

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

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ABSTRACT

Background

During epidemic years, influenza attack rates in children exceed 40%. Options for prevention and treatment include the neuraminidase inhibitors: zanamivir and oseltamivir.

Objectives

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

Search strategy

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 1, 2005); MEDLINE (1966 to April 2005); EMBASE (January 1980 to December 2004); the on-line GlaxoSmithKline Clinical Trials Register; the on-line Roche Clinical Trial Protocol Registry and Clinical Trial Results Database (August 2005); and reference lists of articles. We also scrutinised web sites of European and US regulatory bodies and contacted manufacturers and authors.

Selection criteria

Double-blind, randomised, controlled trials comparing neuraminidase inhibitors with placebo or other antiviral drugs in children less than 12 years of age. Additional safety and tolerability data from other sources were also included.

Data collection and analysis

Four authors applied the inclusion criteria to the retrieved studies, assessed trial quality and extracted data. Data were analysed separately for oseltamivir and zanamivir.

Main results

Three trials involving 1500 children with a clinical case definition of influenza were included, of whom 977 had laboratory-confirmed influenza. Overall, trial quality was good. Oseltamivir reduced the median duration of illness by 26% (36 hours) in healthy children with laboratory-confirmed influenza (P value less than 0.0001). The reduction was only 7.7% (10 hours) in 'at risk' (asthmatic) children, and this did not reach statistical significance (P value = 0.54). Zanamivir reduced the median duration of illness by 24% (1.25 days) in healthy children with laboratory-confirmed influenza (P value less than 0.001). No data in 'at risk' children were available. Only oseltamivir produced a significant reduction in the complications of influenza (particularly otitis media), although there was a trend to benefit for zanamivir. We identified one randomised, controlled trial of oseltamivir for the prevention of influenza transmission in households, reporting data from 222 paediatric contacts. Where index cases had laboratory-confirmed influenza, a protective efficacy of 55% was observed, but this did not reach statistical significance (P value = 0.089). The adverse events profile of zanamivir was no worse than placebo, but vomiting was more common in children treated with oseltamivir.

Authors' conclusions

Neuraminidase inhibitors are effective in shortening illness duration in healthy children with influenza, but efficacy in 'at risk' children remains to be proven. Oseltamivir is also effective in reducing the incidence of secondary complications, and may be effective for influenza prophylaxis.

PLAIN LANGUAGE SUMMARY

Neuraminidase inhibitors for preventing and treating influenza in children

Influenza (true "flu") is an infection of the airways caused by a virus. Infection may be treated with neuraminidase inhibitors (zanamivir and oseltamivir), one group of anti-influenza drugs. This review found that both drugs shortened the duration of illness in healthy children by about one day. Oseltamivir also prevented complications of influenza, in particular, ear infections. More research is needed to determine if the drugs are also helpful for: 'at risk' children (who have a pre-existing medical condition); and preventing (rather than treating) influenza in children. Neither drug caused serious side effects.

BACKGROUND

Influenza virus has long been recognised as a significant cause of morbidity and mortality in healthy adult populations but only recently have attempts been made to quantify the burden of disease in children (Izurieta 2000; Neuzil 2000). Influenza in children has been poorly documented because of its non-specific symptoms, the large variety of other circulating viruses (often including a predominance of respiratory syncytial virus), the lack of a readily accessible diagnostic test and the perception that it is a benign illness in childhood. Nonetheless, it is recognised that school age children are the main source of the introduction of influenza into the household (Longini 1982).

During epidemic years, attack rates often exceed 40% in pre-school children and 30% in school age children (Glezen 1978). A retrospective cohort study of a large childhood population in the United States calculated (using rate differences between influenza and peri-influenza seasons) that the annual number of influenza attributable hospitalisations for acute cardiopulmonary conditions ranged from 4 to 104 per 10,000 children, depending on age (Neuzil 2000). Children under the age of six months were the most likely to be hospitalised. Moreover, influenza accounted for a 35% increase in outpatient visits for children less than three years of age and a 10% to 30% increase in the use of antibiotics in children younger than 15 years of age.

Children with chronic medical conditions (asthma, cardiovascular disease, pulmonary disease, immunosuppression, cancer, renal disease, haemoglobinopathies, neurological disease) and those born prematurely are 4 to 21 times more likely to be hospitalised with respiratory complications than healthy children during influenza predominant seasons (Izurieta 2000). In prospective studies of children with asthma who are infected with influenza, the reported incidence of exacerbations has varied widely from 7% to 86% (Pattamore 1992). More recent studies have detected in-

fluenza virus in 5% to 7% of all childhood asthma exacerbations (Freytmuth 1999; Johnston 1995), although this proportion would be expected to vary depending on influenza point prevalence and may be considerably higher during annual epidemics.

Complications of influenza in children include acute otitis media, febrile convulsions, sinusitis, bronchitis, bronchiolitis, croup, pneumonia (viral and bacterial) and Reye's syndrome. Reported incidences of acute otitis media in children with confirmed influenza infection (up to six years of age) have ranged from 21% to more than 50%, with the highest incidence in children less than two years of age (Belshe 1998; Henderson 1982; Neuzil 2002; Ruuskanen 1989).

Epidemiological studies have routinely detected respiratory viruses in nasopharyngeal specimens from 30% to 50% of children with acute otitis media, and recent studies using Polymerase Chain Reaction based assays have indicated viral infection rates of up to 90% (Heikkinen 2000; Henderson 1982; Uhari 1995). Thus, although bacteria can be isolated from the middle ear in approximately 70% of cases of acute otitis media, a substantial proportion of these may in fact be secondary to viral infection (Heikkinen 2000). The mechanism is thought to be a combination of direct cytopathic effects, eustachian tube dysfunction induced by the host's inflammatory response to viral infection and alteration of the susceptibility to bacterial colonisation and adherence, which lead to bacterial invasion of the middle ear (Hayden 2001a; Heikkinen 2000).

Influenza A and B have accounted for approximately 8% to 13% of viruses isolated in acute otitis media (Heikkinen 1999; Henderson 1982; Uhari 1995) but this proportion may vary depending on influenza point prevalence. Indeed, influenza vaccine studies, in which children up to six years of age were immunised before the start of the influenza season, demonstrated a 30% to 36% reduction in the overall incidence of acute otitis media (Belshe 1998; Clements 1995; Heikkinen 1991).

The core ribonucleic acid (RNA) component of influenza virus is surrounded by a protein, the nucleoprotein antigen, which determines the type (A, B or C) of virus. The outer surface of the virus comprises a lipid membrane with two attached glycoprotein antigens. One of these, neuraminidase, plays an important role in the release and propagation of virions from infected cells while the other, haemagglutinin, assists entry into host cells. Neuraminidase and haemagglutinin antigens help determine the strain of the influenza virus. 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 animal reservoirs in southern China). It is the latter phenomenon that may give rise to a pandemic.

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. In contrast, the antiviral drugs amantadine and rimantadine are inactive against influenza B. Zanamivir (GlaxoSmithKline), administered by inhalation, is licensed in the USA for the treatment of influenza in children aged 7 years or more, but is not currently recommended for use in children aged less than 12 years in Europe. It is not licensed in either area for influenza prophylaxis. Oseltamivir (Roche), administered orally, is licensed in the USA for the treatment of influenza in children older than one year, and has received the same licensing approval in Europe. It is also licensed in both areas for influenza prophylaxis in adolescents and adults aged 13 years or older, but not children. Development of peramivir (BioCryst), a third neuraminidase inhibitor, has been discontinued following news that initial findings from a phase III clinical trial (in adults) demonstrated no statistical difference in relief of influenza symptoms between peramivir and control (BioCryst 2002). No paediatric patients were enrolled in trials of the drug (A.K. Schleusner, BioCryst, personal communication, 2002).

A Cochrane review on the use of neuraminidase inhibitors for preventing and treating influenza in healthy adults (Jefferson 2002) found that the drugs reduced the duration of influenza symptoms by one day and were 60% effective in preventing cases of laboratory-confirmed influenza. This review will appraise trials of zanamivir and oseltamivir in children under 12 years of age.

OBJECTIVES

Our objective was to assess the efficacy, safety and tolerability of neuraminidase inhibitors in the treatment and prevention of influenza in healthy and 'at risk' (those with an underlying chronic medical condition) children less than 12 years of age, based on the available randomised controlled trial (RCT) evidence. We also aimed to calculate any reduction in secondary household attack

rates when treating children with influenza with neuraminidase inhibitors.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Double-blind RCTs comparing neuraminidase inhibitors with placebo or other antiviral drugs. 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.

Types of participants

Children less than 12 years of age.

For studies examining the efficacy of influenza treatment, we stipulated that the patients 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; and no clinical evidence of bacterial infection) made by a healthcare professional in a community in which there was an influenza outbreak; laboratory or near-patient test confirmation of influenza.

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

Types of intervention

Neuraminidase inhibitors for treatment or prophylaxis.

Types of outcome measures

Primary outcome measures for treatment were: time to resolution (defined as absence for longer than 24 hours) of important symptoms (cough, temperature above 37.8 °C, headache, myalgia, sore throat, fatigue); time to return to normal activity or time to return to school; secondary household attack rates.

Secondary outcome measures for treatment were: time to reduction in severity of important symptoms; symptom scores; maximum daily temperature; sleep disturbance; paracetamol (antipyretic/analgesic) usage (mg/24 hours); proportion using antibiotics; proportion admitted to hospital; length of hospital stay and incidence of complications (acute otitis media, pneumonia, death). In addition, for children with chronic illness, symptom scores and relevant physiological measurements (for example, in asthma, symptom scores and lung function tests).

Outcome measures for prophylaxis were: incidence of laboratory or near-patient test confirmed influenza, or influenza-like illness.

Outcome measures for adverse events were: incidences of treatment discontinuation/study withdrawal and local and systemic events recorded in clinical trials; qualitative assessment of safety and tolerability data from other sources.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Acute Respiratory Infections Group methods used in reviews.

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2005); MEDLINE (1966 to April 2005); EMBASE (January 1980 to December 2004); the on-line GlaxoSmithKline Clinical Trials Register; and the on-line 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).

Web sites 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 (EMA) (<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).

METHODS OF THE REVIEW

Selection of trials

One review author (MA) screened the titles and abstracts identified from the initial electronic searches (2002). If the study was of possible relevance to the review, or the parameters were not explicit, we obtained the full article. Uncertainty over eligibility was clarified by discussion between three review authors (MA, NM, AH). Titles and abstracts identified when the review was updated (2005) were screened by one review author (NM).

Trial quality assessment

We assessed the quality of controlled trials using a standardised pro-forma covering generation of allocation schedule, concealment of treatment allocation/implementation of masking and completeness of trial. The 0 to 5 Jadad scale (Jadad 1996) was used to assess trial quality. The methodological quality of studies was also documented using the following criteria: baseline differences between experimental groups, diagnostic criteria used and length of follow up. A formal assessment of trial quality was not undertaken for uncontrolled studies contributing safety data only.

Data collection

Three review authors (MA, NM, AH) independently extracted data using standardised data extraction forms. One review author (NM) collated and checked the data. When multiple sources described the same trial they were combined in a single data extraction (NM). These were double-checked independently by a second review author (MA). One review author (NM) extracted data for trials identified when the review was updated (2005).

Some data were reported only in secondary sources (NA130009 - FDA 2003; WV15758 - EMA 2005 and FDA 2004) and were not available from primary sources (peer reviewed journal articles, conference reports). If the parent trial (Study ID) was explicitly stated, and the study fulfilled our inclusion criteria, the data were incorporated into the appropriate data extraction. If however, the parent trial was not explicitly stated, or if details of the study were unavailable, the data were noted separately in the Results section.

If methodological aspects or data presentation were unclear, or significant numerical discrepancies existed between sources reporting results from the same trial, we contacted the

pharmaceutical companies responsible and asked for further information or clarification.

DESCRIPTION OF STUDIES

Sources

Our initial broad electronic search strategy returned 3723 citations (2002). A further 879 citations were returned when the searches were updated (2005). These included references to: four controlled trials of neuraminidase inhibitors in the treatment of influenza infection in children (Imamura 2003; NA130009; WV15758; WV15759/WV15871); five uncontrolled, observational studies of neuraminidase inhibitors in the treatment of influenza in children (Kawai 2003; Machado 2004; Mitamura 2002; Vogel 2002; Yamaura 2003); five controlled trials of neuraminidase inhibitors in the prevention of influenza transmission in families (Monto 2002; NA130010; Welliver 2001; WV16193) and paediatric inpatients (Shinjoh 2004); one uncontrolled, observational study of oseltamivir in the prevention of influenza transmission in paediatric outpatients (Chik 2004); three pharmacokinetic studies of neuraminidase inhibitors (Oo 2001; Oo 2003; Peng 2000); one descriptive study of resistant influenza virus strains emerging in children treated with oseltamivir (Kiso 2004); one case report about a child treated with zanamivir (Gubareva 1998); three retrospective studies of health insurance claims data amongst patients treated with neuraminidase inhibitors, including children (Cole 2002; Loughlin 2002; Nordstrom 2004); and one study on the reliability of a rapid diagnostic test for influenza in children treated with oseltamivir (Hata 2004). We were unable to retrieve one conference abstract of possible relevance despite exhaustive searches in the UK, Australia and the USA (Von Bremen 2003). Data were published across multiple journal articles for trials WV15758 (Dutkowski 2003; Erratum 2001; Reisinger 2004; Whitley 2001) and WV15759/WV15871 (Dutkowski 2003; Johnston 2005). In this review, trials have been referred to by their Study ID rather than by the name of their primary reference.

In addition to published articles, Roche 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). Bibliographic searching identified one further abstract providing data from WV15758 (Reisinger 2000b) and GlaxoSmithKline supplied a conference presentation providing data from trial NA130010 (Hayden 1999). A search of the GlaxoSmithKline Clinical Trial Register identified a further controlled trial of zanamivir in the treatment of influenza infection in children (NA130028) and a search of the Roche Clinical Trial Results Database identified a further controlled trial of oseltamivir in the treatment of influenza in children and adolescents

(NV16871). No additional information was provided directly by first authors of the drug company sponsored studies.

Examination of the FDA web site identified Current Label approval information for oseltamivir (WV15758 - FDA 2004) and zanamivir (NA130009 - FDA 2003). In addition, examination of the EMEA web site identified a European Public Assessment Report for oseltamivir (WV15758 - EMEA 2005). These reports included discussion of drug efficacy and safety in the treatment of influenza in children. No post-marketing reports of adverse events in children were specified by the FDA or EMEA or identified from a search of the UK MHRA Adverse Drug Reactions On-line Information Tracking database (Mark Loughrey, MHRA: Post Licensing Division, personal communication, 2005).

The authors of the more recent UK NHS HTA Report (Turner 2002) confirmed that, to their knowledge, our searches were complete (Dr A. Sutton, personal communication, 2002). Finally, both Roche and GlaxoSmithKline verified that our searches did not omit any trials in the public domain (Dr A. Webster, GlaxoSmithKline and Dr Z. Panahloo, Roche, personal communications, 2005). In particular, the earliest licensing approvals for use in children were February 2000 for zanamivir (in Mexico) and December 2000 for oseltamivir (in the USA). Clinical trials could not have commenced prior to these dates without the knowledge of the pharmaceutical companies.

Treatment trials

In total, six controlled trials of neuraminidase inhibitors for the treatment of influenza in children were identified (Imamura 2003; NA130009; NA130028; NV16871; WV15758; WV15759/WV15871). Of these, three were eligible for the review:

WV15758 was a double-blind RCT assessing the efficacy, safety and tolerability of a five day course of twice daily oral oseltamivir (or placebo) in the treatment of naturally acquired, symptomatic influenza infection in 695 children aged 1 to 12 years. Baseline characteristics of the treatment and control populations are summarised in Table 01.

WV15759/WV15871 (two WV numbers were assigned as the study rolled over two seasons) was a double-blind RCT assessing the efficacy, safety and tolerability of a five day course of twice-daily oral oseltamivir (or placebo) in the treatment of naturally acquired, symptomatic influenza infection in 334 children with asthma aged 6 to 12 years. Baseline characteristics of the treatment and control populations, including severity of baseline asthma, are summarised in Table 02.

NA130009 was a double-blind RCT assessing the efficacy, safety and tolerability of a five day course of twice daily inhaled zanamivir (or placebo) in the treatment of naturally acquired, symptomatic influenza infection in 471 children aged 5 to 12 years. Baseline characteristics of the treatment and control populations are summarised in Table 03.

No data are yet available for NAI30028 and no sub-group data were provided for children aged less than 12 years in NV16871. Imamura 2003 assessed the efficacy of oseltamivir 2 to 4 mg/kg/day or amantadine in the treatment of 162 paediatric inpatients with influenza A infection. A control group was included, but no further details on trial methodology or results are currently available in English. The full report has been published in Japanese and is awaiting translation. It will be included in the next update of the review.

Five additional, uncontrolled treatment trials were identified (Kawai 2003; Machado 2004; Mitamura 2002; Vogel 2002; Yamamura 2003). Because the inclusion criteria were relaxed for safety and tolerability endpoints (to include non-RCT data) one was eligible for the review:

Machado 2004 was an uncontrolled, observational study assessing the efficacy, safety and tolerability of a five day course of twice-daily oral oseltamivir in the treatment of naturally acquired, symptomatic influenza in 319 bone marrow transplant recipients, including 11 children. Limited safety data were provided by the authors for this small group (Dr C. Machado, personal communication, 2005).

See 'Characteristics of included studies', 'Characteristics of excluded studies' and 'Characteristics of ongoing studies' tables for further details.

Prevention trials

In total, five controlled trials of neuraminidase inhibitors for the prevention of influenza in children were identified (NAI30010; Monto 2002; Shinjoh 2004; WV16193; Welliver 2001). Of these, one was eligible for the review:

WV16193 was an open-label RCT assessing the efficacy, safety and tolerability of a ten day course of once-daily oral oseltamivir (or expectant management) in the prophylaxis of influenza infection in household contacts of index cases with influenza-like illness. The study included 222 contacts aged 1 to 12 years, for whom a separate analysis of prophylactic efficacy was conducted. Baseline characteristics were not provided for the paediatric treatment and control populations. Amongst household contacts of all ages, however, less than 3% were using concomitant inhaled short acting bronchodilators, and only 7% had current influenza vaccination. Sixty-six per cent of index cases with laboratory-confirmed influenza had influenza A and 34% had influenza B. As well as randomising contacts to receive oseltamivir prophylaxis or expectant management, all index cases (including 134 children aged 1 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.

No children received oseltamivir in Welliver 2001, and no sub-group data were provided for prophylactic efficacy or safety in children in Monto 2002 or NAI30010. Shinjoh 2004 assessed the

efficacy of a seven to ten day course of once-daily oral oseltamivir 2 mg/kg in the prevention of influenza transmission in 29 paediatric inpatients. A control group was included, but no further details on trial methodology are currently available in English. The full report has been published in Japanese and is awaiting translation. It will be included in the next update of the review.

One additional, uncontrolled prevention trial was identified (Chik 2004). It was not eligible for the review.

See 'Characteristics of included studies' and 'Characteristics of excluded studies' tables for further details.

Other studies

In total, 10 further studies of neuraminidase inhibitors in children were identified (Cole 2002; Gubareva 1998; Hata 2004; Kiso 2004; Loughlin 2002; Nordstrom 2004; Oo 2001; Oo 2003; Peng 2000; Waskett 2001). Because the inclusion criteria were relaxed for safety and tolerability endpoints (to include non-RCT data) three were eligible for the review:

Loughlin 2002 was a retrospective study of health insurance data assessing the incidence of adverse respiratory events among 5450 patients, including 42 children aged less than 12 years, treated with a five day course of twice-daily inhaled zanamivir.

Oo 2003 was an uncontrolled study of the pharmacokinetics, safety and tolerability of a single dose of oral oseltamivir in 12 healthy children aged 1 to 5 years.

Peng 2000 was an uncontrolled study of the pharmacokinetics, safety and tolerability of a single dose of inhaled zanamivir in 24 children aged 3 months to 12 years with signs and symptoms of respiratory illness.

See 'Characteristics of included studies' and 'Characteristics of excluded studies' tables for further details.

METHODOLOGICAL QUALITY

Data for this review were drawn from a range of primary and secondary sources. Although we assessed the quality of controlled trials using the Jadad scoring system (see 'Characteristics of included studies' table), a low Jadad score in this context may reflect limitations in the trial descriptions available rather than in the actual conduct of the trial.

Treatment trials

No significant problems impacting on study quality were identified for WV15758, WV15759/WV15871 or NAI30009 regarding baseline differences between treatment and control groups (Table 01; Table 02; Table 03), length of follow up or diagnostic criteria used for primary endpoints. There were slightly more patients with 'severe' pre-treatment symptom assessment in the treatment arm of NAI30009.

Although not representing a deficiency in any one trial, the number of children vaccinated against influenza was much greater in WV15759/WV15871 (19%) than WV15758 (3%) or NA130009 (2%). This may have modified the effect of oseltamivir in WV15759/WV15871 because the spectrum of influenza illness is often milder in vaccinated children than it is in those who are not vaccinated (Belshe 1998).

The incidences of secondary complications and antibiotic use were examined in detail in WV15758. Diagnoses were made by individual primary care physicians, however, and standardised diagnostic criteria were described only for otitis media. Tympanometry was used to confirm the diagnosis in 54 of 76 cases (71%), but no effort was made to differentiate serous or suppurative otitis media, or viral or bacterial aetiology. Secondary complications and antibiotic use were assessed in NA130009, but no standardised diagnostic criteria were specified. Asthma exacerbations alone were assessed in WV15759/WV15871 and were adequately defined using serial peak expiratory flow (PEF) measurements.

In general, all three studies adhered to the principle of intention-to-treat analysis - although this was not without its problems. In WV15758, three children who were randomised but withdrew before taking any medication were excluded from all analyses and, amongst children with laboratory-confirmed influenza, eight from the control arm and ten from the treatment arm appear to have been excluded from some analyses because of missing efficacy information. In WV15759/WV15871, treatment efficacy endpoints were reported for children with laboratory-confirmed influenza, but not for the overall population of children enrolled on the basis of a clinical case definition of influenza. One child who was randomised but withdrew before taking any medication was excluded from all analyses.

Prevention trials

No significant problems impacting on study quality were identified for WV16193 regarding the length of follow up or diagnostic criteria used. Baseline characteristics appeared similar between overall treatment and control groups, but no comparators were broken-out for the paediatric population.

Although an intention-to-treat analysis was performed, 10 contacts from the control arm and 10 contacts from the treatment arm (across all ages) were excluded from analyses because of missing efficacy, serological or influenza culture information.

This was an open-label study, which raises the possibility of bias in outcomes. The composite primary end point, however, was clearly based on objective (laboratory confirmation of infection; temperature greater than or equal to 37.8 °C) as well as subjective (clinical symptoms of influenza) measures. 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.

Other studies

No formal assessment of study quality was undertaken.

Data synthesis

Primary endpoints for all treatment studies (time to resolution of illness, time to return to normal activity) were reported as median time-to-event data. There was no general agreement between studies on the definition of these composite endpoints or on the statistical techniques used to generate the published summary statistics. For instance, WV15758 censored data from children who withdrew from the study before resolution of symptoms, whereas NA130009 considered children who withdrew from the study before resolution of symptoms as treatment failures (and therefore contributed to the analysis throughout). In the absence of individual patient data, techniques for combining summary statistics from such analyses are not well developed (Centre for Statistics in Medicine, Oxford, UK, personal communication, 2000). Results were therefore reported separately for each study.

Secondary complications in children with laboratory-confirmed influenza are reported as dichotomous data for WV15758 and NA130009, but there was significant clinical heterogeneity between the studies. In particular, the efficacy of oseltamivir and zanamivir in treating extra-pulmonary complications may not be equivalent because the different methods of administration (oral versus inhalation) provide different levels of drug exposure in extra-pulmonary tissues such as the middle ear and sinuses (see 'Discussion'). This is particularly important in studies of influenza in children, amongst whom acute otitis media is the most prevalent secondary complication. In addition, the age ranges of children enrolled for the studies were different: 1 to 12 years (WV15758) compared with 5 to 12 years (NA130009). Rates of acute otitis media are highest in young children, included in WV15758, but excluded from NA130009. Results are therefore reported separately for these two studies. No comparable data were available for WV15759/WV15871.

Incidences of adverse effects were markedly different between the control arms of NA130009 (21%), and those of WV15758 (52%) and WV15759/WV15871 (51%), on the other (see 'Discussion'). We therefore did not combine data across studies of oseltamivir and zanamivir. We did, however, combine data on adverse events from the two studies assessing the effectiveness of oseltamivir (WV15758; WV15759/WV15871). Peto odds ratios were calculated using a fixed-effect model. We examined the summary plots for heterogeneity and assessed this using the I^2 statistic.

Significance levels and confidence intervals reported in the studies have been reproduced in this review, rather than re-calculated. Where appropriate, however, we calculated confidence intervals not reported in the studies.

Due to the limited number of RCTs eligible for the review, funnel plots were not appropriate in the assessment of publication bias.

RESULTS

Treatment

Endpoints from each trial were reported both for children with laboratory-confirmed influenza (Lab. Influenza +ve) and, if available, for the intention-to-treat population (all children enrolled on the basis of a clinical case definition of influenza). Where appropriate, we have also reported endpoints in more limited sub-populations.

If there was no general agreement on the definition of a particular endpoint (for example time to resolution of illness), the percentage difference in outcome between treatment and control groups is a more valid comparator between studies than the absolute difference. However, since the absolute difference is of more clinical relevance, where possible, we have reported both.

Time to resolution of illness

WV15758: oseltamivir reduced the median duration of illness by 26% (36 hours) in children with laboratory-confirmed influenza (P value less than 0.0001) and by 17% (21 hours) in the intention-to-treat population (P value = 0.0002).

WV15759/WV15871: a trend to benefit was observed for oseltamivir in asthmatic children with laboratory-confirmed influenza, with a reduction in median duration of illness of 7.7% (10 hours), but this did not reach statistical significance (P value = 0.54); no data were available for the intention-to-treat population.

NA130009: zanamivir reduced the median duration of illness by 24% (1.25 days) in children with laboratory-confirmed influenza (P value less than 0.001) and by 10% (0.5 days) in the intention-to-treat population (P value = 0.011).

Table 04

In WV15758, oseltamivir reduced the duration of illness in all age groups, with a trend to shorter illness times in both control and treatment groups for older children; no data were provided by age group for NA130009 or WV15759/WV15871.

Table 05

In WV15758, oseltamivir reduced the median time to resolution of illness by 34% (P value less than 0.0001) in children with influenza A, but a reduction of only 8.5% was observed in children with influenza B (not statistically significant; P value = 0.27; WV15758 - EMEA 2005). Conversely, in NA130009, zanamivir significantly reduced the median time to resolution of illness in children with both influenza A and B. No data were available by serotype for WV15759/WV15871.

Table 06

No significant difference was seen between the North America and Europe/Israel arms of NA130009. No data were provided by geographical location for WV15758 or WV15759/WV15871.

Table 07

Time to return to normal activity

WV15758: oseltamivir reduced the median time to return to normal activity by 40% (45 hours) in children with laboratory-confirmed influenza (P value less than 0.0001); no data were available for the intention-to-treat 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 11% (12.6 hours), but this did not reach statistical significance (P value = 0.46); no data were available for the intention-to-treat population.

NA130009: zanamivir reduced the median time to return to normal activity by one day in children with laboratory-confirmed influenza (P value = 0.022) and in the intention-to-treat population (P value = 0.019).

Table 08

In WV15758, a trend to benefit was observed 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 value = 0.003; WV15758 - Reisinger 2004). No data were available by serotype or age group for NA130009 or WV15759/WV15871.

Secondary complications

WV15758: oseltamivir reduced the incidence of physician diagnosed complications requiring antibiotic use by 40% (P value = 0.005) and overall antibiotic use by 24% (P value = 0.03) in children with laboratory-confirmed influenza; no data were available for the intention-to-treat population.

WV15759/WV15871: see 'Asthma exacerbations and pulmonary function'.

NA130009: a trend to benefit was observed for zanamivir in children with laboratory-confirmed influenza, with a 30% reduction in the incidence of complications and a 20% reduction in antibiotic use, but these did not reach statistical significance; no data were available for the intention-to-treat population.

Table 09

Mortality rates were zero in all trials. Two children from WV15758 were hospitalised (both from the control arm, one with dehydration and one with ingestion of a caustic substance), along with three children from WV15759/WV15871 (one from the control arm, with viral encephalitis and two from the treatment arm, with vomiting and abdominal pain). No comparable data were available for NA130009.

Acute otitis media

In WV15758, over the 28 day follow up period, oseltamivir reduced the incidence of physician diagnosed acute otitis media by 44% in children aged 1 to 12 years with laboratory-confirmed influenza without otitis media at enrolment and by 56% in children aged 1 to 5 years. No data were available for the intention-to-treat population and no data were available for WV15759/WV15871 or NA130009.

Table 10; Table 11

Asthma exacerbations and pulmonary function

In WV15759/WV15871, median FEV1 improved by 10.8% by day 6 in children with laboratory-confirmed influenza treated with oseltamivir, compared with 4.7% in children treated with placebo (P value = 0.015). There was a corresponding reduction in the frequency of asthma exacerbations defined by pulmonary function and a trend to a reduction in medical reports of asthma exacerbations captured via the adverse events reporting system. A graphical analysis suggested a marked and rapid reduction in frequency of asthma exacerbations in children who commenced treatment within 24 hours of symptom onset. The effect was much less clear for children who commenced treatment more than 24 hours of symptom onset, but no formal statistical analysis was undertaken.

Table 12

In NA130009, using the entire intention-to-treat population as the denominator (although only 36 children entered the trial with concurrent chronic respiratory conditions), less than 1% of children treated with zanamivir were reported to suffer asthma exacerbations, compared with 1% treated with placebo. Although WV15758 enrolled 16 children with mild asthma, no asthma-specific endpoints are reported.

Secondary household attack rates

No data available.

Miscellaneous additional endpoints

Table 13; Table 14; Table 15; Table 16

A number of secondary endpoints were analysed by influenza serotype. In WV15758, oseltamivir reduced the median duration of all Canadian Acute Respiratory Illness and Flu Scale (CARIFS) symptoms in children with influenza B from 96 hours in the control group to 56 hours in the treatment group, a reduction of 41% (144 children; P value = 0.008). This was comparable to the 35% reduction observed (P value = 0.0042) in children with influenza A (WV15758 - EMEA 2005). Likewise, median duration of fever, cough and coryza in children with influenza B was reduced from 100 hours in the control group to 73 hours in the treatment group, a reduction of 27% (P value = 0.01). No data for this endpoint were available for children with influenza A. The denominator for the influenza B analyses was reported as n = 144, in contrast to the 148 children with influenza B stated elsewhere in Whitley 2001. In NA130009, zanamivir significantly reduced the time to resolution of illness, with no concomitant use of relief medications,

in children with influenza B from 6.75 days in the control group to 4.5 days in the treatment group, a reduction of 33% (120 children; P value less than 0.001); and in children with influenza A from 6.0 days in the control group to 5.25 days in the treatment group, a reduction of 12.5% (226 children; P value = 0.047). No data were available by serotype for WV15759/WV15871.

Prevention

WV16193: oseltamivir prophylaxis reduced the incidence of laboratory-confirmed, symptomatic influenza by 64% (P value = 0.019) in all paediatric contacts, but a reduction of only 55% was observed in paediatric contacts of index cases with laboratory-confirmed influenza (not statistically significant; P value = 0.089).

Table 17

Safety and tolerability

Data from controlled treatment trials

WV15758 and WV15759/WV15871: see meta-analysis Comparison 01.01. In our pooled analysis the overall rate of adverse events was similar for oseltamivir and placebo in the intention-to-treat population (odds ratio 0.87; 95% confidence intervals (CI): 0.68 to 1.12; I² = 0%), although children treated with oseltamivir were more likely to experience vomiting (Comparison 01.05) than those treated with placebo (odds ratio 1.68; 95% CI 1.15 to 2.47; I² = 0%). More than 90% of children enrolled in WV15758 took all scheduled drug doses, and 96% of children enrolled in WV15759/WV15871 received a total of 9 or 10 doses. Dutkowski 2003 (WV15758) reported a pooled safety analysis of 1032 children, of whom 515 received oseltamivir. This included data for three children who received oseltamivir in a small pilot study (Dr Z. Panahloo, Roche, personal communication, 2002 - no further details of study available), combined with data for the 1029 children from WV15758 and WV15759/WV15871. No significant extra information was therefore provided. Among children with asthma in the intention-to-treat population of WV15759/WV15871 who were influenza negative on laboratory testing, oseltamivir did not affect PEF or FEV1 (median change in PEF from baseline 5.6% in placebo group compared with 5.9% in treatment group) and nor did it cause an excess of asthma exacerbations. There is therefore no evidence to suggest that oseltamivir exerts any adverse effects on respiratory function.

NA130009: see Comparison 02.01. No significant difference in the rate of adverse events was observed in children treated with zanamivir, compared with placebo, in the intention-to-treat population. Less than 1% of patients 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 8 to 10 drug doses.

Data from controlled prevention trials

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. None withdrew because of tolerability problems. Vomiting occurred in 31 of 158 children who received twice-daily treatment (21%) compared with 10 of 99 children who received once daily prophylaxis (10%).

Data from other studies

Loughlin 2002: no inpatient or emergency department adverse respiratory events were identified in the 42 children dispensed zanamivir.

Machado 2004: only 3 of 11 children enrolled in the study were treated with oseltamivir; no adverse events were noted (Dr C. Machado, personal communication, 2005).

Oo 2003: a total of 7 gastrointestinal adverse events were reported in the 12 children given a single dose of oseltamivir (diarrhoea, abdominal pain, vomiting); none was severe.

Peng 2000: no serious adverse events were reported in the 24 children treated given a single dose of zanamivir; only one adverse event (an episode of headache) was felt by the study physician possibly to be related to the study medication.

FDA 2003 (NA130009) reports additional information from children without acute influenza-like illness who received an investigational prophylactic regime of zanamivir (no further details; Study ID not given); 132 children received zanamivir and 145 children received placebo. Among these children, nasal signs and symptoms (treatment 20%, control 9%), cough (treatment 16%, control 8%) and throat/tonsil discomfort and pain (treatment 11%, control 6%) were reported more frequently with zanamivir than placebo. In addition, in a subset with chronic respiratory disease, lower respiratory adverse events (described as asthma, cough or viral respiratory infections which could include influenza-like symptoms) were reported in 7 of 7 zanamivir recipients and 5 of 12 placebo recipients. A pooled safety analysis including a total of 609 children, of whom 291 received zanamivir, is also provided; the results are qualitatively and quantitatively similar to those reported for NA130009, with no excess of any individual adverse event in children treated with zanamivir.

Post-marketing surveillance

No post-marketing reports of adverse drug reactions in children (including bronchospasm) were identified for oseltamivir or zanamivir. Across patients of all ages, FDA 2003 (NA130009), FDA 2004 and EMEA 2005 (WV15758) list the following adverse events identified during post-marketing use of oseltamivir: rash, swelling of the face or tongue, toxic epidermal necrolysis, arrhythmia, seizure, confusion, aggravation of diabetes, hepatitis and abnormal liver function tests. The adverse events listed for zanamivir were: allergic or allergic-like reaction including oropharyngeal oedema, arrhythmia, syncope, seizures, bronchospasm, dyspnoea, facial oedema and rash (including serious cutaneous reactions). The use of zanamivir is not currently recommended in children or adults with chronic respiratory disease (including

asthma) because of the perceived risk of bronchospasm associated with its use (NA130009 - FDA 2003). The use of oseltamivir off-license in children less than one year of age is specifically discouraged, as animal toxicology studies have shown deaths in seven day old rats given very high doses (WV15758 - FDA 2004). The effect may be related to immaturity of the blood-brain barrier.

DISCUSSION

Oseltamivir and zanamivir produced significant reductions in time to resolution of illness in both children with a clinical case definition of influenza (the intention-to-treat population) and children with laboratory-confirmed influenza. Where prescription of neuraminidase inhibitors is based on a clinical case definition (using a list of symptoms suggestive of influenza infection), benefits will be reduced in proportion to the specificity of the case definition for influenza infection. In the clinical trials included in this review, this specificity ranged from 54% (WV15759/WV15871) to 73% (NA130009). In primary care, the accuracy of diagnosis may be reduced. For example, 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).

The benefits of neuraminidase inhibitors may therefore be enhanced by the use of near-patient testing. 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). Results of these tests should therefore be interpreted in light of the performance characteristics of the particular test used, as well as influenza virus activity surveillance data from the community.

Successful treatment with neuraminidase inhibitors in children and 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 36 (NA130009) to 48 (WV15758, WV15759/WV15871) hours of symptoms onset. Amongst children aged 14 years or less 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.

Although public health surveillance is able to specify the serotype of influenza circulating at a given time (in the UK, for example, the Health Protection Agency: <http://www.hpa.org.uk/default.htm>) many near-patient tests currently available are unable to distinguish influenza serotype. Whereas zanamivir produced significant

reductions in time to resolution of illness in children with both influenza A and B, the only significant reductions for oseltamivir in children with influenza B were in median duration of all CARIFS symptoms and median duration of fever, cough and coryza (composite secondary endpoints). Reductions in time to resolution of illness and time to return to normal activity (primary endpoints) did not reach statistical significance. This raises concern that oseltamivir may not be as effective in treating influenza B compared with influenza A.

Oseltamivir is an oral medication and suitable for children aged 1 to 12 years. Zanamivir is delivered by inhalation and is only suitable for children aged five years or older. Even amongst children aged 5 to 12 years, however, problems generating adequate peak inspiratory flow rates are common (entry to NA130009 was limited to children able to properly use the Diskhaler). For example, Peng 2000 described 16 children aged 5 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 (NA130009) 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.

Only oseltamivir produced a significant reduction in the incidence of physician-diagnosed complications of influenza. There was a trend to benefit for zanamivir. Amongst children using the Diskhaler, however, 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 2001b). 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. This may be particularly important in children, amongst whom acute otitis media is the most frequent complication of influenza.

Notwithstanding some uncertainty about the diagnostic criteria used in study WV15758 (see 'Methodological quality'), oseltamivir treatment of children with laboratory-confirmed influenza produced a reduction of approximately 50% in the incidence of acute otitis media. The data suggest a number needed to treat (NNT) of 11 children aged 1 to 12 years to prevent one case, assuming treatment of all children, regardless of the presence of acute otitis media at enrolment and including the full 28 day

follow up period (95% CI 6 to 40). Amongst children aged one to five years, in whom acute otitis media is more common, the NNT is only five (95% CI 3 to 14). 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). The use of neuraminidase inhibitors may therefore have a considerable impact on the overall incidence of acute otitis media during the influenza season.

Given the higher rate of complications of influenza infection in children with underlying chronic medical conditions, and assuming a fixed-effect, the benefits of neuraminidase inhibitors in these 'at risk' children should in theory be higher than in the general paediatric population. It follows that, where economic factors are limiting, neuraminidase inhibitors may be targeted toward these children. The assumption of a fixed-effect, however, may not be valid. There were no data for zanamivir in 'at risk' children (it is not recommended for patients with chronic respiratory conditions) and, for oseltamivir, the reduction in time to resolution of illness in 'at risk' children (with asthma) was not statistically significant. Similarly, in an additional study of oseltamivir for the treatment of influenza in 329 children and adolescents aged 6 to 17 years with asthma (NV16871; not eligible for this review as no data were broken out for children aged less than 12 years) no difference was observed in time to resolution of symptoms in children with laboratory-confirmed influenza. Whilst oseltamivir was associated with an improvement in indices of pulmonary function, the clinical significance of this is not clear. Current evidence does not therefore support the preferential prescription of neuraminidase inhibitors for 'at risk' children.

Only one (open-label) study of neuraminidase inhibitors 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 value = 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 value = 0.021). In clinical practice, it is not possible to make this distinction. At present, therefore, the evidence supporting the use of oseltamivir for the prevention, rather than treatment, of influenza in children remains weak.

Adverse events are difficult to separate from the symptoms and complications of influenza infection itself when these events are assessed in treatment trials, and the markedly different incidences reported for the control arms of WV15758 and WV15759/WV15871, as compared with NA130009, presumably relate to systematic differences in study design (resulting in

different sensitivities for detection and reporting of mild events). Assuming that only adverse events reported in excess in treatment over control populations represent true drug related adverse events, vomiting alone occurred more frequently among children treated with oseltamivir, however no adverse events were attributable to zanamivir. 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 (NA130009 - FDA 2003; Williamson 2000). We did not, however, 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.

The emergence of strains of influenza resistant to amantadine and rimantadine, with no decrease in virulence, has been well documented. One potential advantage of neuraminidase inhibitors is that the development of viral resistance may be a less significant problem. However, resistance can arise either through mutations in haemagglutinin or neuraminidase (Zambon 2001b). In WV15758, 5.5% (10 out of 182) of oseltamivir-treated children developed a drug-resistant strain of influenza A, but there were no clinical sequelae. Another study of oseltamivir treatment in children with influenza isolated neuraminidase mutants with variable degrees of oseltamivir resistance in 18% (9 out of 50) patients (Kiso 2004). There has already been a report of an oseltamivir-resistant strain of the H5N1 strain of influenza in a 14 year old Vietnamese girl who received a three day course of prophylactic oseltamivir (75 mg once daily) whilst caring for her infected brother. No further isolates of virus were obtained subsequent to doubling her oseltamivir dosage, and she subsequently recovered from infection (Mai Le 2005). 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 NA130009, 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. Data from animal studies suggest that NAI-resistant mutants are often less infectious and pathogenic than wild-type influenza virus (Mendel 1998; Yen 2005) and, to date, there have been no reports of transmission of NAI-resistant strains of influenza in humans - although transmission of viable oseltamivir-resistant mutants has been demonstrated in animal models (Herlocher 2004; Yen 2005). There is an indication that specific neuraminidase mutations may not confer resistance to the entire class of drugs (Mishin 2005).

We identified several negative results reported by regulatory bod-

ies 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 European Medicines Agency (WV15758 - EMEA 2005). Whether these omissions represent true publication bias (failure to publish negative results) or publication lag (extended time from study completion to study publication for negative results) is not clear, although the latter is well known to exaggerate treatment effects in early meta-analyses (Hopewell 2002). In general, both Roche and GlaxoSmithKline were willing to supply conference abstracts/posters and references to published data but (with the exception of a number of clarifications by Roche) would not provide re-analyses or additional data.

Statistically significant results must be interpreted within the context of the large number of secondary endpoints presented for each of the trials. No adjustment was made in statistical analyses for the multiple comparisons (WV15758; not mentioned for NA130009 and WV15759/WV15871) and it was not clear whether many of the endpoints were pre-specified in the trial design or calculated post-hoc.

Two 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. The second UK NHS HTA Report, however, 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 NA130009, whereas this review also included important data on the use of oseltamivir in 'at risk' children from WV15759/WV15871. Endpoints in Turner 2002 are reported separately for WV15758 and NA130009, with no pooling of data across the trials and were commensurate with those stated in this review (Table 18). For NA130009, 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, and provided that therapy can be commenced within 48 hours of the start of the illness, oseltamivir may be considered for the

treatment of children aged 1 to 12 years with influenza infection. This is likely to shorten the duration of symptoms, hasten the return to normal activities and reduce the incidence of secondary complications, notably acute otitis media (children aged 1 to 12 years Number needed to treat (NNT) = 11 (95% CI 6 to 40) to prevent one case; children aged 1 to 5 years NNT = 5 (95% CI 3 to 14) 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 NNT to prevent one case of acute otitis media would be doubled to 22.

Oseltamivir may be considered for use in children aged 1 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.

Neuraminidase inhibitors should not, on the basis of current evidence, be targeted specifically for 'at risk' children (with underlying chronic medical conditions) as benefit has not been shown in this population (oseltamivir and zanamivir) and bronchospasm remains a theoretical risk (zanamivir).

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. A greater selectivity in reporting a limited number of highly relevant primary clinical outcome measures is also needed to avoid the problems of multiple comparisons.

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 and zanamivir would allow clarification of the efficacy of the drugs in treating secondary complications and the frequency of drug-related adverse events.

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.

POTENTIAL CONFLICT OF INTEREST

None declared

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* Indicates the major publication for the study

TABLES

Characteristics of included studies

Study	Loughlin 2002
Methods	Retrospective study of health insurance claims data October 1999 to April 2000
Participants	Patients (including children aged less than 12 years) prescribed a 5 day course of twice-daily inhaled zanamivir 10 mg
Interventions	N/A
Outcomes	Respiratory events occurring within 10 days of zanamivir prescription and requiring Emergency Department or inpatient care

Characteristics of included studies (Continued)

	Patient satisfaction not assessed
Notes	
Allocation concealment	D – Not used
Study	Machado 2004
Methods	Uncontrolled, observational study April 2001 to April 2002
Participants	Bone marrow transplant recipients (including children aged less than 12 years) with upper respiratory tract symptoms (no further details) a clear chest radiograph and laboratory-confirmed influenza infection
Interventions	5 day course of twice-daily oral oseltamivir 75 mg or twice daily amantadine 100 mg when oseltamivir not available
Outcomes	Fever > 39 °C, rigors and chills, illness duration >/= 7 days, hospitalisation, pneumonia Side effects Patient satisfaction not assessed
Notes	
Allocation concealment	D – Not used
Study	NA130009
Methods	Double-blind, randomised, placebo-controlled trial Multicentre trial: 67 sites in US, Canada, Europe/Israel Recruitment period during northern hemisphere winter season 1998/1999 (January 11th 1999 to April 19th 1999) Study approved by ethics committees and conducted in accordance with the Declaration of Helsinki (amended)
Participants	Children aged 5 to 12 years with influenza-like illness </= 36 hours duration, temperature >/= 37.8 °C and no clinical evidence of bacterial infection
Interventions	5 day course of twice-daily inhaled zanamivir 10 mg (or placebo) Relief medications were provided to patients, who were advised to refrain from taking them unless necessitated by the severity of their symptoms
Outcomes	Time to alleviation of clinically significant symptoms: (1) cough none or mild and (2) arthralgia/myalgia + sore throat + chills/feverishness + headache absent or minimal and (3) temperature </= 37.8 °C for 3 consecutive assessments (24 hours) Not explicitly stated whether time to alleviation was measured from the commencement of treatment or the start of illness Other pre-specified outcomes included: time to return to normal activity, incidence of complications of influenza, maximum daily temperature, use of relief medications and number of days of moderate or severe cough Follow up 14 to 28 days (depending on persistence of symptoms) Patient satisfaction not assessed
Notes	Jadad score 5/5
Allocation concealment	A – Adequate
Study	Oo 2003
Methods	Uncontrolled pharmacokinetic study

Characteristics of included studies (Continued)

Participants	Healthy children aged 1 to 5 years
Interventions	Single dose of oral oseltamivir 30 to 45 mg (depending on age)
Outcomes	Adverse events occurring over 2 days following oseltamivir dosing Patient satisfaction not assessed
Notes	
Allocation concealment	D – Not used

Study Peng 2000

Methods	Uncontrolled pharmacokinetic study
Participants	Children aged 3 months to 12 years with signs and symptoms of respiratory illness
Interventions	Single dose of inhaled zanamivir 10 mg Eight children aged less than five years received the drug via a nebuliser and facemask whereas 16 children aged 5 to 12 years used the Diskhaler
Outcomes	Adverse events occurring over 24 hours following zanamivir dosing Patient satisfaction not assessed
Notes	
Allocation concealment	D – Not used

Study WV15758

Methods	Double-blind, randomised, placebo-controlled trial Multicentre trial in US (70 sites) and Canada (10 sites) Recruitment period during northern hemisphere influenza season 1998/1999 Study approved by institutional review boards and conducted in accordance with the principles of the Declaration of Helsinki (amended). All caregivers provided written informed consent before enrolment. Patients also gave written consent if they were old enough to understand the risks and benefits of the study
Participants	Children aged 1 to 12 years with influenza like illness < 48 hours duration (temperature ≥ 37.8 °C and at least one of cough or coryza)
Interventions	5 day course of twice-daily oral oseltamivir 2 mg/kg to max 100 mg dose (or placebo) All patients 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	Time to resolution of illness from start of treatment: first time at which (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 for at least 24 hours Symptoms were also evaluated using the Canadian Acute Respiratory Infection and Flu Scale (CARIFS; including 18 different influenza symptoms, rated on a scale of 0 to 3) Follow up 28 days There was no explicit list of pre-specified (rather than post-hoc) secondary endpoints Patient satisfaction not assessed
Notes	Jadad score 5/5
Allocation concealment	B – Unclear

Study WV15759/WV15871

Methods	Double-blind, randomised, placebo-controlled trial
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Characteristics of included studies (Continued)

	Multi-centre 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 subject, 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 or hospital care with < 48 hours influenza symptoms (temperature ≥ 37.8 °C plus cough or coryza)
Interventions	5 day course of twice-daily oral oseltamivir 2 mg/kg (or placebo)
Outcomes	Time to freedom from illness from first dose of study drug: first time at which (1) symptoms alleviated (no or minor problem on symptom questionnaire) (2) returned to normal health and activity (return to school or normal style of play behaviour) (3) temperature ≤ 37.2 °C for 24 hours Percentage change from baseline in peak expiratory flow (PEF) and frequency of asthma exacerbations (defined as > 20% reduction from highest PEF recorded during follow up) Symptoms also evaluated using the Canadian Acute Respiratory Infection and Flu Scale (CARIFS - described above) Follow up 28 days There was no explicit list of pre-specified (rather than post-hoc) secondary endpoints Patient satisfaction not assessed
Notes	Jadad score 4/5 No details of method of randomisation methodology given
Allocation concealment	B – Unclear

Study	WV16193
Methods	Open-label, randomised, controlled trial Parallel group trial in Europe and North America during the 2000 to 2001 influenza season Study approval obtained from local institutional review boards or ethics committees, and study conducted in compliance with the Declaration of Helsinki (amended). Written informed consent obtained from all individuals (or their legal guardian, as appropriate) prior to participation in the study
Participants	Household contacts of index cases with influenza-like illness (temperature ≥ 37.8 °C plus cough and/or coryza) during a documented community influenza outbreak. Both contacts and index cases included children aged 1 to 12 years
Interventions	Index cases: 5 day course of twice-daily oral oseltamivir 30 to 75 mg (depending on age) Household contacts: 10 day course of once-daily oral oseltamivir at the same age-adjusted dose (or placebo) Households were randomised by cluster, so that all contacts in the same household received the same treatment
Outcomes	Proportion of households with at least one secondary case of laboratory-confirmed influenza during 10 day prophylaxis period A similar analysis was carried out for the proportion of contacts developing symptomatic, laboratory-confirmed influenza, and specifically for children aged 1 to 12 years. This is the endpoint reported in this review Follow up 30 days Patient satisfaction not assessed
Notes	Jadad score 2/5 Open-label trial design

No details of method of randomisation methodology given

Allocation concealment D – Not used

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 (NAI3009) and FDA 2004 (WV15758).

Characteristics of excluded studies

Study	Reason for exclusion
Chik 2004	Prospective, uncontrolled, observational study examining the efficacy of oseltamivir prophylaxis in 32 patients aged 6 to 23 years immunocompromised by chemotherapy or bone marrow transplantation. Not eligible for analysis of prophylactic efficacy; no paediatric safety data provided
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
Gubareva 1998	Case report of zanamivir-resistant influenza B emerging in an immunocompromised girl aged 18 months treated for 2 weeks with nebulised zanamivir
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
Kawai 2003	Multi-centre, uncontrolled, observational study examining the efficacy of oseltamivir treatment in 779 patients (including children) with influenza confirmed by rapid detection test. Not eligible for analysis of treatment efficacy; full report in Japanese, not translated
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
Mitamura 2002	Uncontrolled, observational study examining the efficacy of oseltamivir treatment in 131 children with influenza confirmed by a rapid diagnostic kit. Not eligible for analysis of treatment efficacy; full report in Japanese, not translated
Monto 2002	Double-blind, randomised, placebo-controlled trial of zanamivir for the prevention of influenza in 487 households, including children aged 5 to 12 years as index cases and household contacts. Contacts received zanamivir or placebo, but index cases were not given antiviral therapy. Results were analysed by family, and no sub-group data were provided for prophylactic efficacy or safety in paediatric contacts
NAI30010	Double-blind, randomised, placebo-controlled trial of zanamivir for the prevention of influenza in 337 families, including children aged less than 12 years as index cases and household contacts. Both contacts and index cases received zanamivir or placebo. Results were analysed by family, and no sub-group data were provided for prophylactic efficacy or safety in paediatric index cases or contacts. GlaxoSmithKline was unable to supply this extra information (Dr A. Webster, GlaxoSmithKline, personal communication, 2002)
NV16871	Randomised, double-blind, placebo-controlled trial of oseltamivir for the treatment of influenza-mediated asthma symptoms and exacerbations in 329 patients with asthma aged 6 to 17 years. Unpublished report on Roche Clinical Trial Results Database; no sub-group data provided for treatment efficacy or safety in children aged 6 to 12 years. The company were unable to supply this extra information (Dr Zoya Panahloo, Roche, personal communication, 2005)
Nordstrom 2004	Retrospective study of health insurance claims data examining the frequency of skin reactions in association with oseltamivir use in 102119 patients, including 21905 children aged 1 to 12 years. No paediatric safety data provided
Oo 2001	Study 1: uncontrolled single dose study of pharmacokinetics of oseltamivir in 18 healthy children and adolescents aged 5 to 18 years. Study 2: randomised, placebo-controlled trial of pharmacokinetics of oseltamivir in 92 children aged 1 to 12 years with influenza symptoms. No clinical endpoint data

Characteristics of excluded studies (Continued)

Vogel 2002	Uncontrolled, observational study examining the efficacy of zanamivir or oseltamivir (1 case) treatment in 56 patients aged 8 to 95 years with laboratory-confirmed influenza. Not eligible for analysis of treatment efficacy; no paediatric safety data provided
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	Double-blind, randomised, placebo-controlled trial of oseltamivir for the prevention of influenza in 374 households, including children aged less than 12 years as index cases but not household contacts. Contacts received oseltamivir or placebo, but index cases were not given antiviral therapy. Therefore, no children received oseltamivir in this study
Yamaura 2003	Uncontrolled study examining re-consultation rates and medication dispensing fees in 234 patients (including 146 children) treated with oseltamivir for 2, 3 or 5 days. Not eligible for analysis of treatment efficacy; full report in Japanese, not translated

Characteristics of ongoing studies

Study	NAI30028
Trial name or title	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled Zanamivir 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in children
Participants	519 children
Interventions	5 day course of twice-daily inhaled zanamivir 10 mg
Outcomes	Time until alleviation of symptoms, maximum daily temperature, time to return to normal activities, mean symptoms score
Starting date	Not given
Contact information	Dr Alison Webster, GlaxoSmithKline
Notes	Trial completed, but data not yet available (Dr Alison Webster, GlaxoSmithKline, personal communication, 2005)

ADDITIONAL TABLES

Table 01. Baseline characteristics: WV15758

Characteristic	Intention-to-treat		Lab. influenza +ve		Notes
	Treatment	Control	Treatment	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 from Reisinger 2004
Age distribution	NO DATA	NO DATA	</= 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 from Dr Z Panahloo, Roche, personal communication, 2002

Table 01. Baseline characteristics: WV15758 (Continued)

Characteristic	Intention-to-treat		Lab. influenza +ve		Notes
Gender	173 female (50%)	172 female (49%)	110 female (51%)	115 female (49%)	Data from Reisinger 2004
Ethnicity	222 Caucasian (65%)	229 Caucasian (65%)	145 Caucasian (67%)	162 Caucasian (69%)	Data from Reisinger 2004
	62 Hispanic (18%)	61 Hispanic (17%)	72 other (33%)	73 other (31%)	
	37 black (11%)	39 black (11%)			
	7 oriental (2%)	6 oriental (2%)			
	16 other (5%)	6 other (5%)			
Currently vaccinated	11 (3%)	10 (3%)	4 (2%)	6 (3%)	Data from Whitley 2000a
	1 (0%) vaccination status unknown	0 (0%) vaccination status unknown			
Previously vaccinated	21 (6%); 6 (2%) vaccination status unknown	13 (4%); 3 (1%) vaccination status unknown	NO DATA	NO DATA	Data from Whitley 2000a
Duration of illness before enrolment	NO DATA	NO DATA	Median 26.7 hours	Median 28.0 hours	
Enrolment temperature (Fahrenheit)	NO DATA	NO DATA	102.0° (range: 96.8 to 106.3)	101.8° (range: 97.8 to 106.8)	
Illness severity at enrolment	NO DATA	NO DATA	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 a chronic medical condition)	7 (2%) 'mild asthma'	9 (3%) 'mild asthma'	NO DATA	NO DATA	Data from Dr Z. Panahloo, Roche, personal communication, 2002

Table 02. Baseline characteristics: WV15759/WV15871

Characteristic	Intention-to-treat		Lab. influenza +ve		Notes
	Treatment	Control	Treatment	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 Caucasian	143 Caucasian	73 Caucasian	85 Caucasian	

Table 02. Baseline characteristics: WV15759/WV15871 (Continued)

Characteristic	Intention-to-treat		Lab. influenza +ve		Notes
	(88%)	(87%)	(87%)	(90%)	
	8 Black (5%)	8 black (5%)	11 other (13%)	10 other (10%)	
	1 Oriental (1%)	2 oriental (1%)			
	3 Asian (2%)	0 Asian (0%)			
	9 other (5%)	11 other (7%)			
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	NO DATA	NO DATA	Data from Whitley 2000a
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)	
FEV1 % predicted at baseline	77.4% (SD 23.2)	77.8% (SD: 21.4)	75.6% (SD: 21.4)	81.0% (SD: 20.1)	

Table 03. Baseline characteristics: NAI30009

Characteristic	Intention-to-treat		Lab. influenza +ve	
	Treatment	Control	Treatment	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)
Sex	97 female (43%)	116 female (47%)	68 female (41%)	91 female (50%)
Ethnicity	201 white (90%)	223 white (90%)	148 white (90%)	162 white (89%)
Currently vaccinated	6/224 (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	Mean 38.7 (SD +/- 0.64); 3 patients with temperature < 37.8 at

Table 03. Baseline characteristics: NAI30009 (Continued)

Characteristic	Intention-to-treat		Lab. influenza +ve	
			enrolment	enrolment
Illness severity at enrolment	125 overall moderate symptom assessment (56%) 71 overall severe symptom assessment (32%)	151 overall moderate symptom assessment (61%) 56 overall severe symptom assessment (23%)	86 overall moderate symptom assessment (53%) 56 overall severe symptom assessment (34%)	107 overall moderate symptom assessment (59%) 47 overall severe symptom assessment (26%)
Influenza serotype	N/A	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 concurrent chronic respiratory condition requiring regular medication	14 (6%) children with concurrent chronic respiratory condition requiring regular medication	NO DATA	NO DATA

Table 04. Median time to resolution of illness

Study ID	Group	N	Time to resolution	Reduction	Notes
WV15758	Intention-to-treat	T = 344 C = 351	T = 105 hours (95% CI 91 to 112) C = 126 hours (95% CI 117 to 137)	17% (21 hours) P = 0.0002	
	Laboratory-confirmed influenza	T = 217 C = 235	T = 101.3 hours (95% CI 89 to 118) C = 137.0 hours (95% CI 125 to 150)	26% (36 hours) P < 0.0001	
WV15759/WV158711	Intention-to-treat	T = 170 C = 164	NO DATA	NO DATA	
	Laboratory-confirmed influenza	T = 84 C = 95	T = 123.9 hours C = 134.3 hours	7.7% (10.4 hours) P = 0.54	Amongst patients who started treatment < 24 hours after onset of symptoms (T = 31, C = 41) the reduction was much greater (39.8 hours; 25%; P = 0.078). Amongst patients who started treatment > 24 hours after onset of symptoms (T = 53, C = 54) the reduction was correspondingly less (3.9 hours)
NAI30009	Intention-to-treat	T = 224	T = 4.5 days	10%	

Table 04. Median time to resolution of illness (Continued)

Study ID	Group	N	Time to resolution	Reduction	Notes
		C = 247	C = 5.0 days	(0.5 days; 95% CI 0.0 to 1.5) P = 0.011	
	Laboratory-confirmed influenza	T = 164 C = 182	T = 4.0 days C = 5.25 days	24% (1.25 days; 95% CI 0.5 to 2.0) P < 0.001	Another analysis in which missing data were censored at patients' last non-alleviated diary entry gave similar results

Table 05. Median time to resolution of illness by age

Study ID	Group	Age	N	Time to resolution	Reduction	Notes
WV15758	Laboratory-confirmed influenza	</= 2 years	T = 39 C = 55	T = 139 hours (95% CI 103 to 160) C = 161 hours (95% CI 139 to 171) (overlapping CIs)	14% (23 hours)	Denominators exclude children for whom no efficacy data were available (Dr Z. Panahloo, Roche, personal communication, 2002)
		3 to 5 years	T = 68 C = 56	T = 99 hours (95% CI 85 to 124) C = 137 hours (95% CI 98 to 153) (overlapping CIs)	28% (38 hours)	See above
		> 5 years	T = 102 C = 114	T = 90 hours (95% CI 76 to 109) C = 125 hours (95% CI 114 to 141) (non-overlapping CIs)	28% (35 hours)	See above

Table 06. Median time to resolution of illness by serotype

Study ID	N	Influenza serotype	Time to resolution	Notes
WV15758	T = 150 C = 153	A	Reduction: 34% P < 0.0001	Data from EMEA 2005
	T = 66 C = 82	B	T = 125.3 hours C = 137.0 hours Reduction: 8.5% (11.7 hours) P = 0.27	
NA130009	T = 106 C = 120	A	T = 4.0 days C = 5.0 days	

Table 06. Median time to resolution of illness by serotype (Continued)

Study ID	N	Influenza serotype	Time to resolution	Notes
			Reduction: 1.0 days (95% CI 0.0-1.5) P = 0.049	
	T = 58 C = 62	B	T = 4.0 days C = 6.0 days Reduction: 2.0 days (95% CI 1.0-3.5) P < 0.001	

Table 07. Median time to resolution of illness by geographical area

Study ID	Group	Geographical area	N	Time to resolution
NAI30009	Laboratory-confirmed influenza	North America	T = 96 C = 105	T = 4 days C = 5 days Reduction: 1 day (95% CI 0-1.5); P = 0.026
	Laboratory-confirmed influenza	Europe/Israel	T = 8 C = 77	T = 4 days C = 5.5 days Reduction: 1.5 days (95% CI 0.5-3.0) P = 0.004

Table 08. Median time to return to normal activity

Study ID	Group	N	Time to return	Reduction	Notes
WV15758	Intention-to-treat	T = 344 C = 351	NO DATA	NO DATA	
	Laboratory-confirmed influenza	T = 209 C = 225	T = 67.1 hours C = 111.7 hours	40% (44.6 hours) P < 0.0001	Information from Reisinger 2004. Analysis excludes children for whom no efficacy data were available
WV15759/WV15871	Intention-to-treat	T = 170 C = 164	NO DATA	NO DATA P = 0.019	
	Laboratory-confirmed influenza	T = 84 C = 95	T = 101.4 hours C = 114 hours	11% (12.6 hours) P = 0.46	Amongst patients who started treatment < 24 hours after onset of symptoms (T = 31, C = 41) the reduction was 16.0 hours (13%; P = 0.16). Amongst patients who started treatment > 24 hours after onset of symptoms (T = 53, C =

Table 08. Median time to return to normal activity (Continued)

Study ID	Group	N	Time to return	Reduction	Notes
NAI30009	Intention-to-treat	T = 224 C = 247	NO DATA	NO DATA	54) the reduction was -3.5 hours (-3.7%; P = 0.81) Not clear whether the reduction of one day refers to the intention-to-treat population, or to children with laboratory-confirmed influenza, or to both
	Intention-to-treat	T = 164 C = 182	NO DATA	NO DATA	See above

Table 09. Secondary complications

Study ID	Group	N	Overall rate	Acute otitis media	Bronchitis	Pneumonia	Sinusitis	Total antibiotic use	Notes
WV15758	Laboratory-confirmed influenza	T = 217 C = 235	T = 36 (17%) C = 65 (28%) Relative Risk Reduction: 40% P = 0.005	T = 26 (12%) C = 50 (21%) Relative Risk Reduction: 44% (95% CI 13-64) P < 0.05 See Table 10 for further details.	T = 2 (1%) C = 6 (3%)	T = 3 (1%) C = 4 (2%)	T = 7 (3%) C = 9 (4%)	T = 68 (31%) C = 97 (41%) Relative Risk Reduction: 24% P = 0.03	Data from Hayden 2000. Overall rate represents physician-diagnosed complications requiring antibiotic use developing on or after study day 3
NAI30009	Laboratory-confirmed influenza	T = 164 C = 182	T = 16% C = 23% Relative Risk Reduction: 30% Non-significant. Absolute Risk Reduction: 7% (95% CI -1 to -	NO DATA	NO DATA	NO DATA	NO DATA	T = 12% C = 15% Relative risk reduction: 20% Non-significant.	

Table 09. Secondary complications (Continued)

Study ID	Group	N	Overall rate	Acute otitis media	Bronchitis	Pneumonia	Sinusitis	Total antibiotic use	Notes
			15)						

Table 10. Incidence of acute otitis media

Study ID	Group	Age	N	Up to day 10	Up to day 28	Notes
WV15758	Laboratory-confirmed influenza	1 to 12 years	T = 217 C = 235	T = 18 (8%) C = 37 (16%) Relative Risk Reduction: 47% (95% CI 10-69) Absolute Risk Reduction: 7% (95% CI: 1.5-13)	T = 26 (12%) C = 50 (21%) Relative Risk Reduction: 44% (95% CI 13-64) P < 0.05 Absolute Risk Reduction: 9% (95% CI 2.5-16)	Children were stratified for the presence of acute otitis media at enrolment. We report the number of cases of acute otitis media which developed after enrolment for these two different denominators. Data for children aged 1 to 12 years from Whitley 2001, Hayden 2000 and Winther 2000; acute otitis media diagnosed over day 3 to day 10 and day 3 to day 28 respectively
		1 to 5 years	T = 110 C = 116	T = 13 (12%) C = 28 (24%) Relative Risk Reduction: 50% Absolute Risk Reduction: 12% (95% CI: 2-22)	T = 16 (15%) C = 38 (33%) Relative Risk Reduction: 55% Absolute Risk Reduction: 18% (95% CI: 7-29)	
	Laboratory-confirmed influenza without acute otitis media at enrolment	1 to 12 years	T = 183 C = 200	T = 18 (10%) C = 37 (19%) Relative Risk Reduction: 47% Absolute Risk Reduction: 9% (95% CI 2-16)	T = 26 (14%) C = 50 (25%) Relative Risk Reduction: 44% Absolute Risk Reduction: 11% (95% CI 3-19)	See above

Table 10. Incidence of acute otitis media (Continued)

Study ID	Group	Age	N	Up to day 10	Up to day 28	Notes
		1 to 5 years	T = 86 C = 89	T = 13 (15%) C = 28 (31%) Relative Risk Reduction: 52% (95% CI 14-73) Absolute Risk Reduction: 16% (95% CI 4-29)	T = 16 (19%) C = 38 (43%) Relative Risk Reduction: 56% (95% CI 28-74) Absolute Risk Reduction: 24% (95% CI 11-37)	See above

Table 11. Duration/severity of acute otitis media

Study ID	Group	Age	N	Duration/severity	Notes
WV15758	Children with laboratory-confirmed influenza diagnosed with acute otitis media over day 1 to day 28	1 to 12 years	T = 29 C = 53	Median duration acute otitis media T = 7 days C = 10 days Number of children with acute otitis media lasting <10 days: T = 19 (66%) C = 29 (55%)	All data from Winther 2000 Acute otitis media diagnosed in children aged 1 to 12 years over day 1 to day 28, compared with day 3 to day 28 in Table 10.
	Children with laboratory-confirmed influenza with acute otitis media at enrolment	1 to 12 years	T = 33 C = 33	Number of children with acute otitis media lasting < 10days from enrolment T = 26 (79%) C = 20 (61%) Number children with acute otitis media at: day 0 T = 33 (100%) C = 33 (100%) d6 T = 10 (36%) C = 18 (64%) d10 T = 4 (16%) C = 7 (27%) d28 T = 2 (7%) C = 5 (19%)	All data from Winther 2000 Whitley 2001 reports 69 children with laboratory-confirmed influenza with otitis media at baseline (T=34, C=35). Three of these children are excluded from the analysis in Winther 2000 because they were judged to have chronic otitis media (Dr Z. Panahloo, Roche, personal communication, 2002).

Table 12. Asthma exacerbations: WV15759/WV15871

Group	N	Measured by PEF*	Medical reports	Notes
Intention-to-treat	T = 170 C = 164	NO DATA	T = 14 (8%) C = 17 (10%)	
Laboratory-confirmed influenza	T = 84 C = 95	T = 68% C = 51% P = 0.031	T = 10 (12%) C = 16 (17%) P = 0.4	*number of children within 20% of their best PEF (as recorded during study) on day 7

Table 13. Duration/severity of cough

Study ID	Group	N	Duration/severity	Notes
WV15758	Intention-to-treat	T = 344 C = 351	NO DATA	
	Laboratory-confirmed influenza	T = 217 C = 235	Median duration T = 39 hours (95% CI 32-51) C = 71 hours (95% CI 63-81) Reduction: 45% (32 hours) P = 0.0008	
NAI30009	Intention-to-treat	T = 224 C = 247	Moderate/severe cough on day 2 to day 5 less common in treatment group P = 0.026	A reduction in severity of cough was also noted in influenza-infected children treated with zanamivir 1 day after treatment initiation
	Laboratory-confirmed influenza	T = 164 C = 182	Moderate/severe cough on day 2 to day 5 less common in treatment group P = 0.001 Moderate/severe cough on day 2: T = 53% C = 69% Absolute Risk Reduction: 16% (95% CI 5.4-26.9) P = 0.003	

Table 14. Use of relief medications

Study ID	Group	N	Use of medication
WV15758	Intention-to-treat	T = 344 C = 351	NO DATA
	Laboratory-confirmed influenza	T = 217 C = 235	Median total paracetamol consumption: T = 40 mg/kg C = 59 mg/kg Reduction: 31% P = 0.002 Proportion of children receiving any paracetamol during treatment period: T = 88%

Table 14. Use of relief medications (Continued)

Study ID	Group	N	Use of medication
			C = 92%
NAI30009	Intention-to-treat	T = 224 C = 247	Less use in treatment group P = 0.016
	Laboratory-confirmed influenza	T = 164 C = 182	Less use in treatment group P = 0.005

Table 15. Other endpoints: WV15758 and WV15759/WV15871

Study	Group	N	CARIFS Median duration of all CARIFS items	Fever Median duration	Coryza Median duration	Overall severity Median 'area- under-curve' cumulative CARIFS symptom scores
WV15758	Laboratory-confirmed influenza	T = 217 C = 235	T = 63 hours C = 100 hours Reduction: 36% (36 hours) p<0.0001	T = 44 hours (95% CI 40 to 48) C = 68 hours (95% CI 55 to 78) Reduction: 37% (25 hours) P < 0.0001	T = 43 hours (95% CI 31 to 53) C = 66 hours (95% CI 43 to 77) Reduction: 35% (23 hours) P = 0.09	T = 960 C = 1358 P = 0.002
WV15759/WV15871	Laboratory-confirmed influenza	T = 84 C = 95	T = 90.4 hours C = 116 hours Reduction: 22% (25 hours) P = 0.12 Amongst patients who started treatment <24 hours after onset of symptoms (T=31, C=41) the reduction was 24 hours (21%; p=0.08). Amongst patients who started treatment >24 hours after onset of symptoms (T=53, C=54) the reduction was 25.7 hours (22%; p=0.35).	NO DATA	NO DATA	T = 1543 C = 1731 P = 0.08 Amongst patients who started treatment <24 hours after onset of symptoms (T=31, C=41) the reduction was much greater (T = 1582, C = 1830; P = 0.049). Amongst patients who started treatment >24 hours after onset of symptoms (T = 53, C = 54) the reduction was correspondingly less (T = 1500, C = 1568; P = 0.39).

Table 15. Other endpoints: WV15758 and WV15759/WV15871 (Continued)

Study	Group	N	CARIFS	Fever	Coryza	Overall severity
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Table 16. Other endpoints: NA130009

Group	N	Endpoint	Notes
		Median time to alleviation of clinically significant symptoms with no use of relief medications	
Intention-to-treat	T = 224 C = 247	T = 5.0 days C = 6.0 days Reduction: 1.0 days (95% CI 0.0 to 1.75) P = 0.0022	This benefit was also present in sensitivity analyses Significance level reported as P = 0.002, although 95% CI includes 0.0 days.
Laboratory-confirmed influenza	T = 164 C = 182	T = 5.0 days C = 6.5 days Reduction: 1.5 days (95% CI 0.5 to 2.25) P < 0.001	

Table 17. Prevention of influenza

Study ID	Group	Serotype	N	Influenza cases*	Protective efficacy	Notes
WV16193	All paediatric contacts (intention-to-treat)	N/A	T = 104 C = 111	T = 7 (7%) C = 21 (19%)	64% (95% CI 15.8 to 85) P = 0.019	*number of contacts developing symptomatic, laboratory-confirmed influenza
	Paediatric contacts of index cases with laboratory-confirmed influenza	A+B	T = 55 C = 74	T = 6 (11%) C = 18 (24%)	55% (95% CI -13 to 82) P = 0.089	
		A	T = 24 C = 45	T = 3 (13%) C = 7 (24%)	49% (95% CI -72 to 85) P = 0.28	
		B	T = 31 C = 29	T = 3 (10%) C = 7 (24%)	60% (95% CI -71.5 to 91) P = 0.218	
	Paediatric contacts of index cases with laboratory-confirmed influenza (virus negative at baseline)	A+B	T = 47 C = 70	T = 2 (4.3%) C = 15 (21%)	80% (95% CI 22 to 95) P = 0.021	This analysis excluded paediatric contacts found to have +ve influenza virus swabs at the start of prophylactic treatment
	Paediatric contacts	A+B	T = 22	T = 1 (4.5%)	82%	Data from Hayden

Table 17. Prevention of influenza (Continued)

Study ID	Group	Serotype	N	Influenza cases*	Protective efficacy	Notes
	of paediatric index cases with laboratory-confirmed influenza		C = 36	C = 9 (25%)	(95% CI -25 to 97)	2002

Table 18. Comparison of this review with Turner 2002

Trial	Source	Group	Endpoint	Endpoint	Endpoint
			Reduction in median time to resolution of illness	Reduction in median time to return to normal activities	Relative risk reduction in complications requiring antibiotic treatment:
WV15758	Turner 2002	Intention-to-treat	20.9 hours (95% CI 6.1 to 35.7); 17%	30.1hrs (95% CI 16.8 to 43.3); 30%	NO DATA
	This review	Intention-to-treat	21 hours; 17%; P = 0.0002	NO DATA	NO DATA
	Turner 2002	Laboratory-confirmed influenza	35.8 hours (95% CI 18.2 to 53.3); 26%	44.6 hours (95% CI 25.4 to 63.7); 40%	24%; OR 0.65 (95% CI 0.43 to 0.97)
	This review	Laboratory-confirmed influenza	36 hours; 26%; P < 0.0001	44.6 hours; 40%; P < 0.0001	24%; P = 0.03
NA130009	Turner 2002	Intention-to-treat	Healthy children: 1.0 day (95% CI 0.5 to 1.5); 20% 'At risk' children: 2.0 days (95% CI -2.9 to 6.9); 35%	Healthy children: 0.5 days (95% CI -0.3 to 1.3); 8.3% 'At risk' children: 1.0 days (95% CI -1.5 to 3.5); 14%	NO DATA
	This review	Intention-to-treat	0.5 days (95% CI 0.0 to 1.5); 10%; P = 0.011	1 day; P = 0.019	NO DATA
	Turner 2002	Laboratory-confirmed influenza	Healthy children: 1.0 day (95% CI 0.4 to 1.6); 20% 'At risk' children: 3.8 days (95% CI -0.1 to 7.6); 66%	Healthy children: 0.5 days (95% CI -0.4 to 1.4); 8.3% 'At risk' children: 2.5 days (95% CI 0.6 to 4.4); 36%	20%
	This review	Laboratory-confirmed influenza	1.25 days (95% CI 0.5 to 2.0); 24%; P < 0.001	1 days; P = 0.022	20%; non-significant

ANALYSES

Comparison 01. Oseltamivir

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Any adverse event	2	1029	Odds Ratio (Fixed) 95% CI	0.87 [0.68, 1.12]
02 Serious adverse events	2	1029	Odds Ratio (Fixed) 95% CI	2.00 [0.60, 6.69]
03 Adverse events leading to study withdrawal	2	1029	Odds Ratio (Fixed) 95% CI	1.00 [0.37, 2.68]
04 Nausea	2	1029	Odds Ratio (Fixed) 95% CI	0.77 [0.40, 1.46]
05 Vomiting	2	1029	Odds Ratio (Fixed) 95% CI	1.68 [1.15, 2.47]
06 Diarrhoea	2	1029	Odds Ratio (Fixed) 95% CI	0.81 [0.52, 1.25]

Comparison 02. Zanamivir

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Any adverse event	1	471	Odds Ratio (Fixed) 95% CI	0.76 [0.50, 1.17]
02 Serious adverse events	1	471	Odds Ratio (Fixed) 95% CI	3.32 [0.13, 81.97]
03 Adverse events leading to study withdrawal	1	471	Odds Ratio (Fixed) 95% CI	Not estimable

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Child; Humans

COVER SHEET

Title	Neuraminidase inhibitors for preventing and treating influenza in children
Authors	Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M
Contribution of author(s)	AH (Anthony Harnden) conceived the idea for the review and drafted the protocol with AS (Aziz Sheikh). MA (Mkael Symmonds-Abrahams) conducted electronic searches and AH and NM (Nicholas Matheson) liaised with pharmaceutical companies. NM collated extracted data and NM and MA wrote the review. AS commented on the text and AH edited the final document. NM updated the review. RP (Rafael Perera) commented on the statistical methods and the final document.
Issue protocol first published	2000/4
Review first published	2003/3
Date of most recent amendment	05 October 2006
Date of most recent SUBSTANTIVE amendment	20 September 2006

What's New	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.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	14 April 2005
Date authors' conclusions section amended	06 November 2005
Contact address	Dr Nicholas Matheson Flat 4 143 George Street London W1H 5LB UK E-mail: nickmatheson@yahoo.com Tel: +44 7715 102602
DOI	10.1002/14651858.CD002744.pub2
Cochrane Library number	CD002744
Editorial group	Cochrane Acute Respiratory Infections Group
Editorial group code	HM-ARI

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Oseltamivir, Outcome 01 Any adverse event

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 01 Oseltamivir

Outcome: 01 Any adverse event

Study	Treatment n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
WV15758	168/344	185/351		68.2	0.86 [0.64, 1.15]
WV15759/WV15871	83/170	84/164		31.8	0.91 [0.59, 1.40]
Total (95% CI)	514	515		100.0	0.87 [0.68, 1.12]

Total events: 251 (Treatment), 269 (Control)
 Test for heterogeneity chi-square=0.05 df=1 p=0.82 I²=0.0%
 Test for overall effect z=1.09 p=0.3

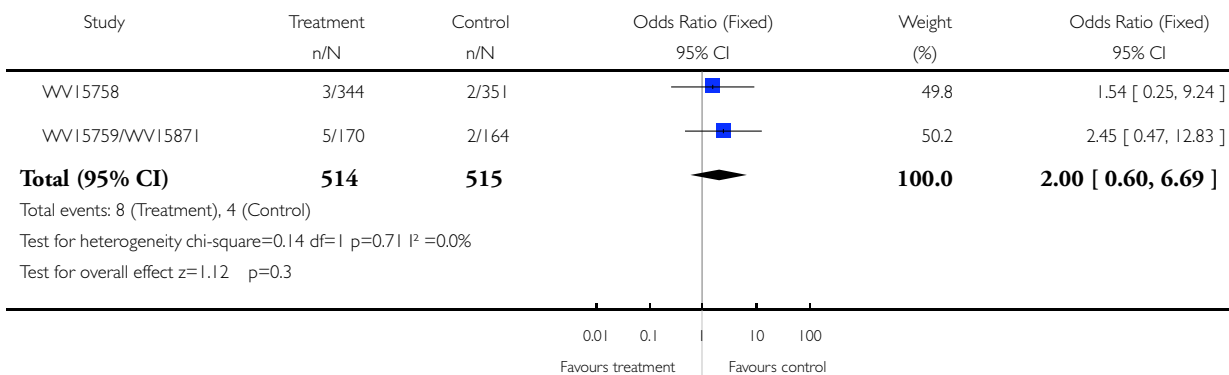
0.01 0.1 10 100
 Favours treatment Favours control

Analysis 01.02. Comparison 01 Oseltamivir, Outcome 02 Serious adverse events

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 01 Oseltamivir

Outcome: 02 Serious adverse events

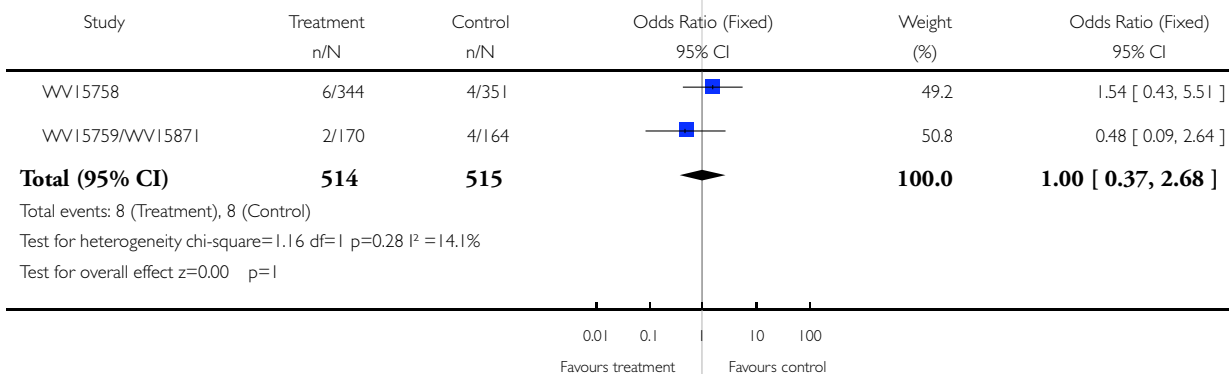


Analysis 01.03. Comparison 01 Oseltamivir, Outcome 03 Adverse events leading to study withdrawal

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 01 Oseltamivir

Outcome: 03 Adverse events leading to study withdrawal

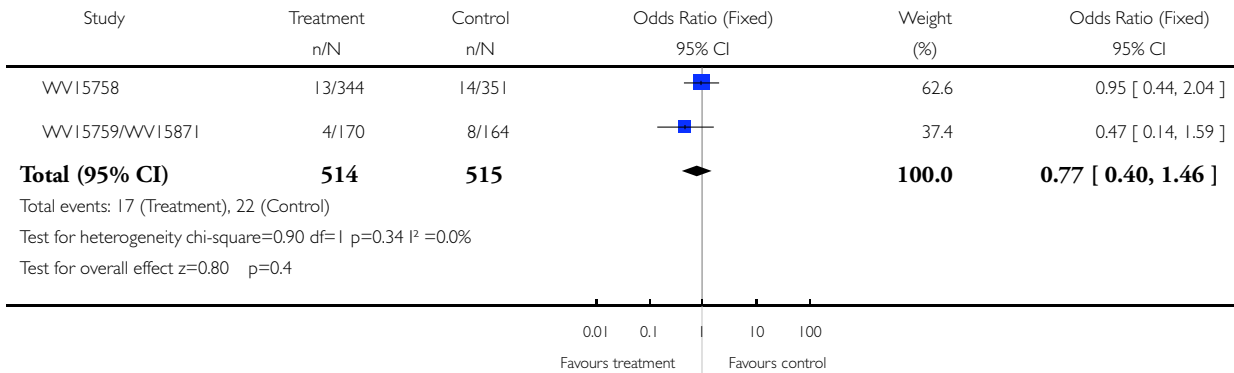


Analysis 01.04. Comparison 01 Oseltamivir, Outcome 04 Nausea

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 01 Oseltamivir

Outcome: 04 Nausea

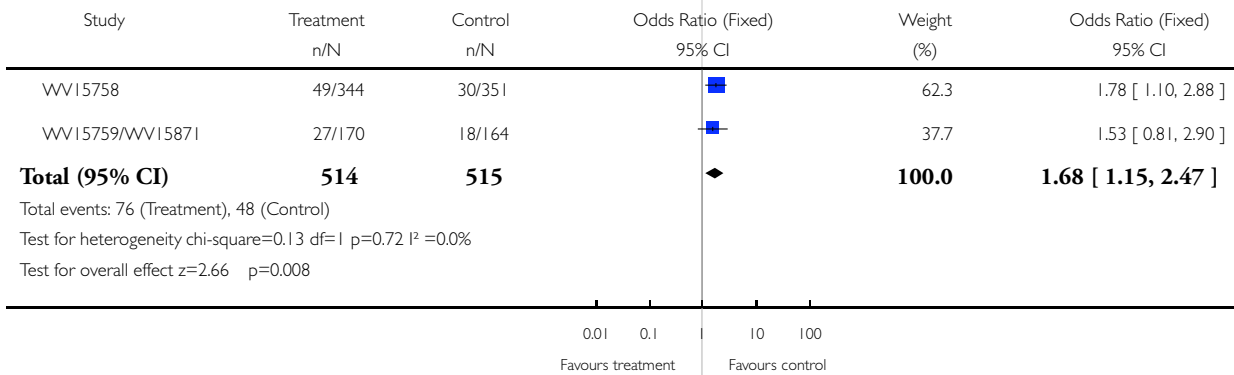


Analysis 01.05. Comparison 01 Oseltamivir, Outcome 05 Vomiting

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 01 Oseltamivir

Outcome: 05 Vomiting

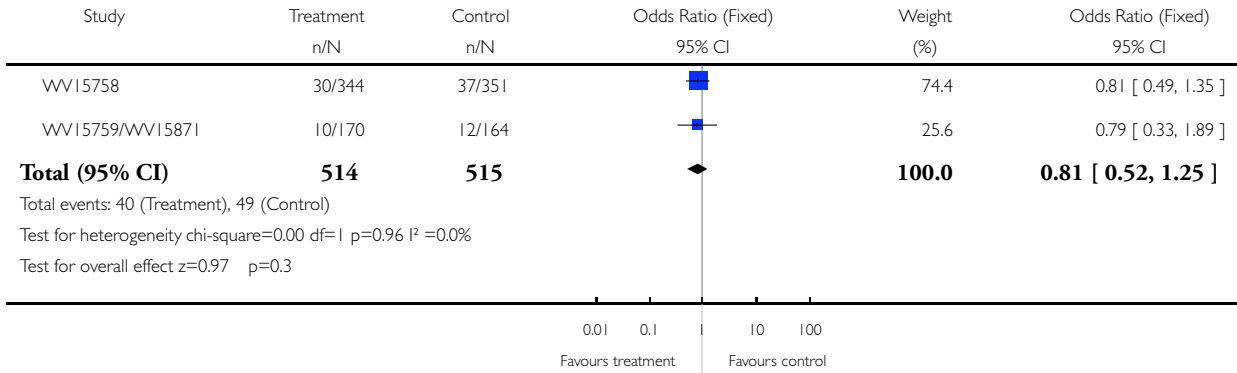


Analysis 01.06. Comparison 01 Oseltamivir, Outcome 06 Diarrhoea

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 01 Oseltamivir

Outcome: 06 Diarrhoea

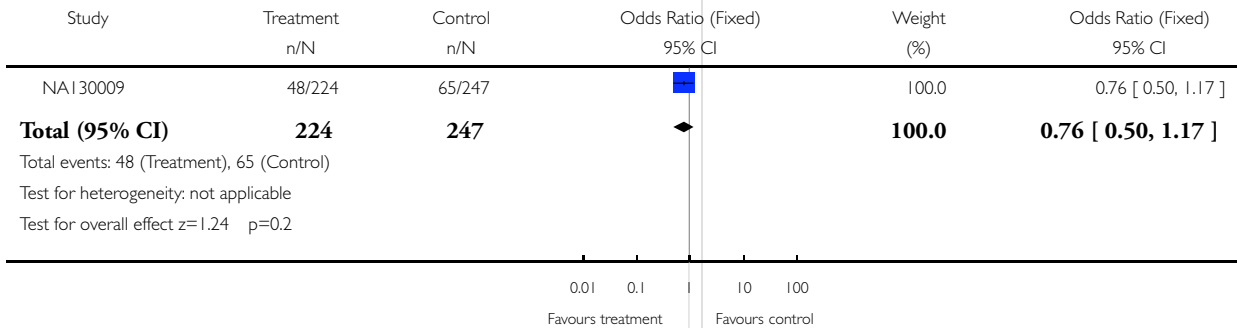


Analysis 02.01. Comparison 02 Zanamivir, Outcome 01 Any adverse event

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 02 Zanamivir

Outcome: 01 Any adverse event

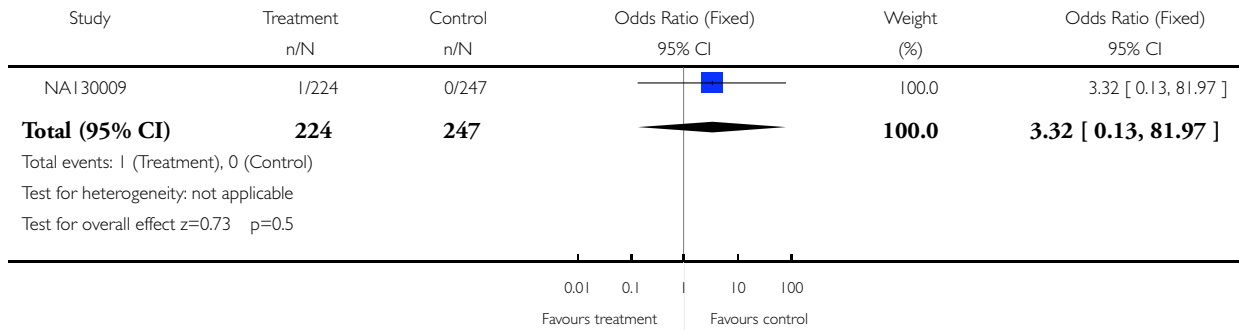


Analysis 02.02. Comparison 02 Zanamivir, Outcome 02 Serious adverse events

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 02 Zanamivir

Outcome: 02 Serious adverse events



Analysis 02.03. Comparison 02 Zanamivir, Outcome 03 Adverse events leading to study withdrawal

Review: Neuraminidase inhibitors for preventing and treating influenza in children

Comparison: 02 Zanamivir

Outcome: 03 Adverse events leading to study withdrawal

