	A randomised, double-blind, placebo-controlled trial to assess the safety and efficacy of intravenous peramivir in the treatment of seasonal influenza virus infection. Did not include paediatric cases aged <= 12 years
Kubo 2007	A small randomised trial comparing the addition of a Japanese traditional herbal medicine to treatment with oseltamivir
LaForce 2007	A randomised controlled trial of prophylaxis with zanamivir, but did not include a paediatric population aged <= 12 years
Lin 2004	A randomised open controlled trial of oseltamivir in the treatment of influenza in a high-risk population
Lin 2006	A randomised, open-label, controlled trial to evaluate the efficacy and safety of oseltamivir in Chinese patients with chronic respiratory diseases or chronic cardiac disease
Machado 2004	An observational study of the use of oseltamivir in patients who have received a bone marrow transplant
Mitamura 2002	Between January 2000 to July 2002 they enrolled 162 children admitted to hospital, treated with oseltamivir 2 mg/kg/day and 4 mg/kg/day amantadine and compared them to an untreated group, measuring the duration of fever and length of stay

Study	Reason for exclusion
	The article was reviewed by a native Japanese-speaking lab member. It was excluded as it was not a RCT; the comparison groups were derived from a separate cohort of patients in a previous year
Nordstrom 2004	A retrospective cohort study of skin reactions in patients with influenza treated with oseltamivir. The study focused on 2 primary cohorts: influenza with oseltamivir and influenza without oseltamivir. The incidence rate ratios of skin reactions in paediatric cases aged <= 12 years were not reported separately
NV16871	This was a RCT of the use of oseltamivir in the treatment of symptomatic influenza in children and adolescents aged from 6 to 17 with asthma. The primary outcome was the change in FEV1 over the dosing period from their worst recording on days 1 to 2. The analysis was by infected, intention-to-treat The study suffered from low recruitment. Furthermore, only 28% of those enrolled had laboratory-confirmed influenza The study has not been published in a peer-reviewed journal Roche were unable to supply us with subgroup data for children 12 years or less of age. This trial was therefore excluded from the primary analysis
NV20236	This was an open-label trial, which enrolled 56 children aged between 1 and 12 years, who, in the view of the primary care physician, may benefit from 6 weeks of continuous influenza prophylaxis with oral oseltamivir. The primary outcome was to assess its safety and tolerability, with a secondary outcome measure of incidence of influenza As this trial did not contain a control group it was excluded from the analysis
Okamoto 2005	A case series of 103 consecutive infants < 1 year old treated with oseltamivir for influenza
Oo 2003	A pharmacokinetic study in children. No cases of influenza
Peters 2008	A retrospective cohort study
Sato 2005	A non-blinded, randomised trial in which children aged 12 and under who were seen in clinic, tested positive for influenza A or B with a rapid antigen diagnostic kit, and admitted to hospital within 48 hours on clinical grounds, and without "obvious bacterial infection or underlying illness" were recruited. The treatment arms were oseltamivir, zanamivir via jet-nebuliser and placebo (of an unknown nature). The primary outcome was time to resolution of fever This study was rejected on that basis that the primary outcome of time to resolution of fever is not the same as ours, furthermore they did not detail antipyretic usage; it was non-blinded; and the use of in hospital participants
Sato 2008	Recruited symptomatic, influenza-positive children across four influenza seasons from 2001 to 2005 presenting to a Japanese paediatric outpatient. The guardian was offered oseltamivir as treatment; the 15% who declined made up the control group. They compared oseltamivir's efficacy in curtailing the length of fever compared to controls, and depending on the type of influenza Excluded as non-randomised, unblinded trial, with a surrogate primary outcome measure
Shapira 2010	Abstract of a randomised, placebo-controlled trial to establish the safety and tolerability of a 12-week course of oseltamivir prophylaxis in haemopoietic stem cell transplant recipients. Data on paediatric cases aged <= 12 years were not reported separately
Sugaya 2007	Observational study of the effect of the type of influenza on the duration of fever in children treated with oseltamivir

Study	Reason for exclusion
Sugaya 2008	Observational study comparing the length of fever in influenza A and B with treatment with oseltamivir, zanamivir and those who opted not to receive neuraminidase inhibitors
Tamura 2005	Study compared 3 groups of children with influenza: children < 1 year old treated with oseltamivir, older children treated with oseltamivir and no treatment. Treatment was not randomly allocated or blinded
Tan 2002	A randomised controlled trial undertaken in adults
Vogel 2002	An observational study comparing the length of illness before and after the availability of neuraminidase inhibitors
Waskett 2001	Pooled analysis of safety data from double-blind, randomised, placebo-controlled trials of oseltamivir for the treatment of influenza, including trials in children aged 1 to 12 years. Conference abstract; no paediatric safety data provided
Welliver 2001	A randomised controlled trial of prophylaxis with oseltamivir. Children aged <= 12 years were not recruited
Yamaura 2003	An observational study comparing the re-consultation rate with differing periods of treatment with oseltamivir (a natural experiment due to supply shortages)

FEV1: forced expiratory volume in one second
h: hour
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

ISRCTN43083885

Methods	Phase II double-blind randomised clinical trial
Participants	Inclusion criteria: age >= 1 year; fever >= 38.0 °C; at least 1 respiratory symptom (cough, dyspnoea, sore throat); illness (onset of fever, respiratory symptoms or constitutional symptoms began in the last 7 days); evidence of severe respiratory disease from influenza or avian influenza Exclusion criteria: pregnancy; breastfeeding; receipt of oseltamivir within the last week; receipt of oseltamivir at higher than standard doses within the last 14 days or during this acute illness, whichever is longer; history of allergy or severe intolerance to oseltamivir; alternate explanation for the clinical findings as determined by the investigator with the information immediately available; creatinine clearance of less than 10 ml/min
Interventions	Oseltamivir standard dose versus higher dose twice daily for 5 days
Outcomes	Primary: Negative reverse transcriptase polymerase chain reaction (RT-PCR) for viral RNA in nose and throat swabs at day 5 in patients with severe influenza infections Secondary: Negative RT-PCR for viral RNA in nose and throat swabs at days 5 and 7 in patients with severe influenza infections Negative RT-PCR for viral RNA in nose and throat swabs at days 5 and 7 in patients with severe human influenza infections

ISRCTN43083885 *(Continued)*

	Negative RT-PCR for viral RNA in nose and throat swabs at days 5 and 7 in patients with severe avian influenza infections Time to sustained negativity of RT-PCR and viral culture in any sample in patients with avian influenza infections Tolerability of high-dose versus standard-dose oseltamivir (incidence and duration of clinical symptoms, number of serious and grade IV adverse events) Frequency of clinical failure in the treatment of severe influenza and avian influenza at days 5 and 10
Notes	Trial completed but no publications available apart from one case report (de Jong 2005)

NCT00298233

Methods	Phase II double-blind randomised trial
Participants	Inclusion criteria: at least 1 respiratory symptom (cough, dyspnoea or sore throat), evidence of severe influenza or avian influenza. Exclusion criteria: received more than 72 hours of oseltamivir (6 doses) within 14 days, received oseltamivir at higher than standard doses within the last 14 days or during current acute illness (whichever is longer), history of allergy or severe intolerance of oseltamivir, alternate explanation for the clinical findings, creatinine clearance less than 10 ml/minute, pregnant or breastfeeding
Interventions	Standard dose for severe influenza: oseltamivir 75 mg twice daily orally (or equivalent dose adjusted for age, weight and kidney function) for 5 to 10 days or placebo High dose for severe influenza: oseltamivir 150 mg twice daily orally (or equivalent dose adjusted for age, weight and kidney function) for 5 to 10 days Standard dose for avian influenza: oseltamivir 75 mg twice daily orally (or equivalent dose adjusted for age, weight and kidney function) for 5 to 10 days or placebo High dose for avian influenza: oseltamivir 150 mg twice daily orally (or equivalent dose adjusted for age, weight and kidney function) for 5 to 10 days
Outcomes	Primary: percentage of participants with severe influenza that have no viral shedding at day 5, as assessed by negative Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) for viral RNA in nose and throat swabs Secondary: clinical, virologic and exploratory endpoints
Notes	No further details given on secondary outcomes

NCT00412737

Methods	Double-blind, randomised placebo-controlled trial
Participants	Solid organ transplant or haemopoietic stem cell transplant recipients; aged >= 1 year; negative for an influenza rapid diagnostic test; no influenza-like illness symptoms
Interventions	Oseltamivir 75 mg capsules for oral administration; oseltamivir dry powder for suspension for oral administration. Duration of treatment = 12 weeks
Outcomes	Primary: relative incidence of laboratory-confirmed clinical influenza in the 2 treatment groups

NCT00412737 *(Continued)*

	Secondary: adverse events, laboratory parameters, vital signs, physical examination findings, phenotypic +/- genotypic resistance
Notes	

NCT00867139

Methods	Trial with 2 randomised arms and 1 open-label arm
Participants	Inclusion criteria for randomised arms (both needed): age >= 7 years, influenza infection (i.e. upper respiratory tract infection) Inclusion criteria for open-label arm (at least 1 criteria required): young age (1 to 6 years) with any influenza severity, proven or probable H1N1 (H274Y) OR history of asthma OR older age (>= 7 years) with no asthma and moderate to severe influenza and/or failure in randomised study monotherapy arm Inclusion criteria for all participants: able to provide informed consent or informed consent may be provided by a guardian, immunocompromised Exclusion criteria: nausea that prevents taking oral medications; use of antiviral medication within 10 days (unless switched from randomised to open-label TCAD (TCAD = amantadine hydrochloride, ribavirin and oseltamivir phosphate); creatinine clearance less than 30 ml/min; current clinical evidence of a recognised or suspected uncontrolled non-influenza infectious illness with onset prior to screening; known hypersensitivity to amantadine, ribavirin, oseltamivir or zanamivir; women who are pregnant, attempting to become pregnant or breastfeeding; psychiatric or cognitive illness or recreational drug/alcohol use that would affect patient safety and/or compliance; uncontrolled seizure disorder or history of seizure activity within 12 months prior to study participation; any significant finding in the patient's medical history or physical exam on Day 1 that, in the opinion of the investigator, would affect patient safety or compliance with the dosing schedule; documented influenza B viral co-infection
Interventions	TCAD randomised arm: TCAD Neuraminidase monotherapy arm: zanamivir or oseltamivir TCAD open-label arm: TCAD for participants who cannot tolerate or are ineligible to receive zanamivir
Outcomes	Primary: safety Secondary: viral load, proportion of patients not shedding virus at day 5 +/-1 and 10 +/-1, viral resistance, duration of symptoms, frequency of confirmed pneumonia, duration of hospitalisation, days on supplemental oxygen, number of ICU admissions and duration, number and duration of intubations, number of deaths, pharmacokinetics of TCAD
Notes	

NV20234

Methods	Randomised, double-blind trial
Participants	Inclusion criteria: age >= 1 year, rapid diagnostic test positive for influenza in 24 hours prior to first dose, immunocompromised (liver and/or kidney transplant, or allogeneic haemopoietic stem cell transplant), receiving immunosuppressant treatment or not immune reconstituted, symptoms suggestive of influenza-like illness

NV20234 *(Continued)*

	Exclusion criteria: influenza vaccination in 2 weeks prior to randomisation, antiviral treatment for influenza in 2 weeks prior to randomisation, > 48 hours between illness onset and first dose of study drug, solid organ transplant other than liver and/or kidney
Interventions	Oseltamivir - conventional dose (30 mg to 75 mg twice daily orally, depending on weight) or high dose (60 mg to 150 mg twice daily orally) for 10 days
Outcomes	Primary: time to alleviation of all clinical influenza symptoms Secondary: virus shedding and viral load, time to resolution of fever, development of secondary illnesses, antibiotic use and hospitalisations, adverse events, laboratory parameters, vital signs
Notes	

Shinjoh 2004

Methods	Details not yet known
Participants	Details not yet known
Interventions	Details not yet known
Outcomes	Details not yet known
Notes	Awaiting copy of full-text review for translation from Japanese

ICU: intensive care unit
RNA: ribonucleic acid
RT-PCR: reverse transcriptase polymerase chain reaction
TCAD: amantadine hydrochloride, ribavirin and oseltamivir phosphate

DATA AND ANALYSES

Comparison 1. Zanamivir and oseltamivir

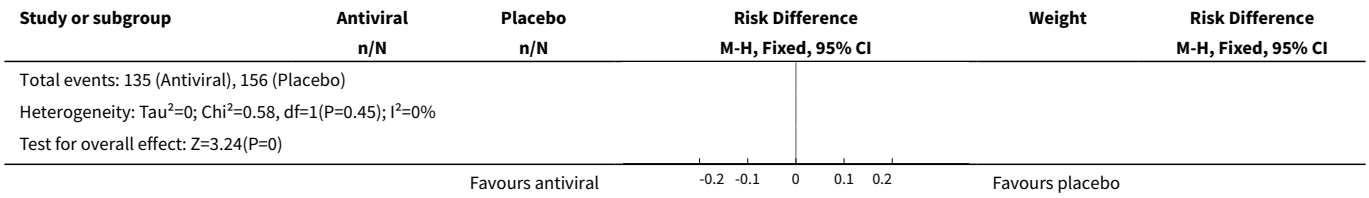
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to resolution of cough	2	585	Risk Difference (M-H, Fixed, 95% CI)	-0.13 [-0.21, -0.05]
2 Incidence of asthma exacerbations in those with confirmed influenza	1	179	Risk Difference (M-H, Random, 95% CI)	-0.05 [-0.15, 0.05]
3 Incidence of otitis media in those with clinical influenza	1	334	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.05, 0.03]
4 Incidence of otitis media in those with confirmed influenza	3		Risk Difference (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Aged 1 to 5 years	2	273	Risk Difference (M-H, Random, 95% CI)	-0.14 [-0.24, -0.04]
4.2 Aged 6 to 12 years	1	208	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.12, 0.05]
4.3 Aged 1 to 12 years	3	816	Risk Difference (M-H, Random, 95% CI)	-0.06 [-0.14, 0.03]
5 Use of antibiotics in those with confirmed influenza	2	798	Risk Difference (M-H, Random, 95% CI)	-0.07 [-0.15, 0.01]
6 Incidence of confirmed influenza in contacts of those with clinical influenza	3	863	Risk Difference (M-H, Random, 95% CI)	-0.08 [-0.12, -0.05]
7 Adverse events in those with clinical influenza	5		Risk Difference (M-H, Random, 95% CI)	Subtotals only
7.1 Any adverse event	4	1766	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.07, 0.01]
7.2 Serious adverse events	5	2172	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.01]
7.3 Adverse events leading to study withdrawal	5	2172	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.01]
7.4 Study withdrawal due to all causes	3	1143	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.02, 0.03]
7.5 Nausea	4	1766	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.00]
7.6 Vomiting - zanamivir	2	737	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.02, 0.02]
7.7 Vomiting - oseltamivir	3	1435	Risk Difference (M-H, Random, 95% CI)	0.06 [0.03, 0.10]
7.8 Diarrhoea	5	2172	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.03, 0.00]

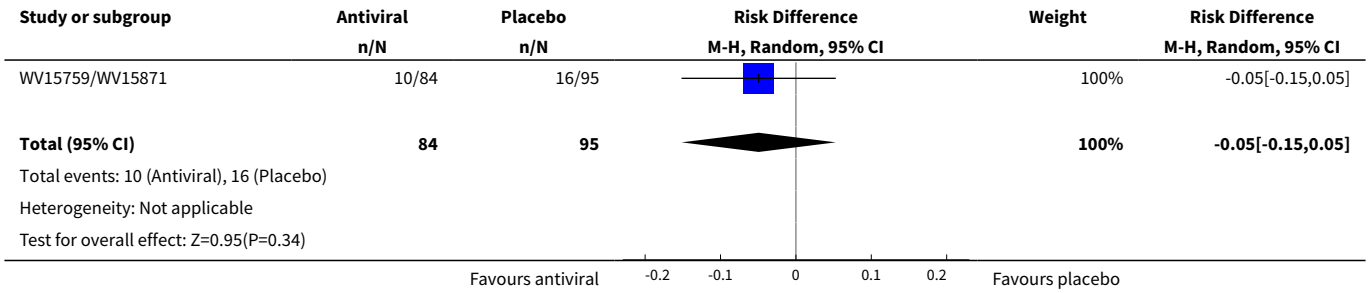
Analysis 1.1. Comparison 1 Zanamivir and oseltamivir, Outcome 1 Time to resolution of cough.

Study or subgroup	Antiviral n/N	Placebo n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
NAI30009	87/164	125/182		61.99%	-0.16[-0.26,-0.05]
NAI30028	48/160	31/79		38.01%	-0.09[-0.22,0.04]
Total (95% CI)	**324**	**261**		**100%**	**-0.13[-0.21,-0.05]**

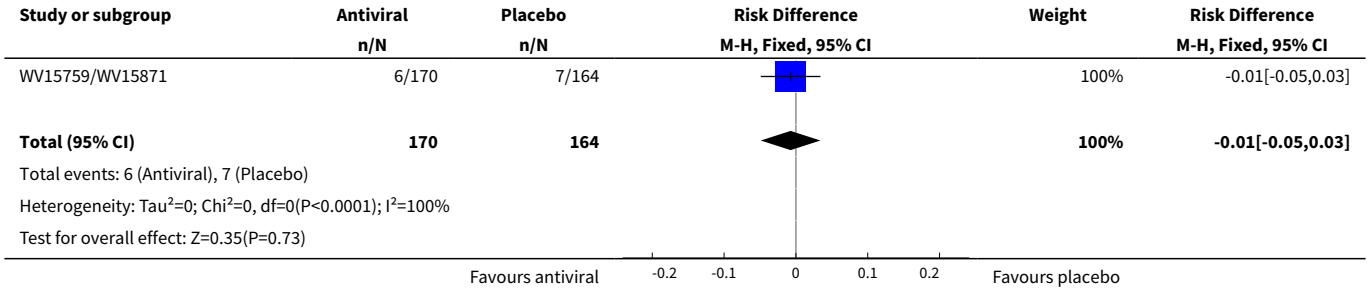
Favours antiviral
Favours placebo



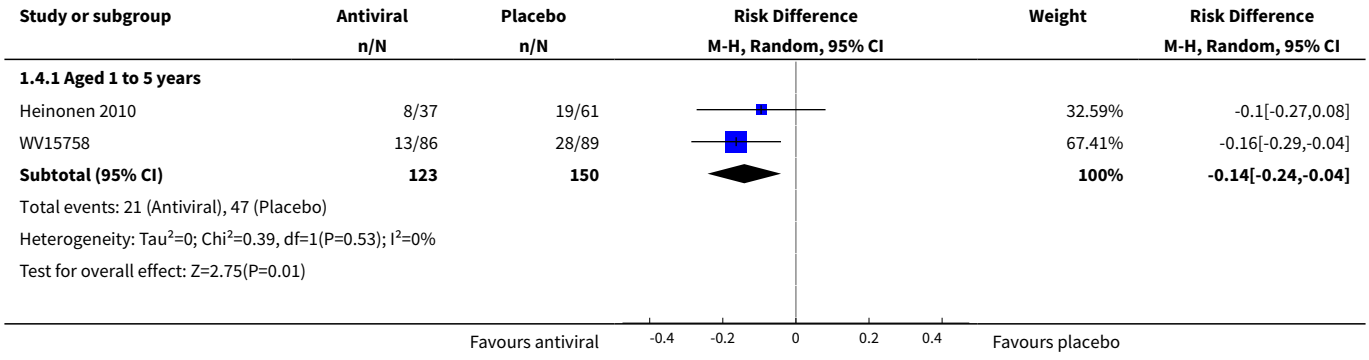
Analysis 1.2. Comparison 1 Zanamivir and oseltamivir, Outcome 2 Incidence of asthma exacerbations in those with confirmed influenza.

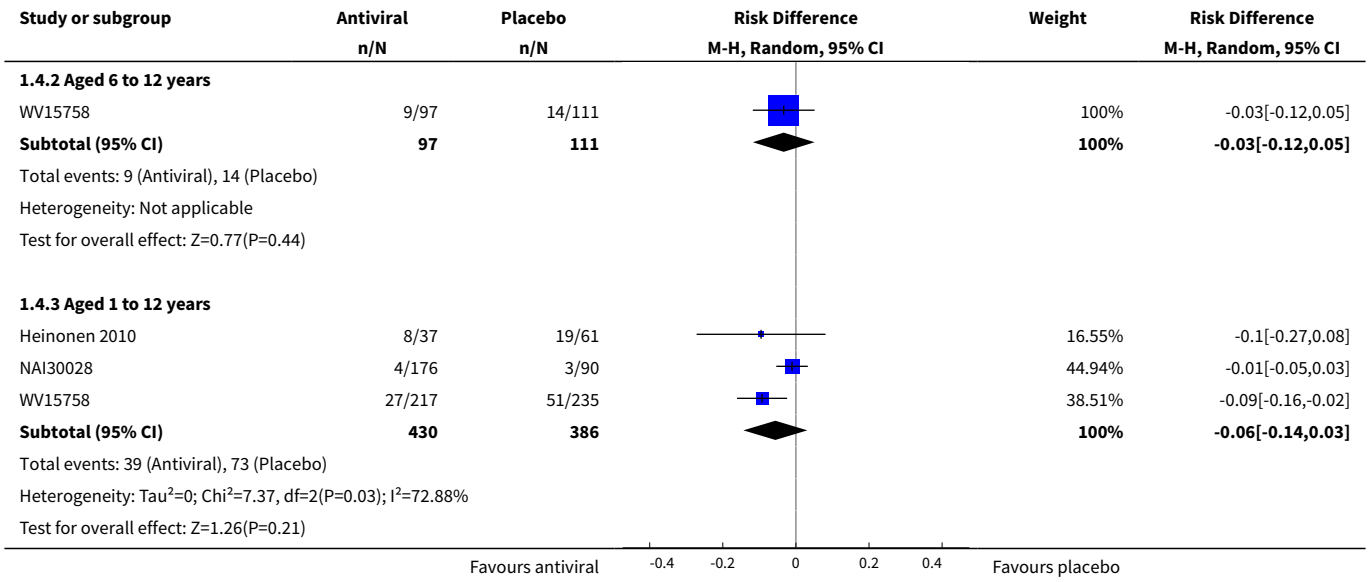


Analysis 1.3. Comparison 1 Zanamivir and oseltamivir, Outcome 3 Incidence of otitis media in those with clinical influenza.

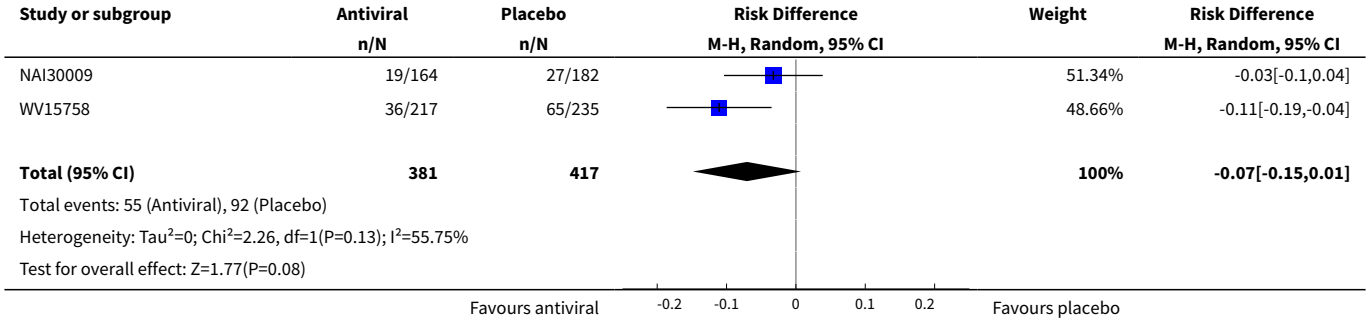


Analysis 1.4. Comparison 1 Zanamivir and oseltamivir, Outcome 4 Incidence of otitis media in those with confirmed influenza.

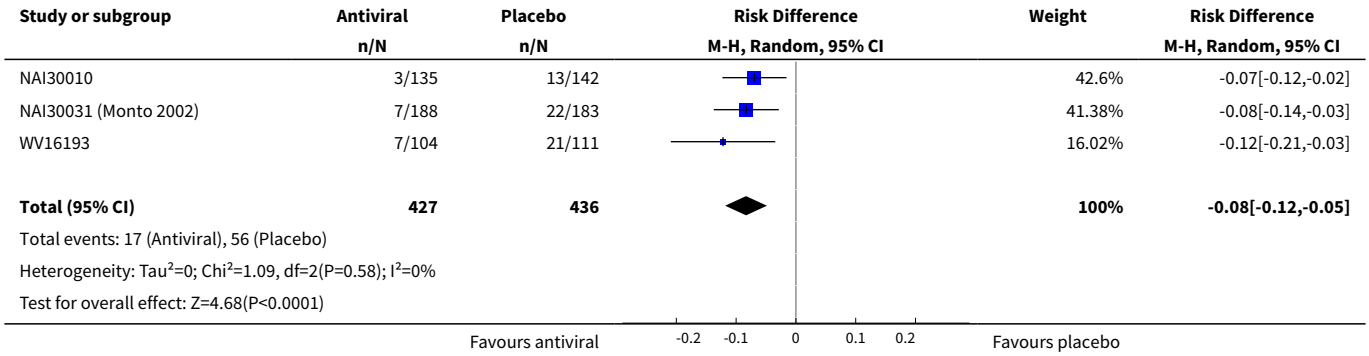




Analysis 1.5. Comparison 1 Zanamivir and oseltamivir, Outcome 5 Use of antibiotics in those with confirmed influenza.

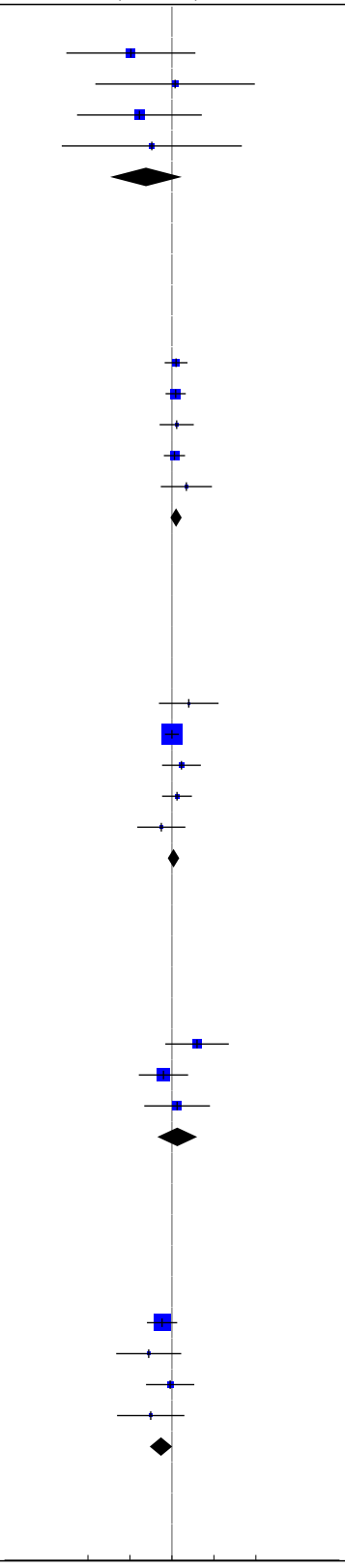


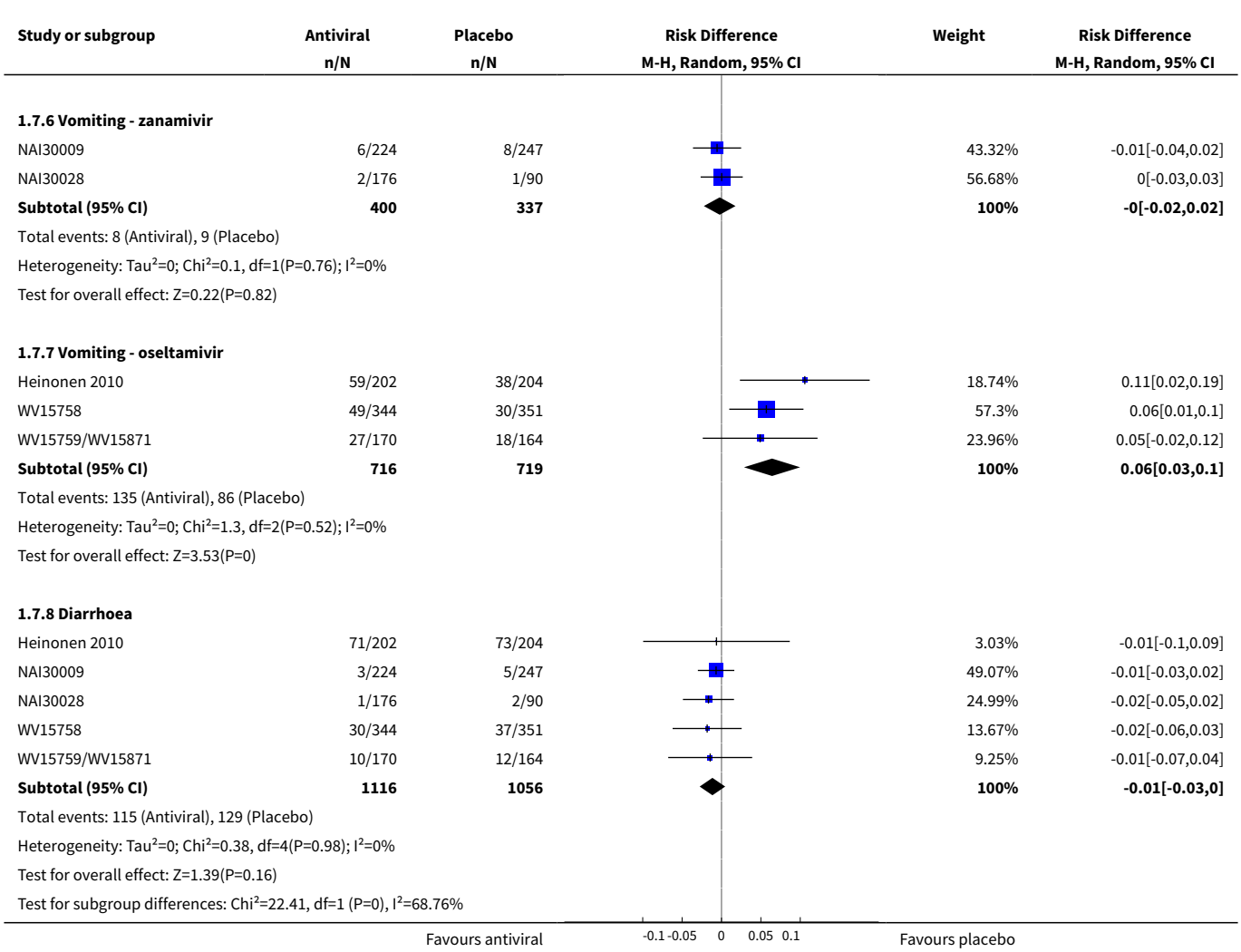
Analysis 1.6. Comparison 1 Zanamivir and oseltamivir, Outcome 6 Incidence of confirmed influenza in contacts of those with clinical influenza.



Analysis 1.7. Comparison 1 Zanamivir and oseltamivir, Outcome 7 Adverse events in those with clinical influenza.

Study or subgroup	Antiviral n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.7.1 Any adverse event					
NAI30009	48/224	65/247		30.88%	-0.05[-0.13,0.03]
NAI30028	30/176	15/90		20.22%	0[-0.09,0.1]
WV15758	168/344	185/351		33.04%	-0.04[-0.11,0.04]
WV15759/WV15871	83/170	84/164		15.86%	-0.02[-0.13,0.08]
Subtotal (95% CI)	**914**	**852**		**100%**	**-0.03[-0.07,0.01]**
Total events: 329 (Antiviral), 349 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.79, df=3(P=0.85); I^2=0%					
Test for overall effect: Z=1.42(P=0.16)					
1.7.2 Serious adverse events					
Heinonen 2010	1/202	0/204		24.47%	0[-0.01,0.02]
NAI30009	1/224	0/247		31.28%	0[-0.01,0.02]
NAI30028	1/176	0/90		10.92%	0.01[-0.01,0.03]
WV15758	3/344	2/351		28.46%	0[-0.01,0.02]
WV15759/WV15871	5/170	2/164		4.87%	0.02[-0.01,0.05]
Subtotal (95% CI)	**1116**	**1056**		**100%**	**0[-0,0.01]**
Total events: 11 (Antiviral), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.87, df=4(P=0.93); I^2=0%					
Test for overall effect: Z=1.44(P=0.15)					
1.7.3 Adverse events leading to study withdrawal					
Heinonen 2010	9/202	5/204		3.68%	0.02[-0.02,0.06]
NAI30009	0/224	0/247		67.21%	0[-0.01,0.01]
NAI30028	2/176	0/90		8.71%	0.01[-0.01,0.03]
WV15758	6/344	4/351		14.74%	0.01[-0.01,0.02]
WV15759/WV15871	2/170	4/164		5.66%	-0.01[-0.04,0.02]
Subtotal (95% CI)	**1116**	**1056**		**100%**	**0[-0,0.01]**
Total events: 19 (Antiviral), 13 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.87, df=4(P=0.42); I^2=0%					
Test for overall effect: Z=0.55(P=0.58)					
1.7.4 Study withdrawal due to all causes					
Heinonen 2010	11/202	5/204		29.62%	0.03[-0.01,0.07]
NAI30009	5/224	8/247		42.25%	-0.01[-0.04,0.02]
NAI30028	5/176	2/90		28.13%	0.01[-0.03,0.05]
Subtotal (95% CI)	**602**	**541**		**100%**	**0.01[-0.02,0.03]**
Total events: 21 (Antiviral), 15 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.76, df=2(P=0.25); I^2=27.46%					
Test for overall effect: Z=0.53(P=0.6)					
1.7.5 Nausea					
NAI30009	1/224	4/247		55.23%	-0.01[-0.03,0.01]
NAI30028	1/176	3/90		11.94%	-0.03[-0.07,0.01]
WV15758	13/344	14/351		21.69%	-0[-0.03,0.03]
WV15759/WV15871	4/170	8/164		11.14%	-0.03[-0.07,0.01]
Subtotal (95% CI)	**914**	**852**		**100%**	**-0.01[-0.03,0]**
Total events: 19 (Antiviral), 29 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.49, df=3(P=0.69); I^2=0%					
Test for overall effect: Z=1.91(P=0.06)					

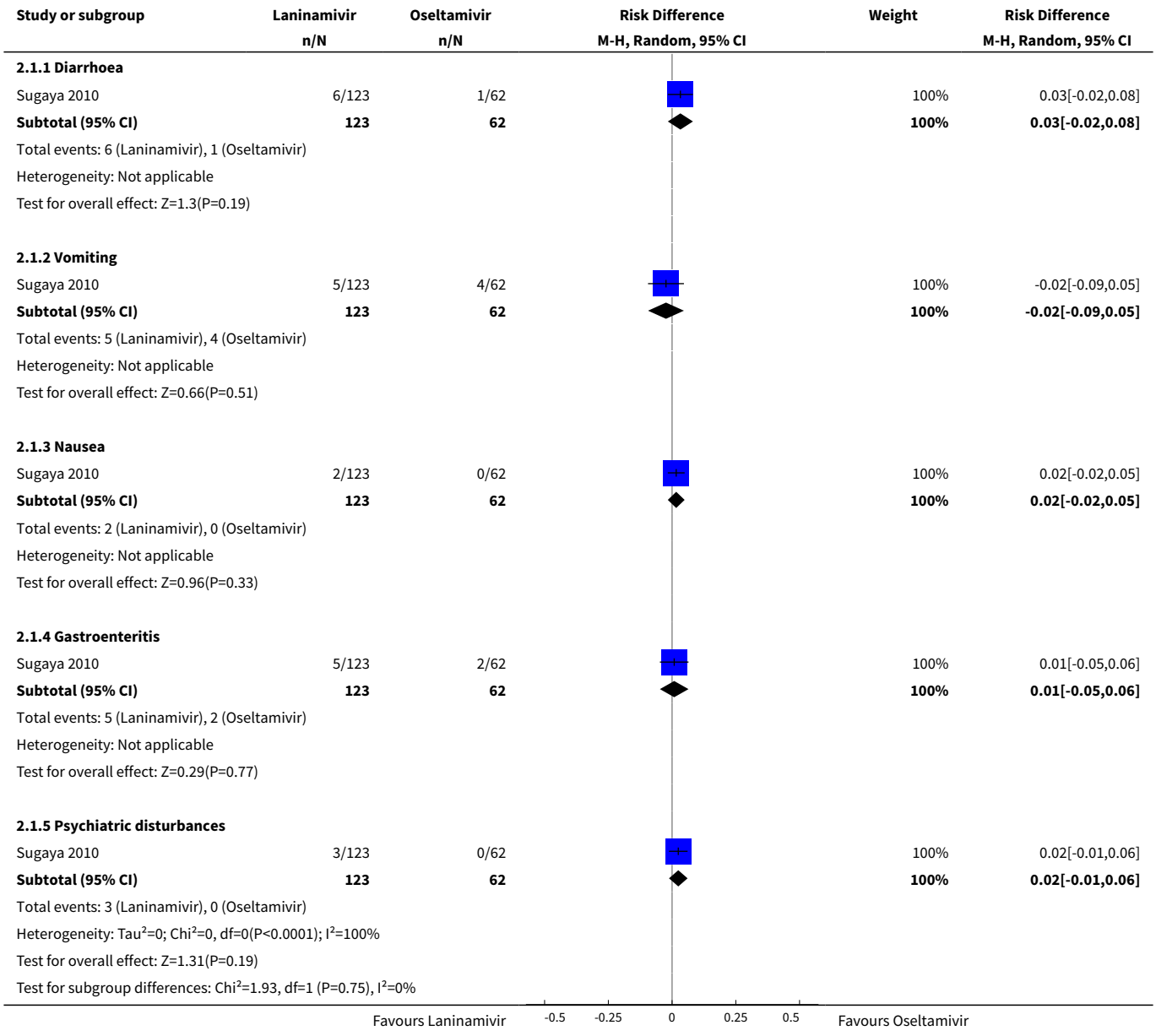




Comparison 2. Laninamivir and oseltamivir

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	1		Risk Difference (M-H, Random, 95% CI)	Subtotals only
1.1 Diarrhoea	1	185	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.02, 0.08]
1.2 Vomiting	1	185	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.09, 0.05]
1.3 Nausea	1	185	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.02, 0.05]
1.4 Gastroenteritis	1	185	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.05, 0.06]
1.5 Psychiatric disturbances	1	185	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.01, 0.06]

Analysis 2.1. Comparison 2 Laninamivir and oseltamivir, Outcome 1 Adverse events.



ADDITIONAL TABLES

Table 1. Baseline characteristics: NAI30009

Characteristic	Suspected influenza (ITT)		ITTI (laboratory-confirmed influenza)	
	Intervention	Control	Intervention	Control
Number	224	247	164	182
Age	Mean 8. 5 years (SD: 2.2)	Mean 8. 9 years (SD: 2.3)	Mean 8.6 years (SD: 2.2)	Mean 9.0 years (SD: 2.3)

Table 1. Baseline characteristics: NAI30009 *(Continued)*

Gender female	97 (43%)	116 (47%)	68 (41%)	91 (50%)
Ethnicity	201 white (90%)	223 white (90%)	148 white (90%)	162 white (89%)
Currently vaccinated	6 (3%)	5 (2%)	2 (1%)	1 (< 1%)
Duration of illness before enrolment	Mean 20.3 hours (SD: 9.4)	Mean 20. 0 hours (SD: 8.8)	Mean 21.6 hours (SD: 9.3)	Mean 20.1 hours (SD: 9.0)
Enrolment temperature (Celsius)	Mean 38.7 (SD +/- 0.67)	Mean 38.6 (SD +/- 0.64)	Mean 38.8 (SD +/- 0.69); 1 patient with temperature < 37.8 at enrolment	Mean 38.7 (SD +/- 0.64); 3 patients with temperature < 37.8 at enrolment
Overall symptom severity at enrolment	125 (56%) moderate 71 (32%) severe	151 (61%) moderate 56 (23%) severe	86 (53%) moderate 56 (34%) severe	107 (59%) moderate 47 (26%) severe
Influenza serotype	A: 106 (47%) B: 58 (26%) A+B: 0 (0%) N/A	A: 120 (49%) B: 62 (25%) A+B: 0 (0%) N/A	A: 106 (47%) B: 58 (26%) A+B: 0 (0%)	A: 120 (49%) B: 62 (25%) A+B: 0 (0%)
'At risk' population (children with a chronic medical condition)	22 (10%) children with chronic respiratory condition	14 (6%) children with chronic respiratory condition	Not reported	Not reported

ITT: intention-to-treat
ITTI: intention-to-treat infected
SD: standard deviation
N/A: not applicable

Table 2. Baseline characteristics: NAI30028

Characteristic	**Symptomatic influenza**	
	Intervention	**Control**
Number	176	90
Age median (range)	7.0 (5 to 14)	8.0 (5 to 14)
Gender: female	66 (37.5%)	37 (41%)
Ethnicity	Not reported	Not reported
Currently vaccinated	Not reported	Not reported
Duration of illness before enrolment	Not reported	Not reported
Enrolment temperature (Celsius)	Not reported	Not reported
Illness severity at enrolment	Not reported	Not reported
Influenza serotype	Not reported	Not reported
'At risk' population (children with a chronic medical condition)	Not reported	Not reported

Table 3. Baseline characteristics: WV15758

Characteristic	ITT (suspected influenza)		ITTI (laboratory-confirmed influenza)		Notes
	Intervention	Control	Intervention	Control	
Number	344	351	217	235	
Age	Median 5 years (range: 1 to 12)	Median 5 years (range: 1 to 12)	Median 5 years (range 1 to 12)	Median 6 years (range 1 to 12)	Data for ITTI from Reisinger 2004
Age distribution	Not reported	Not reported	<= 2 years: 40 (18%) 3 to 5 years: 70 (32%) > 5 years: 107 (49%)	</= 2 years: 58 (25%) 3 to 5 years: 58 (25%) > 5 years: 119 (51%)	Data for ITTI from Dr Z Panahloo, Roche, personal communication, 2002
Gender	173 female (50%)	172 female (49%)	110 female (51%)	115 female (49%)	Data for ITTI from Reisinger 2004
Ethnicity	222 white (65%) 62 Hispanic (18%) 37 black (11%) 7 oriental (2%) 16 other (5%)	229 white (65%) 61 Hispanic (17%) 39 black (11%) 6 oriental (2%) 6 other (5%)	145 white (67%) 72 other (33%)	162 white (69%) 73 other (31%)	Data for ITTI from Reisinger 2004
Currently vaccinated	11 (3%) (vaccination status unknown in 1 (0%))	10 (3%) (vaccination status unknown in 0)	4 (2%)	6 (3%)	Data from Whitley 2000a
Previously vaccinated	21 (6%); 6 (2%) vaccination status unknown	13 (4%); 3 (1%) vaccination status unknown	Not reported	Not reported	Data from Whitley 2000a
Duration of illness before enrolment	Not reported	Not reported	Median 26.7 hours	Median 28.0 hours	
Onset of symptoms > 48 hours	Not reported	Not reported	6 (3%)	7 (3%)	
Enrolment temperature (Fahrenheit)	Not reported	Not reported	102.0°F (range: 96.8 to 106.3)	101.8°F (range: 97.8 to 106.8)	
Illness severity at enrolment	Not reported	Not reported	Median baseline CARIFS symptom score 32 (range: 0 to 52)	Median baseline CARIFS symptom score 30 (range: 5 to 51)	
Influenza serotype	N/A	N/A	A: 150 (69%) B: 66 (31%) A+B: 1 (0%)	A: 153 (65%) B: 82 (35%) A+B: 0 (0%)	
'At risk' population (children with	7 (2%) 'mild asthma'	9 (3%) 'mild asthma'	Not reported	Not reported	Data from Dr Z. Panahloo,

Table 3. Baseline characteristics: WV15758 *(Continued)*

a chronic medical condition)	Roche, personal communication, 2002

ITT: intention-to-treat
ITTI: intention-to-treat infected
CARIFS: Canadian Acute Respiratory Infection and Flu Scale
N/A: not applicable

Table 4. Baseline characteristics: WV15759/WV15871

Characteristic	Intention-to-treat (ITT)		ITTI (laboratory-confirmed influenza)		Notes
	Intervention	Control	Intervention	Control	
Number	170	164	84	95	
Age	Median 9 years (range: 5 to 12 years)	Median 9 years (range 5 to 12 years)	Median 9 years (range 6 to 12 years)	Median 9 years (range 5 to 12 years)	
Sex	59 female (35%)	63 female (38%)	25 female (30%)	35 female (37%)	
Ethnicity	149 white (88%) 21 other (12%)	143 white (87%) 21 other (13%)	73 white (87%) 11 other (13%)	85 white (90%) 10 other (10%)	
Currently vaccinated	31 (18%)	34 (21%)	14 (17%)	11 (12%)	
Previously vaccinated	39 (23%) 5 (3%) vaccination status unknown	37 (23%) 3 (2%) vaccination status unknown	Not reported	Not reported	Whitley 2000
Influenza serotype	N/A	N/A	A: 62%	A: 55%	
'At risk' population (children with a chronic medical condition)	All children had asthma Asthma grade: mild 74 (44%) moderate 83 (49%) severe 13 (8%)	All children had asthma Asthma grade: mild 76 (46%) moderate 80 (49%) severe 8 (5%)	All children had asthma Asthma grade: mild 41 (49%) moderate 40 (48%) severe 3 (3%)	All children had asthma Asthma grade: mild 52 (55%) moderate 39 (41%) severe 4 (4%)	
Time from symptoms onset to first dose	Mean 27.5 hours (SD: 12.1)	Mean 26.9 hours (SD: 12.1)	Mean 27.9 hours (SD: 11.6)	Mean 26.8 hours (SD:11.5)	
Illness severity at enrolment	Median baseline CARIFS symptom score 29.4 (SD 9.9)	Median baseline CARIFS symptom score 30.4 (SD: 8.8)	Median baseline CARIFS symptom score 30.1 (SD: 9.6)	Median baseline CARIFS symptom score 30.9 (SD: 8.7)	
Predicted % of peak flow at baseline	73.2% (SD: 19.2)	72.6% (SD: 18.1)	71.9% (SD: 19.8)	71.0% (SD: 17.0)	
Predicted % of FEV1 at baseline	77.4% (SD: 23.2)	77.8% (SD: 21.4)	75.6% (SD: 21.4)	81.0% (SD: 20.1)	

ITT: intention-to-treat
ITTI: intention-to-treat infected
N/A: not applicable
SD: standard deviation
CARIFS: Canadian Acute Respiratory Infection and Flu Scale
FEV1: forced expiratory volume in 1 second

Table 5. Baseline characteristics: Heinonen 2010

Characteristic - all age groups	Confirmed influenza	
	Intervention	Control
Number	37	61
Age mean (SD)	2.3 (0.8)	2.5 (0.8)
Age distribution (%)	1 to < 2 years =18 (48.6%) 2 to < 3 years = 9 (24.3%) 3 to < 4 years = 10 (27.0%)	1 to < 2 years =19 (31.1%) 2 to < 3 years = 23 (37.7%) 3 to < 4 years = 19 (31.1%)
Gender: female (%)	14 (37.8%)	23 (37.7%)
Ethnicity	Not reported	Not reported
Currently vaccinated (%)	3 (8.1%)	10 (16.4%)
Time from onset of fever to first dose of study medication: mean (SD)	11.1 (6.9)	8.8 (6.6)
Highest temperature before randomisation (Celsius): mean (SD)	38.9 (0.5)	38.9 (0.5)
Illness severity at enrolment	Not reported	Not reported
Influenza serotype	Not reported	Not reported
'At risk' population (children with a chronic medical condition)	Not reported	Not reported
Day care attendance	16 (43.2%)	32 (52.5%)
Preterm birth	5 (13.5%)	3 (4.9%)
Diagnosis of asthma	2 (5.4%)	2 (3.3%)

SD: standard deviation

Table 6. Baseline characteristics: NAI30010

Characteristic - all age groups	Index cases		Household contacts	
	Prophylaxis	Control	Prophylaxis	Control
Number	163	158	414	423

Table 6. Baseline characteristics: NAI30010 *(Continued)*

			(135 children contacts < 12 years)	(142 children contacts, 12 years)
Age years (SD)	20.0 (14.5)	18.9 (13.1)	25.9 (15.6)	26.5 (16.4)
Females	86 (53%)	99 (63%)	236 (53%)	225 (53)
Ethnicity: white	148 (91%)	138 (87%)	377 (91%)	372 (88%)
Currently vaccinated	20 (12%)	13 (8%)	57 (14%)	78 (18%)
Index cases with influenza-confirmed:	78 (48%)	79 (50%)	Not reported	Not reported
Influenza A	51 (31%)	52 (33%)		
Influenza B	27 (17%)	27 (17%)		
Underlying respiratory condition	10 (6%)	11 (6%)	10 (6%)	10 (6%)

No baseline characteristics data are available for the subgroup of children aged under 12 years
SD: standard deviation

Table 7. Baseline characteristics: NAI30031

Characteristic - all age groups	Index cases		Contact cases	
	Prophylaxis	Control	Prophylaxis	Control
Number	245	242	661	630
Age (SD)	18.5 (13.4)	19.0 (13.4)	27.2 (16.1)	27.4 (15.9)
Females	124 (51%)	137 (57%)	363 (55%)	336 (53%)
Ethnicity: white	225 (92%)	226 (93%)	614 (93%)	596 (95%)
Vaccinated prior to randomisation	19 (8%)	13 (5%)	72 (11%)	60 (10%)
Underlying respiratory condition	30 (12%)	29 (12%)	70 (11%)	77 (12%)
Laboratory-confirmed influenza	129 (52.6%)	153 (63.2%)	Not reported	Not reported

No data are available for the subgroup of children aged under 12
SD: standard deviation

Table 8. Baseline characteristics: WV16193

Characteristic - all age groups	Index cases		Contact cases	
	Prophylaxis	Expectant	Prophylaxis	Expectant
Participants (all ages)	150	148	410	402
< 12 years	69	65	107	115

Table 8. Baseline characteristics: WV16193 *(Continued)*

Mean age (range)	14.0 (1 to 60)	14.0 (2 to 66)	23.5 (1 to 80)	25.0 (1 to 83)
Females	92 (61%)	72 (49%)	227 (55%)	219 (54%)
Vaccinated prior to randomisation	Not reported	Not reported	31 (8%)	29 (7%)
Laboratory-confirmed influenza	90 (60%)	94 (64%)	*	*
Influenza A (of those with influenza)	56 (62%)	65 (69%)		
Influenza B (of those with influenza)	34 (38%)	29 (31%)		

No baseline characteristics data are available for the subgroup of children aged under 12 years
*Outcome assessed in study but results not reported

Table 9. Baseline characteristics: Sugaya 2010

Characteristics	**Confirmed influenza**		
	Laninamivir octanoate 40 mg	**Laninamivir octanoate 20 mg**	**Oseltamivir**
Age (years): mean (SD)	6.8 (1.4)	6.9 (1.5)	6.7 (1.5)
Range	3 to 9	4 to 9	3 to 9
Number (%) female	29 (47.5%)	25 (41.0%)	28 (45.2%)
Mean height (cm) +/- SD	120.72 (9.39)	120.83 (9.43)	121.60 (10.44)
Mean weight (kg) +/- SD	23.09 (5.40)	23.12 (4.93)	23.68 (5.23)
Number (%) vaccinated against influenza	34 (55.7%)	30 (49.2%)	22 (35.5%)
Number (%) positive for influenza on rapid diagnostic test	61 (100.0%)	61 (100.0%)	62 (100.0%)
Number (%) with laboratory-confirmed influenza	61 (100.0%)	61 (100.0%)	58 (93.5%)
Mean axillary temperature (°C) +/- SD	38.86 (0.54)	38.84 (0.65)	38.63 (0.53)
Mean duration of illness before treatment (hours) +/- SD	18.19 (7.74)	18.19 (8.13)	19.09 (8.50)

SD: standard deviation

Table 10. Resolution of influenza illness: antiviral versus placebo

Study	Median days to resolution or alleviation of symptoms			Median days to resolution of illness§			Median days to return to school or normal activities		
	Antiviral	Control	Difference (95% CI)	Antiviral	Control	Difference (95% CI)	Antiviral	Control	Difference (95% CI)
Confirmed influenza									
NAI30009	4·0	5·25	1.25 (0.5 to 2.0) P < 0.001	—	—	—	*	*	1 day (NA) P = 0.022
NAI30028	5.0	5.5	0.5 (NA) P = NA	—	—	—	36% (62/172) at day 5	28% (25/89) at day 5	RD = 0.08 (-0.04 to 0.20) P = 0.19
WV15758	2.6	4.2	1.5 (NA) P < 0.0001	4.2	5.7	1.5 (0.3 to 2.5) P < 0.0001	*	*	*
WV15759/ WV15871	3.8	4.8	1.1 (NA) P < 0.12	5.2	5.6	0.4 (NA) P = 0.54	4.2	4.8	0.5 (NA) P = 0.46
Heinonen 2010[a]	10.4	13.3	2.8 (NA) P < 0.001	4.3	5.7	1.4 (NA) P = 0.004	2.0	4.0	2.0 (NA) P = 0.01
Clinical influenza									
NAI30009	4.5	5.0	0.5 (0.0 to 1.5) P = 0.011	—	—	—	*	*	1 day (NA) P = 0.019
NAI30028	—	—	—	—	—	—	—	—	—
WV15758	*	*	*	4.4	5.3	0.9 (0.2 to 1.9) P = 0.0002	*	*	*
WV15759/ WV15871	*	*	*	*	*	*	*	*	*
Heinonen 2010	—	—	—	—	—	—	—	—	—

CI: confidence interval
NA: not available
RD: risk difference
§Median days to resolution of illness defined as alleviation of symptoms + return to normal activities + afebrile

*Outcome assessed in study but results not reported
—Outcome not assessed in study
αChild's absence from day care for median days to return to school or normal activities (children aged one to three years)

Table 11. Resolution of influenza symptoms: antiviral versus placebo

Study	Time to resolution of fever			Time to resolution of cough		
	Median number of days (95% CI or IQR) or proportion with fever (%)			Median number of days (95% CI) or proportion with cough (%)		
	Antiviral	Control	Difference (95% CI)	Antiviral	Control	Difference (95% CI)
Confirmed influenza						
NAI30009	*	*	*	At day 2, 87/164 (53%)	At day 2, 125/182 (69%)	RD = -0.16 (-0.26 to -0.05) P = 0.003
NAI30028	At day 5, 11/167 (7%)	At day 5, 6/83 (7%)	RD = -0.01 (-0.07 to 0.06) P = 0.92	At day 5, 48/160 (30%)	At day 5, 31/79 (39%)	RD = -0.09 (-0.22 to 0.04) P = 0.16
WV15758	1.8 (1.7 to 2.0)	2.8 (2.3 to 3.3)	1, P = 0.0001	1.6 (1.3 to 2.2)	3.0 (2.6 to 3.4)	1.3, P = 0.0008
WV15759/ WV15871	*	*	*	*	*	*
Heinonen 2010	1.7 (IQR: 0.9 to 2.9)	2.9 (IQR: 1.2 to 4.7)	1.2, P = 0.004	—	—	—
Clinical influenza						
NAI30009	*	*	*	*	*	*
NAI30028	—	—	—	—	—	—
WV15758	*	*	*	*	*	*
WV15759/ WV15871	*	*	*	*	*	*
Heinonen 2010	—	—	—	—	—	—

CI: confidence interval
IQR: Interquartile range
*Outcome assessed in study but results not reported
RD: risk difference
—Outcome not assessed in study

Table 12. Resolution of influenza symptoms: laninamivir octanoate 40 mg versus laninamivir 20 mg versus oseltamivir

Study	Median hours to resolution of illness			Median difference in hours to resolution of illness		
	Laninamivir octanoate 40 mg	Laninamivir octanoate 20 mg	Oseltamivir	Laninamivir octanoate 40 mg versus oseltamivir	Laninamivir octanoate 20 mg versus oseltamivir	Laninamivir octanoate 40 mg versus laninamivir octanoate 20 mg
Sugaya 2010	55.4 (46.3 to 81.3)	56.4 (43.7 to 69.2)	87.3 (67.9 to 127.9)	-31.9 (-43.4 to 0.5), P = 0.059	-31.0 (-50.3 to -5.5), P = 0.009	-1.0 (-9.0 to 22.4), P = 0.372

APPENDICES

Appendix 1. Previous searches

Search terms used were 'Zanamivir OR Relenza OR Oseltamivir OR Tamiflu OR Laninamivir OR Peramivir OR "Neuraminidase Inhibitor"'.

We searched the following databases: MEDLINE, EMBASE and the Cochrane Controlled Trials Register.

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, Issue 1); MEDLINE (1966 to April 2005); EMBASE (January 1980 to December 2004); the online GlaxoSmithKline Clinical Trials Register; and the online Roche Clinical Trial Protocol Registry and Clinical Trial Results Database (August 2005). A dialogue was established with Roche and GlaxoSmithKline and, if relevant, we contacted first authors of retrieved studies.

We searched MEDLINE and CENTRAL using the following search terms, which were adapted to search the other electronic databases. There were no language restrictions.

MEDLINE (WebSpirs)
#1 oseltamivir
#2 zanamivir
#3 neuraminidase inhibitors
#4 #1 or #2 or #3
#5 explode 'Influenza-' / all subheadings in MIME,MJME
#6 influenz*
#7 #5 or #6
#8 explode 'Neuraminidase-' / all subheadings in MIME,MJME
#9 neuraminidase
#10 #8 or #9
#11 #7 and #10
#12 #4 and #7
#13 #11 or #12

We also searched bibliographies of included trials, two UK National Health Service (NHS) Health Technology Assessment (HTA) Reports commissioned on behalf of the UK National Institute of Clinical Excellence (NICE) (Burls 2002; Turner 2002 - summary also published as Cooper 2003) and two Canadian Coordinating Office for HTA (CCOHTA) Reports (Brady 2001; Husereau 2001) for any additional relevant trials. Contact was established with the authors of the more recent NHS HTA Report (Turner 2002).

Websites of the US Food and Drug Administration (FDA) (http://www.fda.gov), including MedWatch (the FDA Safety Information and Adverse Event Reporting Program; http://www.fda.gov/medwatch), and the European Medicines Agency (EMEA) (http://www.emea.eu.int) were searched for references to additional trials/data and for post-marketing reports of adverse events (October 2005).

In addition, we contacted the UK Medicines and Healthcare products Regulatory Agency (MHRA) to retrieve any reports of adverse events by companies or practitioners via the Yellow Card Scheme (August 2005).

Appendix 2. Embase.com search strategy

17 #13 AND #16
16 #14 OR #15
15 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1
blind*):ab,ti
14 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
13 #4 AND #12
12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
11 oseltamivir:ab,ti OR zanamivir:ab,ti OR tamiflu:ab,ti OR relenza:ab,ti OR peramivir:ab,ti OR laninamivir:ab,ti OR gs4071:ab,ti
10 'sialidase inhibitor':ab,ti OR 'sialidase inhibitors':ab,ti
9 'neuraminidase inhibitor':ab,ti OR 'neuraminidase inhibitors':ab,ti
8 'sialidase inhibitor'/exp
7 'peramivir'/de
6 'zanamivir'/de
5 'oseltamivir'/de
4 #1 OR #2 OR #3

3 influenza*:ab,ti OR flu:ab,ti
2 'influenza virus a'/exp OR 'influenza virus b'/de
1 'influenza'/exp

WHAT'S NEW

Date	Event	Description
7 March 2012	New citation required but conclusions have not changed	The Cochrane Review title is changed to include '(published trials only)'.

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 3, 2003

Date	Event	Description
1 June 2011	New citation required and conclusions have changed	Oseltamivir reduces the incidence of acute otitis media in children aged one to five years but is associated with a significantly increased risk of vomiting (number needed to harm = 17). Laninamivir octanoate was more effective than oseltamivir in shortening duration of illness in children with oseltamivir-resistant influenza A/H1N1. Three new authors joined the team to update this review.
25 January 2011	New search has been performed	Searches updated. We included three new trials (Heinonen 2010; Sugaya 2010; WV15758 - Winther 2010) and excluded 29 new trials (Deng 2004; Dutkowski 2010; Goldstein 2010; Gums 2008; Holodniy 2008; Hu 2004; Imamura 2003; Ishizuka 2010; Kano 2007; Kashiwagi 2000; Kawai 2005; Kawai 2006; Kawai 2007; Kawai 2008; Kohno 2010; Kubo 2007; LaForce 2007; Lin 2004; Lin 2006; NV20236; Okamoto 2005; Peters 2008; Sato 2005; Sato 2008; Shapira 2010; Sugaya 2007; Sugaya 2008; Tamura 2005; Tan 2002). Two previously included trials were excluded (Machado 2004; Oo 2003) and one previously included trial (Peng 2000) has been reassessed and moved to Additional references. Six studies (ISRCTN43083885; NCT00298233; NCT00412737; NCT00867139; NV20234; Shinjoh 2004) are awaiting classification.
24 March 2008	Amended	Converted to new review format.
5 November 2005	New citation required and conclusions have changed	Additional information is now included on the use of oseltamivir for the treatment of influenza in 'at risk' children, with asthma, and on the use of oseltamivir for the prevention of influenza in children.
31 March 2005	New search has been performed	The review was updated in April 2005. Additional information is now included on the use of oseltamivir for the treatment of influenza in 'at risk' children, with asthma, and on the use of oseltamivir for the prevention of influenza in children
9 December 2002	New search has been performed	Searches conducted. Review first published Issue 3, 2003

CONTRIBUTIONS OF AUTHORS

AH conceived the idea for the review and drafted the protocol.
MS updated the searches for and initiated the writing of the review update in 2009.
KW and PG contributed to the writing and editing of the review update in 2009.
KW, MS and PG updated the review in 2011.
RP commented on the statistical methods of the original review and 2011 update of the review.
All review authors commented on drafts of the 2011 update of this review.

DECLARATIONS OF INTEREST

No funding source nor sponsor had any role in any aspect of this study. None of the authors declare a conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Department of Primary Health Care, University of Oxford, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For those trials comparing neuraminidase inhibitors with other antiviral drugs, the latter must have been proven superior to placebo using appropriate study designs. Additional safety and tolerability data were also included from other sources: non-blinded, non-randomised, non-placebo-controlled studies; post-marketing reports; case reports; company statements; and statements by regulatory agencies.

NOTES

This 2011 updated review will be superseded by the Jefferson 2012 review *Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children.*

INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [adverse effects] [*therapeutic use]; Enzyme Inhibitors [adverse effects] [*therapeutic use]; Guanidines; Influenza, Human [*drug therapy] [*prevention & control]; Neuraminidase [*antagonists & inhibitors]; Oseltamivir [adverse effects] [therapeutic use]; Pyrans; Randomized Controlled Trials as Topic; Sialic Acids; Zanamivir [adverse effects] [analogs & derivatives] [therapeutic use]

MeSH check words

Child; Child, Preschool; Humans; Infant