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Health Technology Assessment
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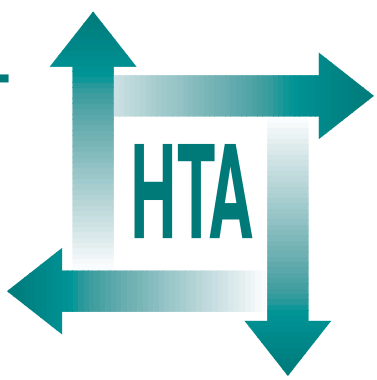

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The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources.

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Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

coryza Cold symptoms, e.g. a runny nose.

EQ-5D (EuroQol-5 dimensions) Standardised assessment method for quality of life, used in cost–utility studies.

GG167 Development drug name of zanamivir.

Meta-analysis Method of combining results from different studies to produce a summary statistic.

Oseltamivir An oral neuraminidase inhibitor co-developed by Gilead Sciences Inc and Hoffman La Roche Ltd marketed under the trade name Tamiflu®.

Relenza® Trade name for zanamivir.

Reye's syndrome A rare disease of children, which usually occurs in the recovery phase of a viral illness, and is characterised by encephalitis and liver failure.

RWJ-270201 An oral neuraminidase inhibitor currently under-going Phase III trials by Johnsons & Johnson in the USA.

Tamiflu® Trade name for oseltamivir.

Zanamivir An inhaled neuraminidase inhibitor developed by Glaxo Wellcome and marketed under the trade name Relenza®.

List of abbreviations

b.d.	twice a day*
CI	confidence interval
COPD	chronic obstructive pulmonary disease
df	degrees of freedom*
ERVL	Enteric and Respiratory Virus Laboratory
FDA	Federal Drug Association
GP	general practitioner
GPRD	General Practice Research Database
ICER	incremental cost-effectiveness ratio
ILI	influenza-like illness
i.n.	intranasal/intranasally*
IPP	influenza positive population
ITT	intention-to-treat
ITTP	intention-to-treat population
NA	not applicable*
NI	neuraminidase inhibitor
NICE	National Institute for Clinical Excellence
o.d.	once daily*
OTC	over-the-counter
PHLS	Public Health Laboratory Service
QALY	quality-adjusted life-year
q.d.	four times a day*
QoL	quality of life
RCGP	Royal College of General Practitioners
RCT	randomised controlled trial
SD	standard deviation
WMD	weighted mean difference*

* Used only in figures, appendices and tables

Executive summary

Background

Zanamivir is a neuraminidase inhibitor specifically designed to interfere with the replication of influenza A and B viruses. It, therefore, has the potential to be useful in the treatment or prevention of influenza. It is currently licensed for the treatment of influenza in people aged 12 and over with symptoms of influenza when influenza is circulating.

Influenza is a common condition affecting all age groups. It occurs during the winter months and causes significant morbidity and increased mortality. The elderly and those with pre-existing medical problems, such as heart disease and renal disease, are particularly at risk of suffering severe disease or developing complications.

The policy in the UK is to vaccinate at-risk individuals. Otherwise-healthy adults with influenza are encouraged to stay at home and take over-the-counter medications for symptomatic relief. At-risk adults with influenza usually receive non-influenza-specific supportive care. Amantadine, an oral antiviral agent effective for treating influenza but which can cause adverse GI effects, is also available.

Questions addressed by this review

(1) How effective is zanamivir in shortening the time-course, reducing the severity of illness or preventing death in otherwise healthy adults with influenza?
(2) How effective is zanamivir in shortening the time-course, reducing the severity of illness or preventing death in adults at risk of suffering severe adverse outcomes from influenza?
(3) What is the frequency and severity of adverse effects associated with the use of zanamivir in both healthy and at-risk adults?
(4) What is the cost-effectiveness of zanamivir for the treatment of influenza in healthy and at-risk adults?

Methods

A systematic review of randomised controlled trials and economic evaluations addressing the above questions was undertaken and a UK model of cost-effectiveness developed.

Results

Effectiveness in all adults

The results of ten trials were included in the review of effectiveness in all adults. Where possible, they were combined in pooled analyses.

Inhaled zanamivir 10 mg twice daily for 5 days (the licensed dose) was found to reduce the duration of symptoms of influenza by 1 day (95% confidence interval (CI), 0.4 to 1.7) from about 6 to 5 days and the time to return to normal activities by 0.5 days (95% CI, –0.4 to 1.5) from about 7 to 6.5 days (not statistically significant) in the intention-to-treat population (ITTP). In the influenza-positive population (IPP), the treatment effect was marginally larger but this was not significantly different from that in the ITTP.

Effectiveness in at-risk adults

The results of seven trials contributed to the review of effectiveness in at-risk adults. Only one trial recruited an exclusively at-risk population. Six trials in all adults provided data from at-risk subgroups. The pooled analysis was based on 371 in the zanamivir group and 392 in the placebo group.

Inhaled zanamivir 10 mg twice daily for 5 days was found to reduce the duration of symptoms of influenza by 1.16 days (95% CI, 0.13 to 2.19) from about 8 to 7 days in the ITTP and by 1.67 days (95% CI, –0.02 to 3.37) in the IPP. The data did not have the power to demonstrate any differences in hospitalisation or death rates for either group. The drug had a similar adverse event profile to the placebo group.

Economic evaluation

Zanamivir costs £24 for a 5-day course of treatment. Only one cost-effectiveness analysis was

found in the published literature, which was for use in at-risk patients. Although the analysis followed established methods, it was based on one trial with only 37 participants in the zanamivir arm, and some of the assumptions did not reflect the true clinical situation. Therefore, we had limited confidence in its conclusions.

We derived UK-based estimates of cost-effectiveness using all data available. The base-case incremental cost per day of symptom avoided was £50 for all patients when influenza is circulating (i.e. the licensed indication) and £42 for at-risk patients when influenza is circulating. The incremental cost per quality-adjusted life-year (QALY) gained was £65,000 for all adults when influenza is circulating (i.e. the licensed indication) and £54,000 for at-risk adults when influenza is circulating (although this was based on a difference in effect that was not statistically significant).

Sensitivity analyses showed these results to be highly sensitive to a number of parameters. The cost/QALY varied from £15,000 to £117,000/QALY if used in at-risk adults and £18,000 to £341,000/QALY if used in all adults. A significant reduction in price of the drug (to £8) brought the incremental cost-effectiveness ratio (ICER) to £21,000 for all adults when influenza is circulating. Assuming a very large gain in quality of life (QoL) from treatment (influenza utility = 0, no influenza utility = 1) reduced the ICER to £18,000 for all adults when influenza is circulating. Changing the gain in health-related QoL for those at risk produced ICERs that ranged from £15,000 to £54,000, i.e. from a cost/QALY that compares favourably with many other treatments currently used in the NHS to one that has been seen under some circumstances as poor value for money. QoL data collected in a number of trials was not made available. Given the importance of QoL changes for determining the ICERs, empirical patient-level information is vital.

Conclusions

The evidence base for at-risk adults has greatly increased since this product was first reviewed by the National Institute for Clinical Excellence. The data available suggest that it may prove useful when used judiciously in at-risk patients. It will be important to monitor its use and incorporate new trial evidence as it becomes available to confirm this.

Chapter 1

Aims and background

Aims of the review

1. To assess the evidence on the effectiveness and safety of zanamivir for the treatment of influenza in healthy and at-risk adults.
2. To assess the evidence on the cost and cost-effectiveness of zanamivir for the above indications.

This report is based on two pieces of work – an initial rapid review of zanamivir for the treatment of influenza and an analysis of further trial data supplied after completion of the initial review – both carried out to inform the National Institute for Clinical Excellence (NICE) appraisal of zanamivir in December 2000. The monograph also incorporates suggestions for analysis made during external peer review and feedback following the NICE appraisal process.

Description of influenza

Presentation

Influenza is a respiratory infection caused by the influenza virus. It is an acute febrile illness with cough, myalgia and headache. The duration of the acute illness is usually about 3–7 days but cough and malaise can persist for weeks. Complications of influenza include otitis media, pneumonia, secondary bacterial pneumonia, exacerbations of chronic respiratory disease and bronchiolitis in children. Additionally, influenza can cause a range of non-respiratory symptoms and complications, including nausea and vomiting, diarrhoea, febrile convulsions, Reye's syndrome, Goodpasture's syndrome, encephalopathy, transverse myelitis, pericarditis and myocarditis.[1,2]

Diagnosis

The common clinical features of influenza – the abrupt onset of fever combined with systemic symptoms of malaise and myalgia and respiratory symptoms of cough or coryza – can also be caused by a number of other organisms. Adenoviruses, rhinovirus, respiratory syncytial virus, parainfluenza virus and bacterial infections are examples of other causes of an 'influenza-like illness' (ILI). Definitive diagnosis requires laboratory confirmation, which generally takes several days to produce a result.

There are a number of near-patient diagnostic tests that have been promoted commercially, but these are not in general use in the UK.

Agent

Influenza is an orthomyxovirus. There are three known serotypes: influenza A, B and C. Influenza A and B are responsible for nearly all clinical illness. Duration of illness can vary between serotypes and subtypes.

Structure

Influenza virus is made up of a lipid membrane surrounding a protein shell and a core consisting of eight RNA complexes. There are two glycoproteins on the lipid membrane, which act as powerful antigens: neuraminidase (N antigen) and haemagglutinin (H antigen). Haemagglutinin facilitates the entry of the virus into cells of the respiratory epithelium while neuraminidase facilitates the release of newly produced viral particles (virions) from infected cells.

Transmission and replication

Influenza virus is spread through aerosol droplets and infects the epithelium of the upper and lower respiratory tract. Transmission is rapid and virus usually spreads quickly in the community. The incubation period is 1–3 days. People with influenza can start shedding the virus before symptoms appear. Nasal shedding peaks about 48 hours after onset of symptoms and adults usually remain infectious for up to 1 week (up to 2 weeks in children).

The virus attaches itself to the cell membranes in the respiratory tract and invades the host cell, where it uses the host cell machinery to reproduce. Virions are released by lysing the host cells, which leads to breaches in the epithelium and susceptibility to secondary viral and bacterial infections.

The risk of an individual contracting the disease depends on a number of factors:

- the virulence of the circulating strain
- the natural level of immunity (which depends on past exposure to influenza virus or vaccination and the degree of cross immunity from these to the circulating strain)

- general nutritional and health status
- age (both those over 65 years and the very young are at increased risk)
- living arrangements (closed environments, such as residential homes, schools and prisons, pose a much greater risk of transmission).

Epidemiology of influenza

Influenza is a common condition and attacks all age groups. Outbreaks of infection with influenza A occur most years during the winter months.[3] Infections with influenza B are less common (accounting for approximately 20% of outbreaks[2]) and are associated with less severe illness.[2] Outbreaks tend to occur between outbreaks of influenza A.[3]

The UK influenza season runs from week 40 to week 25. Usually, there is an annual outbreak that lasts for up to about 7 weeks in the community. Baseline rates for general practitioner (GP) consultations for influenza or ILI in winter are below 50/100,000 cases per week. These rise to between 50–200/100,000 when influenza virus is circulating. The mean weekly incidences for 1994–1998 are given in *Table 1*.[4] *Figure 1* shows the consultation rates for influenza and ILI for the 1999–2000 influenza season in the UK.

An epidemic is defined as > 400/100,000 cases per week. The last epidemic in the UK occurred in 1989–1990. *Figure 2* shows consultation rates from the Royal College of General Practitioners (RCGP) for influenza and ILI in England and Wales for the preceding 3 years with the 1989–1990 influenza epidemic for comparison.

Influenza causes an excess in deaths. This can be seen in *Figure 3*, where the pattern of all-cause mortality follows the pattern of the influenza outbreaks over the last 11 years in England and Wales. In the UK, 3000–4000 excess deaths are thought to occur each year due to influenza.[3,5–7] The last significant UK epidemic of 1989–1990 was estimated to have caused 29,000 excess deaths.[8]

TABLE 1 *Mean weekly incidence of influenza or ILI (per 100,000 cases of all ages) from 1994 to 1998*[4]

	1994	1995	1996	1997	1998
Mean weekly influenza or ILI rate/100,000 cases of all ages	22.5	52.6	29.2	39.9	28.3

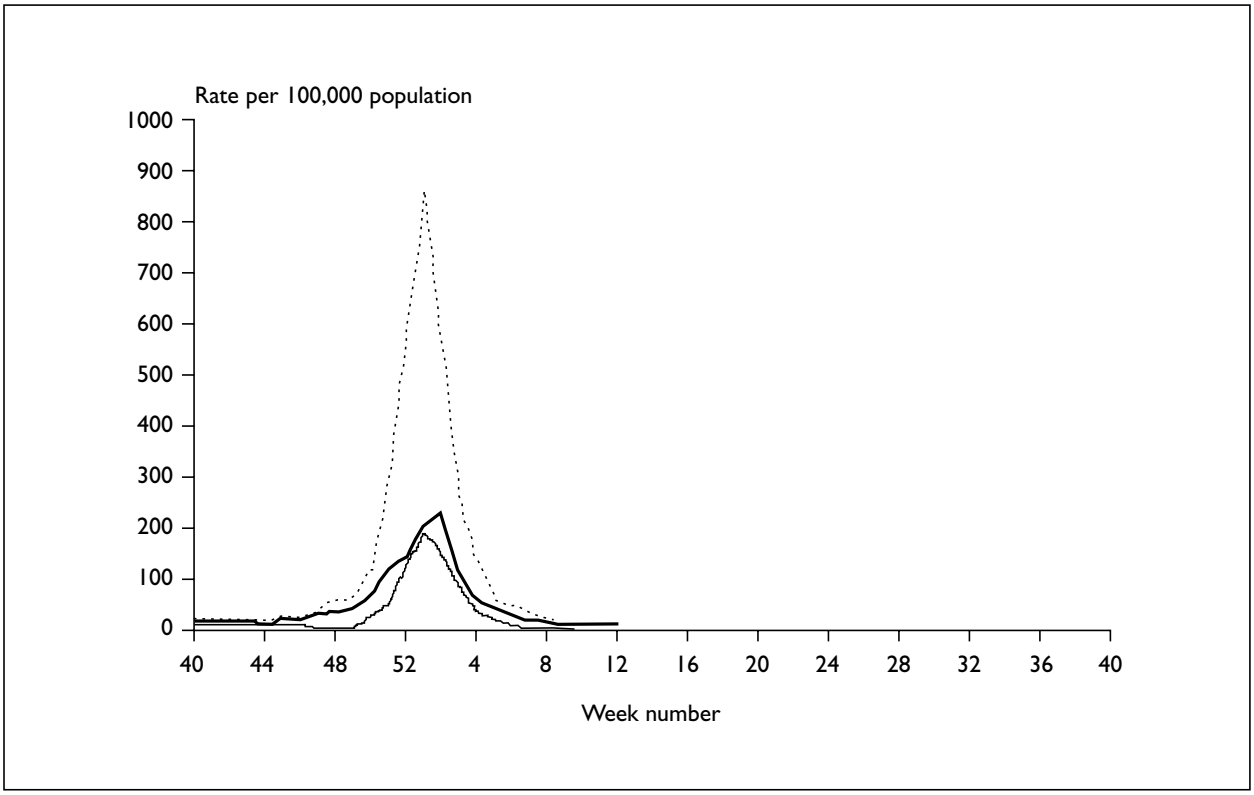

FIGURE 1 *GP consultation rates for influenza and ILI for 1999–2000 in England (——), Wales (——) and Scotland (- - - -)*

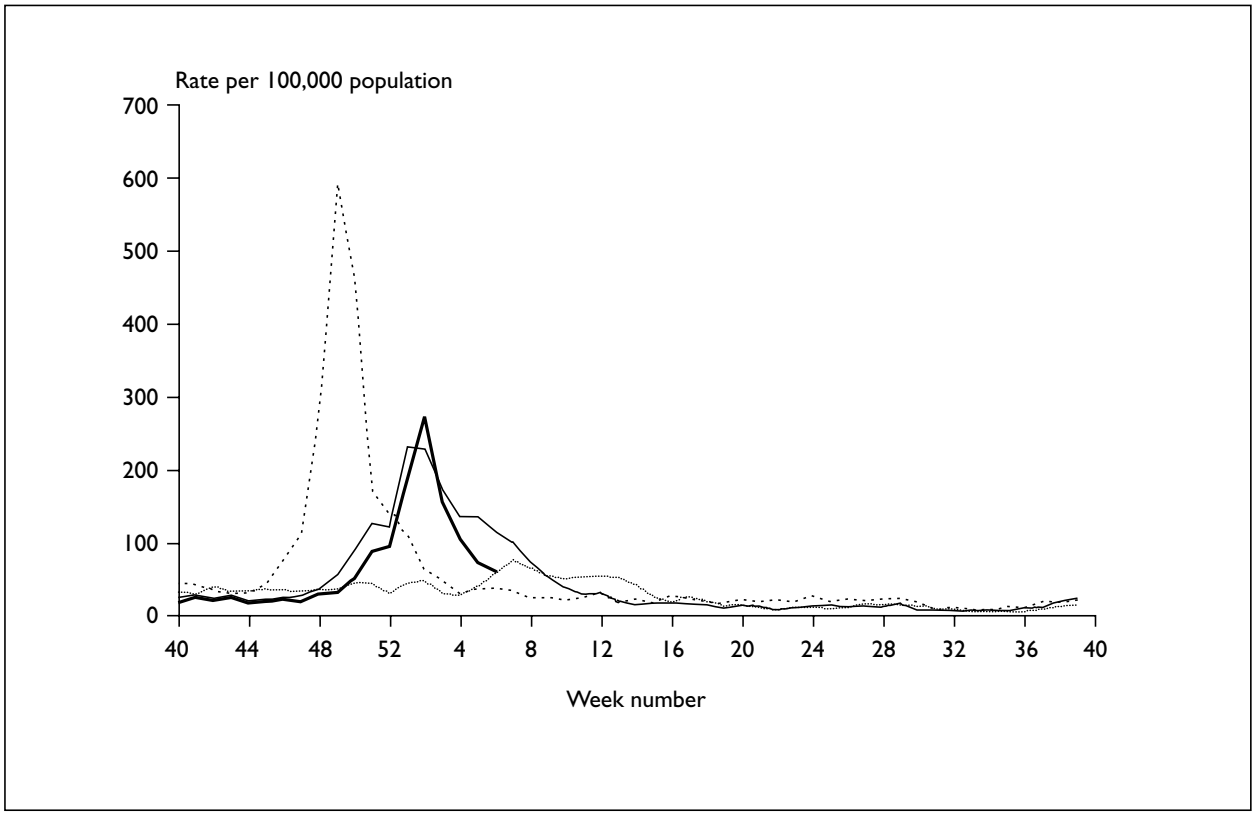

FIGURE 2 *RCGP consultation rates for influenza and ILI in England and Wales in the 1989–1990 epidemic (- - - -), in 1996–1997 (——), 1997–1998 (·····) and 1998–1999 (▬▬)*

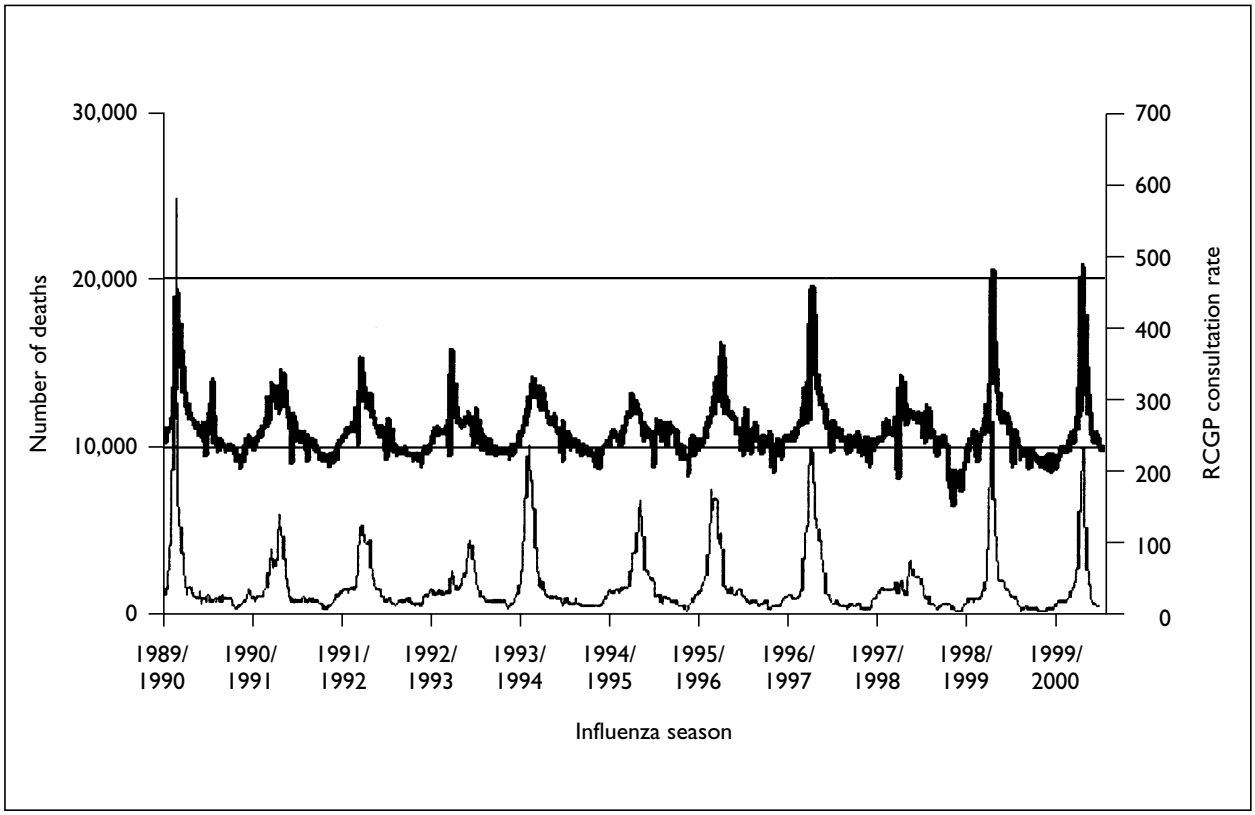

FIGURE 3 *Consultation rates for influenza and ILI (▬▬) and all deaths (——) in England and Wales*

Genetic drift and shift of the virus

Antigenic drift

Minor changes to the amino acid sequence of the haemagglutinin molecules in the virus envelope take place all the time and produce changes in the antigenicity of the virus. This is known as 'antigenic drift'. As haemagglutinin is the main antigen associated with immunity, antigenic drift enables the virus to infect partially immune people who have been exposed in previous winters and tends to cause local and relatively circumscribed epidemics. Influenza A drifts more than influenza B.

Antigenic shift

Major changes in the H and N antigenic configuration, known as 'antigenic shift', lead to the appearance of a new subtype against which there is little circulating natural immunity. This causes major epidemics or pandemics because populations across the world have no immunity to the new strains, e.g. Asian flu in 1957 or Hong Kong flu in 1968–1969. In the 20th century, there were four pandemics caused by antigenic shift. Pandemics cause a very high morbidity and mortality burden.[9] The 1918–1919 pandemic is estimated to have caused up to 40 million deaths worldwide.

Pandemics are thought to originate in southern China where chickens and ducks (the animal reservoir and breeding ground for new strains), pigs (the biological intermediate host) and humans live in very close proximity and provide an environment that permits major changes in antigenic configuration.[10]

Classification

The marked propensity of influenza virus to escape the hosts' immune defences by mutating its external antigenic composition (i.e. its haemagglutinin and neuraminidase) is the basis of the WHO classification system for influenza. This is based on H and N typing. Strains are additionally classified by the antigenic type of the nucleoprotein core (A, B or C), the geographical location of first isolation, strain serial number and year of isolation, with each item separated by a slash (e.g. A/Wuhan/359/95 (H3N2)).

The burden of influenza in the UK

In the UK, the impact of influenza on the community is mainly caused by absence from work and an increased use of medical resources (e.g. visits to GPs, medical treatment and hospitalisations). The burden that influenza imposes on the community is different in each age group. Adults aged 15–64 years account for most primary care consultations for influenza-related illness (see *Table 2*).[11] These figures are derived from the large UK primary care-based study by Meier and colleagues[12] described below.

However, in the elderly, the need for hospitalisation creates an additional burden. *Table 3* gives the medians and interquartile ranges for estimates of hospitalisation rates found in a systematic review of studies from 1980 to 1998 on the epidemiology of influenza.[11]

Despite the need for hospitalisation and the burden of excess deaths, influenza and ILI remain predominantly a primary care-based problem in the UK. In a large study based on the General Practitioner Research Database (GPRD) with a study population of 141,293 subjects with ILI, 83,911 (59.4%) received drugs on prescription.[12] The most frequently prescribed drugs were antibiotics (45.2%) followed by antipyretics/

TABLE 2 *Age distribution of influenza-associated GP visits*[11]

Age group	Children (1–14 years)	Adults (15–64 years)	Elderly (> 65 years)	Total
Proportion of visits (%)	15.4	72.4	12.2	100

TABLE 3 *Hospitalisation rates for influenza*[11]

Age group	Number of studies	Total sample size	Hospitalisation rates/100,000 cases of ILI				
			Minimum	25% percentile	Median	75% percentile	Maximum
Children (1–14 years)	6	950	113	117	142.5	173	262
Adults (15–64 years)	11	1495	34	65	93	228	294
Elderly (> 65 years)	9	6451	119	378	589	819	1806

analgesics (22.5%). Influenza cases were approximately six times more likely to use drugs on prescription than an age, sex, practice and calendar time-matched random control sample of the base population.[12] Within a random sample of 600 subjects, 67.7% (95% confidence interval (CI), 63.8 to 71.5) consulted the general practice only once for influenza, 3.8% (95% CI, 2.4 to 5.7) were referred to a specialist and 1.3% (95% CI, 0.6 to 2.6) were hospitalised for influenza or directly related clinical complications.[12]

Technology under evaluation – zanamivir (Relenza®)

In recent years, a new generation of antiviral compounds known as neuraminidase inhibitors (NIs) have been developed. As neuraminidase plays an essential role both in the entry of viral particles into the target cell and the subsequent release of virions, NIs are designed to block this enzyme to prevent both the uptake and release of influenza A and B virions. Theoretically, NIs could prove to be useful for preventing infection or for treating infected individuals to reduce the severity of the illness.[13]

NIs that have developed to Phase III clinical trials or beyond include:

- inhaled zanamivir (formerly known as GG167), developed by Glaxo Wellcome, UK (since writing this report the company's name has changed to GlaxoSmithKline) and marketed under the trade name Relenza®
- oral oseltamivir (Tamiflu®; formerly known as RO 64-0796 or GS 4104) co-developed by Gilead Sciences Inc, UK and Hoffman La Roche Ltd, UK
- oral RWJ-270201 developed by BioCryst Pharmaceuticals and Johnson & Johnson, USA, and currently undergoing Phase III trials in the USA.[14]

Zanamivir is a so-called second generation NI, whereas oseltamivir represents the third generation of such compounds.

Currently, zanamivir is the only NI licensed for treating influenza in adults (aged 12 and over) in the UK. Oseltamivir is awaiting approval in Europe for the treatment of influenza A and B infection in adults and children aged ≥ 1 year, and for the prophylaxis of influenza in adults and adolescents.[15–17] Launch is anticipated before the 2002–2003 influenza season.

Glaxo Wellcome have no current plans to pursue a licence for treatment in children. The prophylaxis licence extension is also on hold (Glaxo Wellcome, Uxbridge: personal communication, March 2002). Zanamivir has also been approved in the USA for the treatment of influenza in children.

As this review of NIs was commissioned by the HTA Programme to inform NICE's year 2000 guidance on appropriate NI use, it assesses the drug avaliable at that time and its licensed indications in the UK, i.e. zanamivir for the treatment of influenza in adults.

Current service provision

Treatment of influenza

Currently, otherwise healthy individuals with ILIs are discouraged from seeking a medical consultation and advised to stay at home and take over-the-counter (OTC) medications to relieve their symptoms. Until 1999, efforts to prevent or treat influenza have been by vaccines and antivirals (amantadine). In 1999, zanamivir was launched in the UK as an antiviral treatment for influenza.

Amantadine

Amantadine and rimantadine are two antiviral agents that have been used in the prevention and treatment of influenza. Only amantadine is licensed for use in the UK. It acts by blocking the M2 protein ion channel after the virion has invaded the host cell. It prevents the uncoating of viral RNA within the host cell, thereby interfering with the production of the enzymes involved in viral replication and assembly.

Amantadine is effective against influenza A but is not active against influenza B. When given orally, within 48 hours of the onset of influenza A, amantadine can help reduce the severity of the disease. A recent Cochrane review of the use of amantadine and rimantadine for treating influenza A in adults[18] showed that amantadine reduced the duration of fever by 1 day (95% CI, 0.7 to 1.3). It was associated with significant gastrointestinal adverse events.

Overall, the most common adverse effects from amantadine are gastrointestinal and central nervous system symptoms, such as nausea, loss of appetite, light-headedness, insomnia, nervousness and difficulty in concentrating. The maximum recommended dose for treating influenza is 100 mg per day. This is reasonably well tolerated.[19] Doses of 300 mg per day can impair psychomotor performance.

One of the major problems with amantadine has been concern regarding the emergence of resistance. Resistance to amantadine is easily produced in the laboratory setting and resistant strains have been recovered after 6 days of illness in children receiving treatment and in family members receiving post-exposure prophylaxis.[2]

Amantadine is not widely used as a treatment for influenza in the UK, partly because of the perceived potential problems of resistance and adverse effects. In January 2000, however, Alliance Pharmaceuticals Ltd, UK, launched and widely advertised Lysovir®, a formulation of 100 mg amantadine capsules in a 5-day pack, specifically marketed for the treatment of influenza. It costs £2.40 for a 5-day course of treatment.

Zanamivir

Zanamivir was licensed in 1999 for treatment of influenza A and B in individuals aged 12 and over presenting with symptoms typical of influenza when influenza is circulating in the community. Interim guidance issued by NICE in October 1999 did not support its routine use within the NHS.[20]

It was accepted that use of zanamivir within 48 hours of the onset of symptoms reduced the duration of symptoms from a median of 6 to 5 days, but it was felt that this benefit was not worth the cost and potential impact on primary care:

> "The benefit of zanamivir...is modest and on the present evidence is restricted to reducing the symptoms of influenza by one day. The costs of achieving this benefit are uncertain but will be significant.
>
> "The impact, on primary care, of general use in the 1999/2000 influenza season is likely to be disproportionate to the benefits obtained by influenza sufferers, and is likely to distort the wider application of GP resources."

NICE concluded that there was insufficient evidence available to identify other specific groups for whom the product should be prescribed. In the at-risk population they noted:

> "Due to the limited numbers of 'high risk' patients that have been treated with zanamivir (Relenza) in clinical trials, the Institute has not found it possible to conclude that the product reduces the frequency of serious secondary complications in these groups of patients."

This guidance was scheduled for review in September 2000 to allow consideration of the results from a number of trials that were in progress at the time of the interim guidance.

Prevention of influenza

The two strategies available to prevent influenza are immunisation or chemotherapy with antiviral agents.

Immunisation

National policy

Routine immunisation of at-risk individuals is currently recommended in the UK.[3,19] At-risk patients are defined as:

- all those aged 65* or over[21,22]
- patients of any age with:
  - chronic respiratory disease, including asthma
  - chronic heart disease
  - chronic renal disease
  - diabetes mellitus
  - immunosuppression (due to illness or treatment, including asplenia or splenic dysfunction)
- all those living in long-stay residential accommodation.

Immunisation is recommended every year for the above groups. This is important because influenza A and B are constantly undergoing genetic mutations that alter their antigenic structure – it is essential that influenza vaccines contain the H and N components of the circulating strains.

Evidence of effectiveness of immunisation

A recent Cochrane review[23] evaluating the effects of vaccines on influenza found that vaccines reduced the number of cases of influenza A as follows.

- The recommended inactivated parenteral vaccines (the vaccine type generally used in the UK) reduced:
  - serologically confirmed cases by 68% (95% CI, 49 to 79)
  - clinical influenza cases by 24% (95% CI, 15 to 32).
- The recommended live aerosol reduced:
  - serologically confirmed cases by 48% (95% CI, 24 to 64)
  - clinical influenza cases by 13% (95% CI, 5 to 20).

* Previously 75 years old and over.

Analysis of vaccines matching the circulating strain gave higher estimates of efficacy. Vaccines were relatively safe.

The commonest adverse effect is soreness at the immunisation site. Occasionally, vaccinations can cause fever, malaise, myalgia or arthralgia, beginning 6–12 hours after immunisation and lasting for up to 48 hours. Rarely, immediate reactions due to hypersensitivity to egg protein can cause urticaria, angio-oedema, bronchospasm and anaphylaxis.

Vaccines normally contain three components: two subtypes of influenza A and one of influenza B. The decision as to which strains are included in the vaccine is made every year based on an analysis of several thousand influenza viruses at the WHO influenza laboratories. The laboratories assess which strain has been dominant over the previous winter, and look for evidence of new strains that have the potential to spread and against which current vaccines offer poor protection.[24]

Immunisation in practice

Immunisation rates for at-risk patients are low with only about one-third of people for whom it is recommended being vaccinated. Uptake rates have improved over the last decade in England and Wales. A national study of influenza immunisation examined uptake rates by age and risk for the years 1989–1997. Rates were obtained by analysing routinely collected data from patients registered with practices participating in the GPRD in England and Wales from 1989 to 1997.[24] Patients aged ≥ 65 years (without any defined risk) increased their uptake from 20% in 1989–1990 to 26% in 1996–1997. An increase in uptake was also observed for patients aged ≥ 65 years who were in an at-risk group from 33% in 1989–1990 to 44% in 1996–1997. In patients aged < 65 years, uptake ranged from 10 to 12.4% over the study period for those classified at risk, compared to 2–3% in this age group without any defined risk (see *Figure 4*).

Amantadine

National policy

It is recommended that amantadine can be used for prophylaxis during an outbreak of influenza A only in:

- unimmunised patients in at-risk groups (to cover the period while a vaccine takes effect)
- patients in at-risk groups for whom immunisation is contraindicated, for the duration of the outbreak
- healthcare workers and other key personnel, during an epidemic.

The Joint Committee on Vaccination and Immunisation has advised that amantadine should not be used for both prophylaxis and treatment of influenza in the same household because of the risk of resistance.[19]

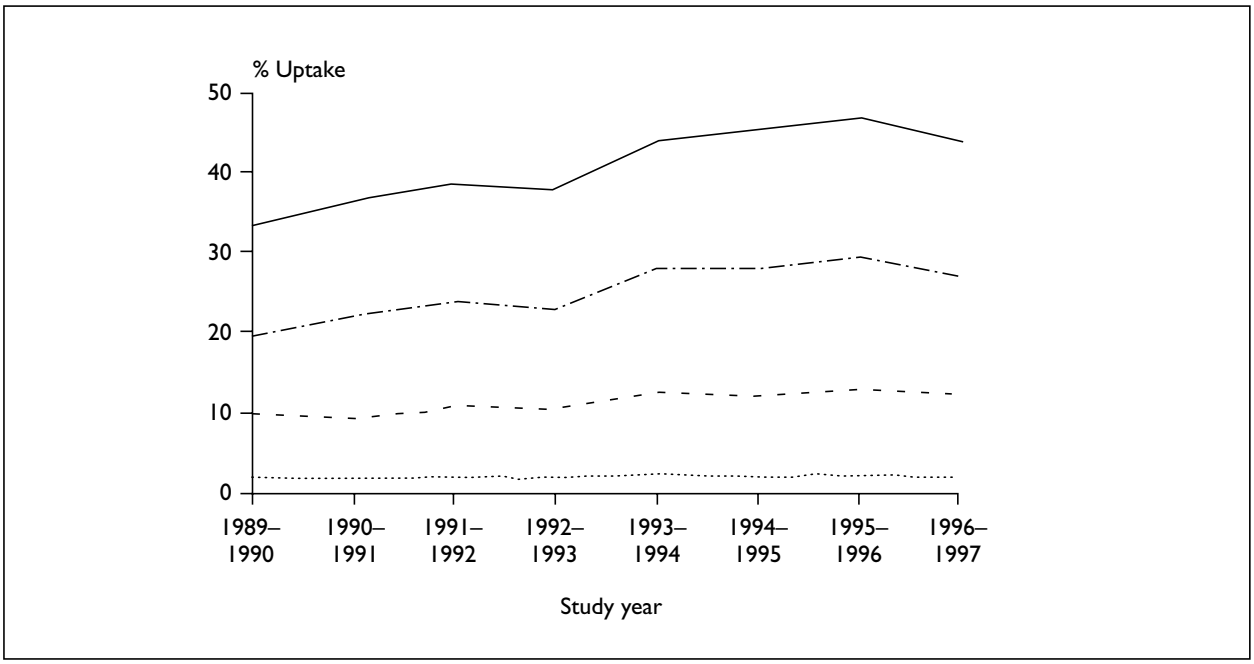

FIGURE 4 *Uptake rates of influenza vaccine in England and Wales during 1989–1997 in high-risk individuals aged ≥ 65 years (——), individuals aged ≥ 65 years at no risk (– · – ·), high-risk individuals aged < 65 years (- - - -) and individuals aged < 65 years at no risk (·····)*

Evidence of effectiveness of amantadine

A recent Cochrane review on the effectiveness of amantadine for preventing influenza A in adults[18] showed that amantadine prevented 23% (95% CI, 11 to 34) of clinical influenza cases and 63% (95% CI, 42 to 76) of serologically confirmed clinical influenza A cases.

Amantadine use in practice

Amantadine has not been used widely for prophylaxis in the UK. In January 2000, Alliance Pharmaceuticals Ltd launched Lysovir, a formulation of 100 mg amantadine capsules in a 14-day pack, marketed for use in the prevention of influenza. It costs £4.80 for a 14-day course of treatment.

Chapter 2
Methods

Review questions

The following questions are addressed in this review by assessing existing evidence.

Effectiveness

1. How effective is zanamivir in shortening the time-course, reducing the severity of illness or preventing death in otherwise **healthy adults** with influenza?
2. How effective is zanamivir in shortening the time-course, reducing the severity of illness or preventing death in **at-risk adults** with influenza? ('At-risk' adults are those who are at high risk of suffering severe adverse outcomes from influenza, such as the elderly or those with pre-existing conditions like renal disease or respiratory illness.)

Adverse effects

3. What is the frequency and severity of adverse effects associated with the use of zanamivir in both healthy and at-risk adults?

Cost and cost-effectiveness

4. What is the cost-effectiveness of zanamivir for the above indications?

The methods of the reviews generally followed the guidance laid out in the West Midlands Development and Evaluation Service Handbook[25] and the NHS Centre for Reviews and Dissemination Report No. 4.[26]

Search strategy

The following electronic databases were searched at 31 March 2000: Cochrane Library 2000, issue 1, MEDLINE (Ovid) 1991–March 2000, MEDLINE (PubMed) 1999–March 2000, EMBASE (Ovid) 1991–March 2000, Science Citation Index (BIDS) 1991–March 2000 and Glaxo Wellcome Clinical Trials Register.

Search terms on Cochrane Library, MEDLINE and EMBASE included the text words zanamivir, Relenza, gg167, gg167 and neuraminidase inhibitors and the index terms influenza and neuraminidase. A full search strategy is available on request. The same text words were used to search Science Citation Index. Studies were limited to humans. No language or age restrictions were applied.

AltaVista and Yahoo search engines were used to search the internet with follow-up of links. Handsearches of *Scrip*, Federal Drug Association (FDA) submissions for new drug applications and conference abstracts were also undertaken and the reference lists of publications identified were reviewed for further citations. Relevant trials and data were also sought from the Glaxo Wellcome submission to NICE.[27]

The search strategy was expanded to look for relevant economic analyses and for information to inform the economic model using MEDLINE for relevant cost and cost-effectiveness studies and searching specialised health economics sources, such as NHS EED and DARE.

Inclusion and exclusion of trials

Two reviewers applied explicit predetermined inclusion criteria independently. Disagreements were resolved through discussion, with reference to a third party where disagreement remained. Inclusion and exclusion decisions were made independently of the detailed scrutiny of the results.

Inclusion criteria for the all-adults group analysis

Studies were included in the final analysis of the review if they met the following criteria.

Study design

Randomised controlled trials (RCTs) or quasi-RCTs.

Population

Adults (defined as 75% of participants aged 12 or over[†]) with naturally occurring influenza symptoms or who had been experimentally inoculated with influenza prior to treatment.

[†] This age cut-off was chosen because it fits with the licensed indication for Relenza.

Intervention
Zanamivir (Relenza).

Comparator
Placebo or other treatment for influenza.

Outcomes
Studies were only included in the review if they reported results of one or more of the following: time to alleviation of symptoms, time to become afebrile, time to return to normal daily activities or secondary illnesses.

Reporting
Only completed trials reporting results for all or almost all recruited patients were included.

Publication
All data were included regardless of publication status.

Exclusion criteria for the all-adults group analysis
- Trials that had not finished recruiting.
- Trials for which only interim results were available.
- Trials reporting results for only some of the participants (i.e. subgroup analyses only).

RCTs found during the searches and subsequently excluded were listed.

Inclusion criteria for the at-risk group analysis
Predetermined criteria were independently applied by two reviewers to determine whether some or all of the data from a study should be included in the at-risk population review (see appendix 1 for flow chart).

Definition of at-risk patients
Influenza poses an increased risk for some individuals who are prone to develop complications, experience a more severe illness or die. We used the same definition of at-risk as used by the UK influenza immunisation programme (see chapter 1).

This definition was essentially similar to that used by Glaxo Wellcome in most of their clinical studies, where at-risk patients were defined as:[27]

- patients with chronic respiratory disease requiring regular medication
- patients with cardiovascular disease (excluding hypertensive patients who had no other cardiovascular disease)
- people aged > 65 years with or without underlying medical conditions
- patients who were immunocompromised or who had endocrine or metabolic conditions (this definition appeared in only one trial).

Data to answer the question about the effectiveness in at-risk patients (question 2) had to come from trials directly recruiting at-risk patients or from an at-risk subset of data from trials where it was **explicit** that high-risk patients had not been excluded during recruitment. Data derived from *post hoc* subgroup analyses from other trials were excluded.

Quality assessment

Two reviewers independently undertook the quality assessment. Disagreements were resolved by discussion, with reference to a third party if disagreement remained. The validity of the studies was assessed by examining the method of randomisation, the comparability of baseline characteristics between different arms, the concealment of allocation, blinding and withdrawals and losses to follow-up for each patient group. A Jadad score was calculated.[28]

Data extraction

Two independent reviewers undertook the data abstraction using a predesigned data extraction form. Data was double entered into an Access 2000 database. Disagreements were resolved by discussion, with consultation of a third party if there was still disagreement. Where information was missing, further information was sought from the authors or industry.

The data that were extracted were:

- details of the study populations and baseline characteristics
- details of the intervention, such as mode of delivery, dose and time of delivery
- individual outcomes measured, such as length of illness, severity of illness, death rates, adverse event rates, antibiotic use or hospitalisation rates
- the results (as percentages or raw numbers) plus any summary measure given (standard deviations (SDs), *p*-values or CIs where available) for both the intention-to-treat population (ITTP) and the influenza positive population (IPP) where possible.

Data synthesis

Results were collated for each review question in summary tables indicating the general pattern of results. Where possible, all results were analysed on an intention-to-treat (ITT) basis.

Where sufficient information was available and the studies were considered sufficiently clinically homogeneous for combination to be informative, meta-analyses were carried out using Cochrane Collaboration Review Manager 4.04 software (Update software) using MetaView 3.1. A random-effects model was used due to the presence of statistical heterogeneity among the trials.

In order to undertake a meta-analysis, standard methodology has required estimates of means and SDs. This information was not available for the majority of studies as results were mainly reported as medians. Moreover, the data had a skewed distribution and summarising data as means and SDs was, therefore, inappropriate.

For the above theoretical reasons and because of the practical constraints of the type of data available, we were constrained to using medians for our pooled analyses. There is no established method for combining medians. In order to combine results, estimates of the uncertainty surrounding the calculated medians are required to weight the studies in the meta-analysis. Glaxo Wellcome provided us with the median and 95% CIs for the time to alleviation of symptoms outcome for both the ITTP and the IPP for two arms of eight trials (Glaxo Wellcome, Uxbridge: personal communication, 16th June 2000), calculated by the method described by Brookmeyer and Crowley.[29]

Where CIs for the medians of each trial arm were unavailable, two methods were used to estimate the precision. Two methods were used in order to test the robustness of the methodology. Firstly, CIs were derived from the cumulative tables given and these were used to obtain an estimate of the uncertainty surrounding the median. Secondly, the *p*-values given in the trial results were used for working backwards (assuming the central limit theorem holds) to derive an estimate of uncertainty. The methodology was also validated by comparing the CIs obtained by calculation to the CIs where available (see appendix 2 for further details).

Chapter 3
Results

Studies identified

Thirty-seven abstracts or full publications that potentially reported relevant trials were identified, several of which reported more than one study and many studies were reported by a number of publications (see appendix 3 for the references for each study[30–68]). Seventeen came from searches of electronic databases and 20 from handsearching reference lists, journals, conference abstracts and contact with experts. Many were duplicate publications of the same studies. Additionally, at the time of searching, there were 28 studies of zanamivir listed on Glaxo Wellcome's Clinical Trials Register.[33]

Full unpublished clinical study reports were made available to us by Glaxo Wellcome for treatment trials NAI30010, NAIA2005, NAIA3002, NAI30008, NAIB2005, NAIB2007, NAIB3001, NAIB3002 and NAIA/B2008.‡ Data from these clinical study reports have been included in this review with permission.

In total, 52 different original studies of zanamivir were found. Data were collected and collated by original study (where possible) using multiple sources for information. In order to simplify the referencing of trials, all studies (in study identification (ID) order) together with all the sources of identified public domain information are listed in appendix 3. In order to prevent duplicate counting of trial data, all publications were mapped to the original studies they reported (see appendix 4 for a list of the publications in alphabetical order of first author together with the original study IDs they mapped to[30,31,34–37,39,40,42,43,45–48,50,51,53–55,57–60,64,65,67–69]).

Two of the trials, NAIA2008 and NAIB2008, are reported together in all data sources, as are the four trials NAIA1001, NAIA1002, NAIA1003 and NAIA1004.‡ Since it was impossible to distinguish the results of the individual studies, these were treated as two studies (NAIA/B2008 and NAIA1001–4), giving a total of 48 studies examined.

Included trials for the all-adults review

Thirteen studies appeared to meet our inclusion criteria (see appendix 5 for full details). Two were Phase I studies with experimental influenza (NAIA1001–4 and NAIA1005‡§), seven were Phase II studies (JNAI-01, NAIA/B2008, NAIB2001, NAIB2003, NAIB2005, NAIB2007 and NAIA2005‡) and four were Phase III studies (NAI30010, NAIA3002, NAIB3001 and NAIB3002‡). We were unable to identify reports of studies NAIA1005, NAIB2001 or NAIB2003 and no unpublished data were made available to us, so the results from these studies could not be incorporated into the review. The results of ten trials are used in this review.

Included trials for the at-risk adults review

We identified one completed unpublished trial in at-risk adults, study NAI30008,‡ which recruited patients 12 years or older with asthma or chronic obstructive pulmonary disease (COPD). The study report for this trial was made available to us by Glaxo Wellcome.[70] Six of the other trials in adults did not exclude at-risk patients (studies NAI30010, NAIA/B2008, NAIA3002, NAIB2007, NAIB3001 and NAIB3002‡), thus meeting the criteria for the inclusion of data from their at-risk subgroups in the at-risk review (see appendix 6 for details).

Excluded trials

Thirty-four studies were excluded: two were not clinical trials, four were not controlled trials, seven did not have a relevant outcome, five were not completed, 13 were prevention trials and three were paediatric trials. (No information about the results were available for a further three trials that met the inclusion criteria;[71–73] see appendix 7 for details of excluded trials.)

‡ See appendix 3 for the references for each study.

§ Insufficient information is available to exclude the possibility that this might have been a prevention rather than treatment trial.

Design and conduct

Validity

All included studies were double-blind RCTs. The trials were generally of a high quality with true masking of investigators and participants, concealment of allocation, ITT analysis and good follow-up with details of dropouts and withdrawals (see appendix 8 for full details).

Interventions and comparators

All trials incorporated into this review had a placebo arm. Different formulations and doses of zanamivir were used in the trials (see appendix 9 for a detailed breakdown by trial):

- 10 mg inhaled twice daily for 5 days (n = 1596)
- 10 mg inhaled plus 6.4 mg intranasally twice daily for 5 days (n = 783)
- 10 mg inhaled plus 6.4 mg intranasally four times a day for 5 days (n = 415)
- 16 mg intranasally six times a day for 4 days (n = 20)
- 16 mg intranasally twice daily for 4 days (n = 11).

Key characteristics of the included studies

NAIA1001–4‡ was a Phase I trial that examined the effectiveness of zanamivir in experimentally induced influenza. The remainder of the trials examined the effectiveness in naturally occurring influenza. The population recruitment age was > 12 years of age for most trials (NAI30010‡ recruited for ≥ 5 years of age but > 75% were adults). Some trials had an upper age limit of 65 years. Influenza was usually defined as presentation with ILI and two of the following: fever ≥ 37.8°C (or sometimes feverishness), cough, headache, sore throat or myalgia (see appendix 10 for a table showing key characteristics of included studies by trial).

Characteristics of the study population

No trials were found that had substantial differences in the baseline characteristics of the different arms that might suggest that randomisation had not worked. The key characteristics of the study populations are given in *Table 4*. It can be seen that the studies recruited a relatively young population compared to the general practice population who present with ILI. Patients also presented in well under 48 hours of symptom duration (as shown in *Table 4*). Patients will present to general practice at variable times after the onset of their symptoms (including > 48 hours) and, if GPs use a 48-hour cut-off point, the average patient treated will tend to have had symptoms for longer than the patients in the trials. This suggests that treatment of patients in general practice may not be as effective as in the trials (because the drug works at an early point in the infection and reproduction cycle). There is also a high prevalence of true influenza among the participants that is much higher than in general practice in the UK.

Outcomes measured

The primary endpoint for all trials was the length of time to alleviation of clinically significant influenza symptoms (reported as median number of days). This was defined as the absence of fever (< 37.8°C) and feverishness, cough, myalgia and sore throat and mild or no headache for 24 hours.

This endpoint was evaluated using patient diary records. Patients were required to record their oral temperature each morning and evening (or four times per day in some trials) and the severity of influenza symptoms of feverishness, headache, cough, sore throat, muscle aches, tiredness or fatigue, loss of appetite and nasal congestion on a four-point scale: 0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe.

The use of median values for this largely subjective endpoint was questioned by the FDA during their review of zanamivir. It was noted that median values could exaggerate small differences in treatment effects since the primary endpoint was very discrete with alleviation occurring in half day units.[74]

Patients who were lost to follow-up or had incomplete diary records were assigned as treatment failures, i.e. no alleviation of symptoms at the end of the study. This can introduce bias especially if there is differential loss to follow-up between the different arms. It would have been more appropriate to have censoring (at the time last seen) for survival data. Dropout rates were not significantly different between arms.

Quality of life (QoL) measures were collected in many of the trials but the results were not available.

Secondary endpoints were less consistent between the trials and included:

- time to resumption of normal activities (defined within a trial as the subject recording 2 days in a row that they were able to carry out normal daily activities)

- time to alleviation of individual symptoms
- time to loss of fever
- time to loss of detectable virus
- maximum daily temperature
- use of relief medication
- patient's overall assessment of symptoms
- investigator's global assessment of symptoms
- incidence of secondary infection/rate of complications/associated use of antibiotics
- viral shedding
- mean symptom scores
- sleep disturbance.

Effectiveness in all adults

Effectiveness data was not always presented in the same way. *Table 5* gives the results for the primary outcome of time to alleviation of symptoms for the ITTP of all trials meeting the inclusion criteria in the all-adult group. Five trials, NAI30010, NAIA2005, NAIB2005, NAIA/B2008 and NAIA3002,[‡] failed to show a statistically significant treatment effect. NAIB3001, NAIB3002, NAIB2007, JNAI-01 and NAIA1001–4[‡] reported statistically significant treatment effects in favour of zanamivir. However, in JNAI-01 and NAIA1001–4,[‡] the data is presented in a way that does not permit it to be used for pooled analysis.

Pooled analyses was undertaken for the trials and outcomes where the CIs had been given or the variability of the data were able to be estimated. Glaxo Wellcome provided details of the medians and CIs for the outcome of time to alleviation of symptoms (Dobson N, Glaxo Wellcome, Uxbridge: personal communication, 2000). For other outcomes, the variability was estimated by using the methods already described. The estimate of the variability derived from the cumulative table method was used where possible. (Trials marked with an asterisk in *Figures 5–15* had the variability calculated by the *p*-value method.) It was not always possible to derive a measure of uncertainty for all trials that met the inclusion criteria: when the medians of the intervention and placebo groups were equivalent the *p*-value method cannot be used and the CI method could not be used when the upper or lower limits were the same or indefinite. As a consequence, the pooled analyses have missing information.

Time to alleviation of symptoms (all adults)

For the 10 mg inhaled zanamivir twice daily dose (the licensed dose), pooled analysis for the main outcome time to alleviation of symptoms showed a reduction of 1 day (95% CI, 0.4 to 1.7) in symptoms, from about 6 to 5 days for the ITTP. As might be expected, zanamivir appeared to be marginally more effective in the IPP than in the ITTP (although this was not a statistically significant difference), reducing symptom duration by 1.4 days (95% CI, 0.8 to 1.9) from just over 6 days to just under 5 days (see *Figure 5*).

The pooled analysis of all zanamivir treatment arms combined compared to placebo for time to alleviation of symptoms is shown in *Figure 6*. It showed similar results.

Time to become afebrile (all adults)

Pooled analysis for the outcome of time to become afebrile showed a non-statistically significant reduction of 0.4 days (95% CI, –0.07 to 0.95) in the duration of fever (which usually lasted for 2–2.5 days), using 10 mg zanamivir. Zanamivir had a similar effect size in the IPP where it reached statistical significance (see *Figure 7*).

Again, the pooled analysis for all zanamivir treatment arms combined compared to placebo for time to become afebrile (see *Figure 8*) showed similar results and the ITTP effect became statistically significant.

Time to return to normal activities (all adults)

Pooled analysis for the outcome of time to return to normal activities showed a non-statistically significant reduction of 0.5 days (95% CI, –0.4 to 1.5) from about 7 days to about 6.5 days for the ITTP using zanamivir 10 mg. In the IPP, there was a statistically significantly reduction in time to return to normal activities by 0.9 days from about 7 days to about 6 days (see *Figure 9*).

The pooled analysis for all zanamivir treatment arms combined compared to placebo for time to return to normal activities is given in *Figure 10* and, again, showed similar estimates of effect (that were statistically significant).

[‡] See appendix 3 for the references for each study.

Effectiveness in at-risk adults

At-risk trials

Trials recruiting only at-risk patients

Study NAI30008‡ was the only trial that specifically recruited an at-risk population.

Population characteristics

The study recruited 525 at-risk individuals. The mean age was 39.4 (range 12–88) with 91% aged < 65, and 60% were influenza-positive (91% influenza A and 9% influenza B) and 23% were vaccinated. Severity of underlying disease was inconsistently recorded but, where recorded, suggested a relatively mild to moderate spectrum of disease severity. For severity of asthma, 43% were reported as mild, 42% as moderate and 15% severe (recorded $n = 246$). For severity of COPD, 29% were recorded as mild, 40% were moderate and 31% were severe (recorded $n = 70$). Baseline characteristics were similar between treatment and control groups.

Effectiveness

The median time to alleviation of symptoms was reduced by 1 day (95% CI, –0.25 to 2.25) in the ITTP and by 1.5 days (95% CI, –1.11 to 4.11) in the IPP. CIs presented here are estimated from the variance deduced from the cumulative frequency tables presented in the submission and do not demonstrate statistical significance. However, Glaxo Wellcome, who have access to the full data set (and, therefore, with more sensitive statistical tests available to them), report that the reduction in time to alleviation of symptoms in the IPP reached statistical significance at $p < 0.009$. Using the full data set, the ITTP results did not reach statistical significance.

There were no statistically significant differences between the treatment and control arms in any complication rates, upper respiratory tract complication rates, lower respiratory tract complication rates or complications requiring the use of antibiotics in the IPP or the ITTP (see *Table 6*). Similarly there were no significant differences in complications requiring changes in respiratory medications.

Safety

Most adverse events were similar to the symptoms of influenza. There were 111 (42%) total adverse events in the placebo group and 99 (38%) in the zanamivir group during treatment and 92 (35%) and 112 (43%) post-treatment, respectively. There were 23 (9%) drug-related adverse events in both groups. There were no deaths.

External validity

The average age of the participants in the trial was younger than the mean age of the population meeting the inclusion criteria of the trial. The most severe end of the disease spectrum may be underrepresented. The symptom onset had to be < 36 hours (not < 48 hours).

Conclusion

This study shows that using zanamivir to treat influenza in patients with underlying respiratory disease produces a benefit that is consistent with that seen in otherwise healthy patients. It showed a similar safety profile.

Integrated analysis of all data for the at-risk population

The following integrated analysis incorporates the findings from NAI30008‡ with the findings for the at-risk subgroups from other trials.

Median time to alleviation of symptoms

The median time to alleviation of symptoms for the pooled analysis was reduced by 1.16 days in the ITTP (95% CI, 0.13 to 2.19) and 1.67 days (95% CI, –0.02 to 3.37) in the IPP (see *Figures 11* and *12*).

Antibiotic use

Information about antibiotic use, although recorded, was not reported in some studies. Where it was reported, the indication for use was not always provided. *Table 7* gives antibiotic use for any indication by trial.

Otherwise healthy adults

Less patients on zanamivir received antibiotics (13.1%) compared to the placebo group (17.7%) in the IPP in otherwise healthy adults. The external validity of extrapolating these results is questionable as the rates are much lower than those found in the large GPRD-based study over a 5-year period where 45.2% of patients presenting with ILI received antibiotics.[12]

In a meta-analysis of seven of the trials included in this review (NAIA2005, NAIB2005, NAIB2007, NAIA/B2008, NAIB3001, NAIA3002 and NAIB3002‡) undertaken by Glaxo Wellcome researchers with access to more detailed data than the authors, the rate of respiratory events leading to use of antibiotics was 18% (139/765)

‡ See appendix 3 for the references for each study.

in the placebo group and 13% (105/807) in the inhaled zanamivir group.[59] This gives a number needed to treat with zanamivir to prevent one patient needing antibiotics of 20 and a relative risk of use of antibiotics of 0.72 (95% CI, 0.57 to 0.91).[59]

At-risk adults

NAI30008[‡] for at-risk patients showed a similar reduction (5%) in both the ITTP and the IPP, which did not reach statistical significance. A meta-analysis of complications requiring antibiotic use in at-risk patients using a fixed-effects model gave an estimate of a 6% (95% CI, 0 to 11) reduction in complications requiring antibiotics (a figure similar to that given by Glaxo Wellcome in their submission to NICE),[27] which was on the borderline of statistical significance (see *Figure 13*).

There was considerable heterogeneity ($p = 0.01$) between the trials and we thus examined the effect using a random-effects model. This gave an estimate of an 8% reduction that was not statistically significant (95% CI, –0.5 to 21; see *Figure 14*).

Subgroup analyses have the risk of producing false-negative results. Since a reduction in antibiotic use is clearly demonstrated in all adults and the results are consistent in at-risk adults, it is reasonable to conclude that this is a true effect (as more trial data accrues this can be confirmed).

Hospitalisation rates

Hospitalisation rates for all causes were extremely low for both the zanamivir arms and the control arms (less than 1% in both). There were no statistically significant differences between the two groups.

Safety

Deaths

There were no deaths reported in any of the studies for zanamivir or placebo.

Adverse events

Most adverse events reported were symptoms typical of influenza. There was no excess of adverse events in the treatment population compared to the controls, as shown in *Table 8*. Details of adverse events by trial are given in appendix 11.

There is no evidence yet of emerging resistance to zanamivir in a clinical setting. A network has been established to undertake surveillance for any future changes in susceptibility and resistance patterns of influenza isolates to zanamivir.[27]

TABLE 4 *Key characteristics of populations recruited*

Study ID*	Mean age (years)		Influenza-positive (%)	Mean duration of symptoms before treatment (hours)	High-risk patients (%)	Period of recruitment	Location
	Placebo	Zanamivir 10 mg					
JNAI-01	29	30	63	26	0	1994–1995	Japan
NAI30010 (index cases)	25	25	Index cases	NA	6.5	1998–1999	USA and Europe
NAIA1001–4	21	21	Experimental influenza		0	1994–1995?	USA
NAIA2005	34	31	50	30	0	1994–1995	USA
NAIA3002	35	35	73	NA	14	1997–1998	USA
NAIA3008	39.9	38.9	60	22.6	100	June 1998–April 2000	USA, Europe and southern hemisphere
NAIA/B2008	36	35	57	29	13	1995–1996	USA and Europe
NAIB2005	34	33	77	NA	0	1994–1995	Europe
NAIB2007	30	30	63	30	12	1995 and 1996	Southern hemisphere
NAIB3001	38	36	71	25	17	1997	Southern hemisphere
NAIB3002	39	36	78	NA	9	1997–1998	Europe

* *See appendix 3 for references for each study*

NA, not applicable

TABLE 5 *Time to alleviation of symptoms (or symptom score if time to alleviation not available) for all adults in the ITTP (published and unpublished data)*

Study ID*	*n*	Placebo	Zanamivir 10 mg inhaled b.d.	Difference (95% CI); *p*-value
JNAI-01	116	59.0% relieved at day 5 25.6% relieved at day 3	77.9% relieved at day 5 55.8% relieved at day 3	$p = 0.0017$
NAI30010 (index cases)	321	Median = 5.5 days ($n = 158$)	Median = 4.5 days ($n = 163$)	1.0 (95% CI, –0.1 to 2.1); $p = 0.101$
NAIA1001–4	51	Median total symptom score = 39 (range = 0–102; $n = 26$)	Median total symptom score = 12 (range 0–71; $n = 31$)	$p < 0.05$
NAIA1005	32	Not available†	Not available†	Not available†
NAIA2005	220	Mean = 5.5 days ($n = 81$)	Mean = 5.3 days ($n = 68$)	2.0% (95% CI, –15 to 19.0); $p = 0.946$
NA1A3002	777	Median = 6.0 days ($n = 365$)	Median = 5.5 days ($n = 412$)	0.5 (95% CI, –0.3 to 1.3); $p = 0.228$
NAIA/B2008	1256	Median = 7.0 days ($n = 422$)	Median = 6.0 days ($n = 419$)	1.0 (95% CI, 0.0 to 2.0); $p = 0.12$
NAIB2001	22	Not available‡	Not available‡	Not available‡
NAIB2003	133	Not available‡	Not available‡	Not available‡
NAIB2005	197	Mean = 6.0 days ($n = 63$)	Mean = 5.0 days ($n = 64$)	12% (95% CI, –7.0 to 30.0); $p = 0.137$
NAIB2007	554	Significant difference between zanamivir and placebo arms in time to alleviation of clinically significant influenza symptoms (data collection stopped at day 5)		$p = 0.003$
NAIB3001	455	Median = 6.5 days ($n = 228$)	Median = 5.0 days ($n = 227$)	1.5 (95% CI, 0.6 to 2.4); $p = 0.011$
NA1B3002	356	Median = 7.5 days ($n = 182$)	Median = 5.0 days ($n = 174$)	2.5 (95% CI, 1.2 to 3.8); $p < 0.001$

* *See appendix 3 for references for each study*
† *Completed Phase I trial with experimental influenza not published. No unpublished information made available*
‡ *Completed Phase II trial not published. No unpublished information made available*
b.d., twice daily

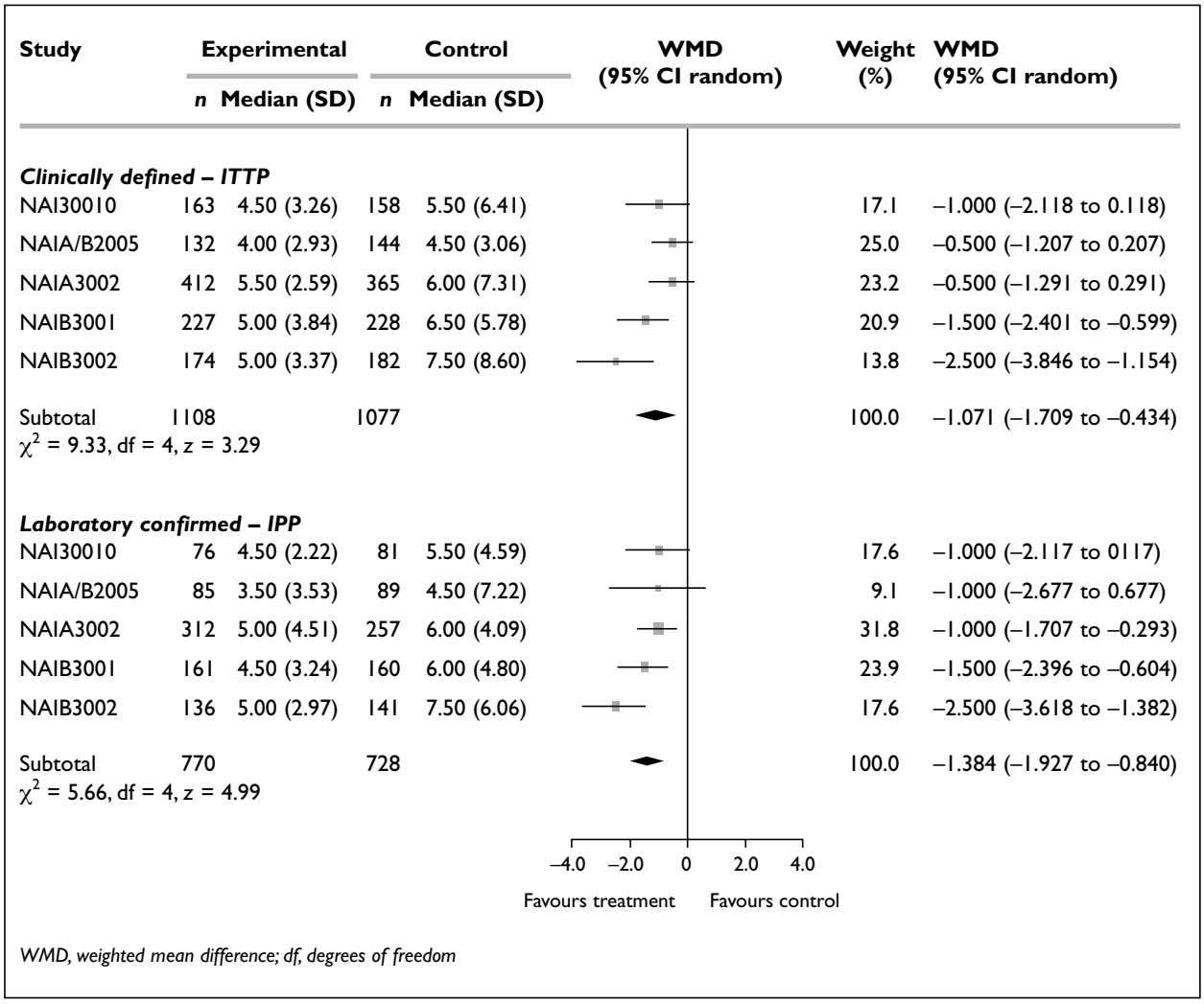

FIGURE 5 *Pooled analysis for time to alleviation of symptoms – 10 mg zanamivir twice daily versus placebo*

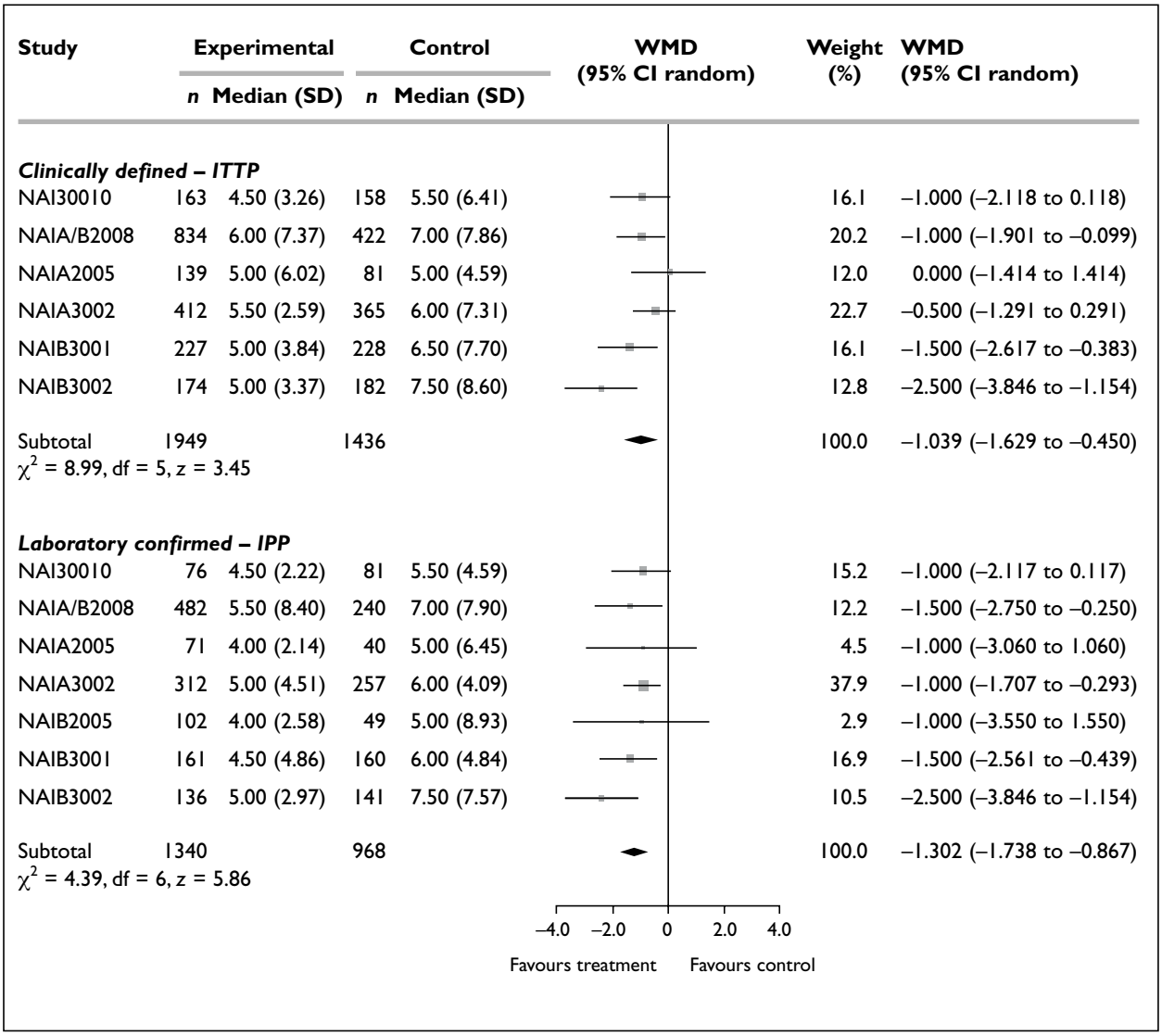

FIGURE 6 *Pooled analysis for time to alleviation of symptoms – all zanamivir treatment arms versus placebo*

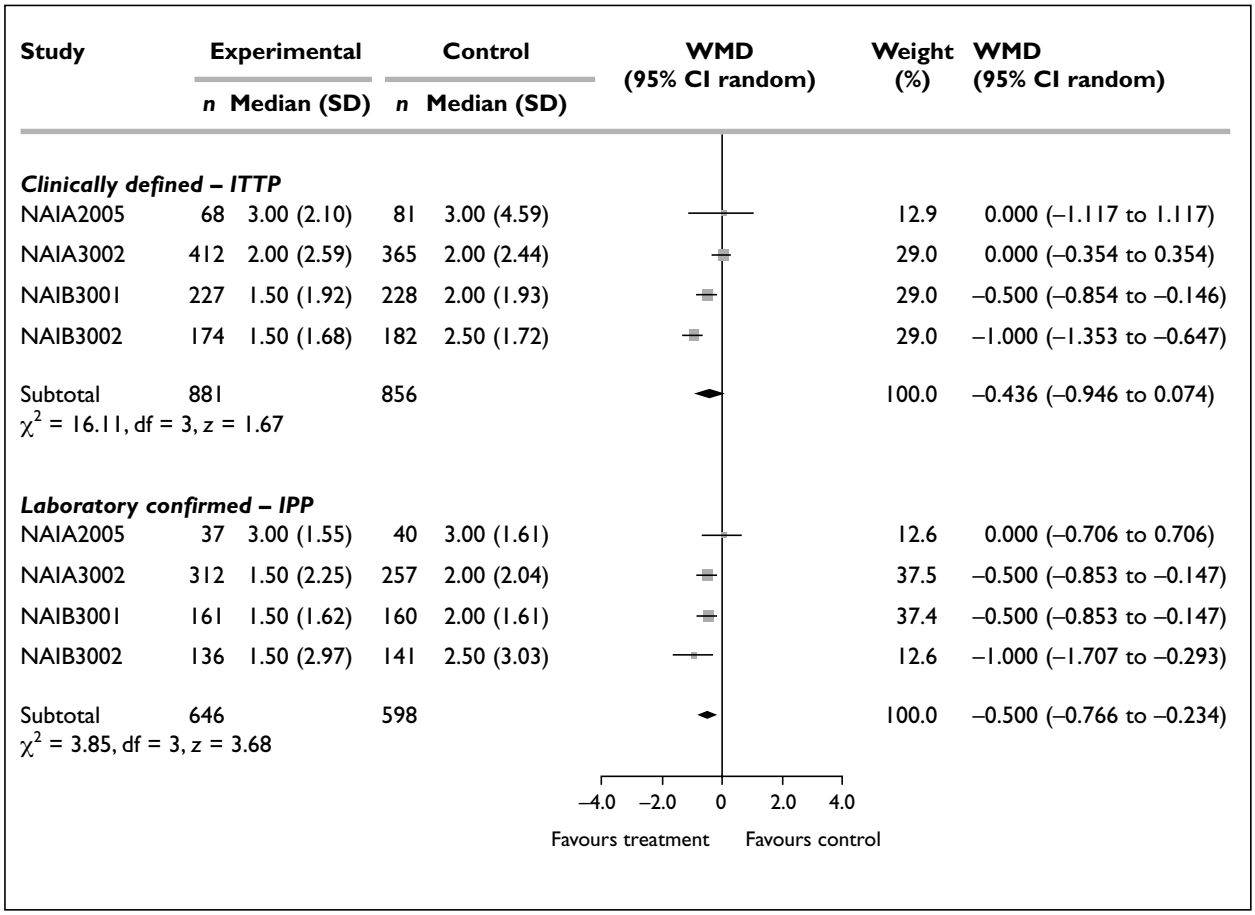

FIGURE 7 *Pooled analysis for time to become afebrile – 10 mg zanamivir twice daily versus placebo*

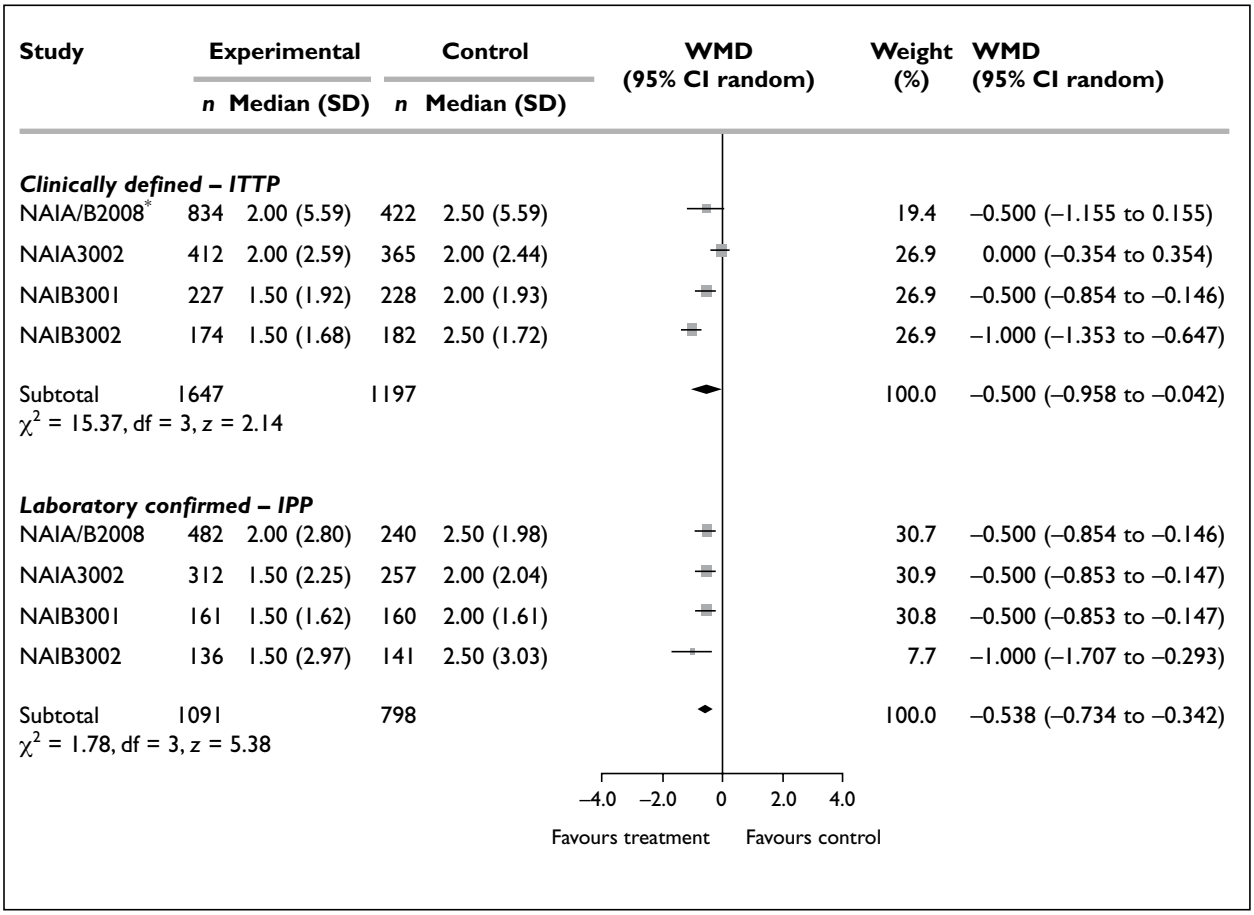

FIGURE 8 *Pooled analysis for time to become afebrile – all zanamivir treatment arms versus placebo*

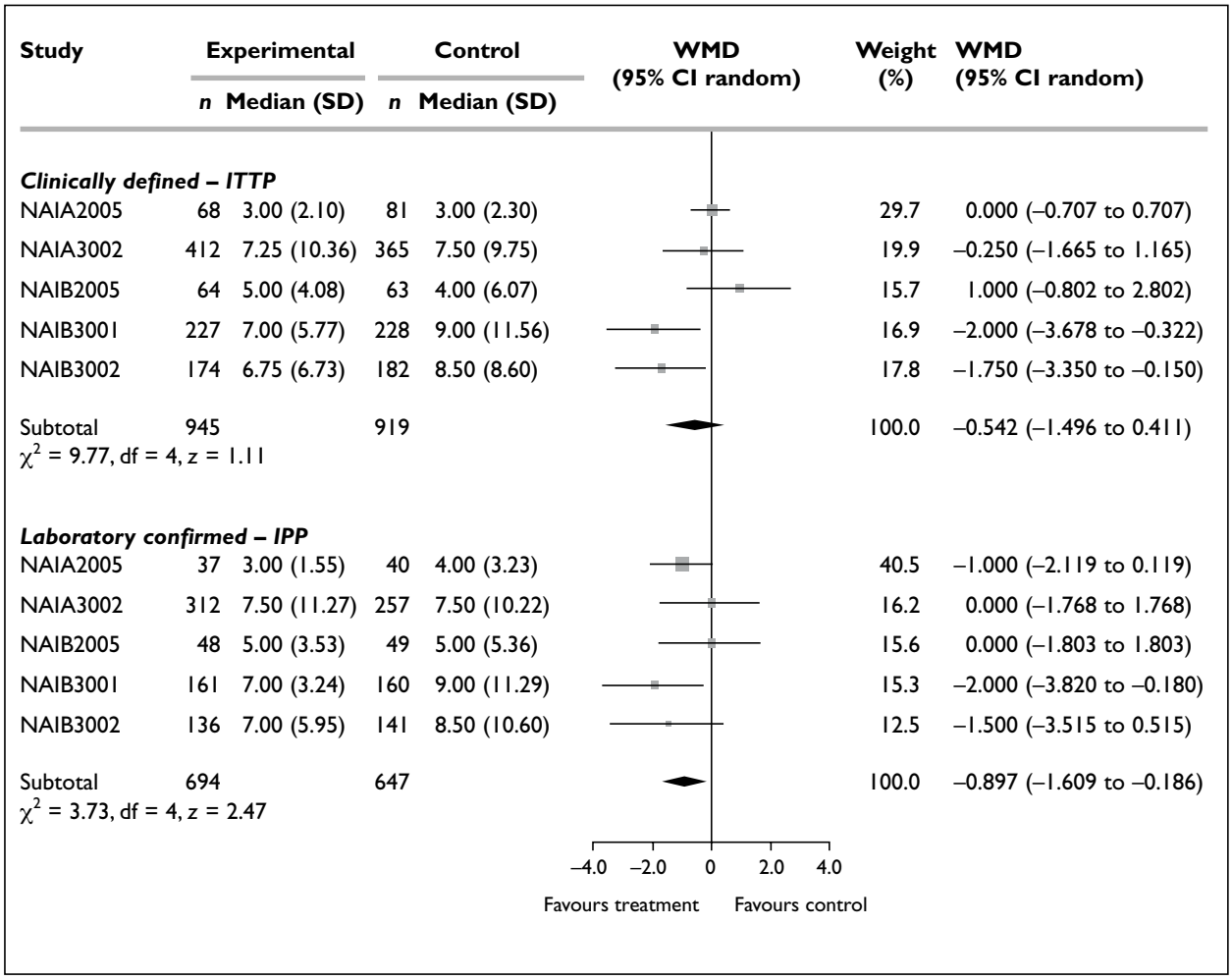

FIGURE 9 *Pooled analysis of time to return to normal activities – 10 mg zanamivir twice daily versus placebo*

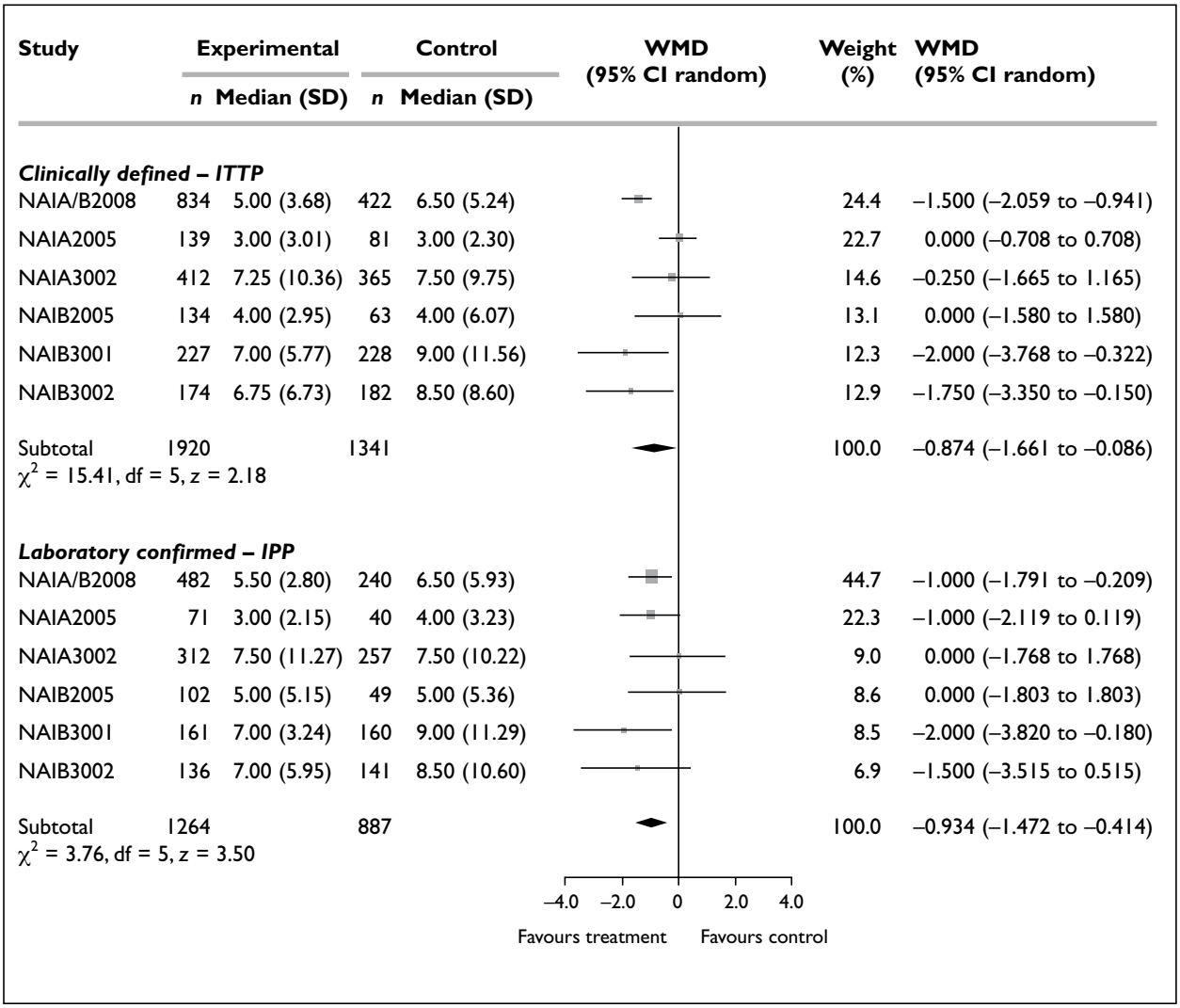

FIGURE 10 *Pooled analysis of time to return to normal activities – all zanamivir treatment arms versus placebo*

TABLE 6 *Complication rates*

	Any			Upper respiratory tract			Lower respiratory tract			Pneumonia		
	Placebo (*n* (%))	**Zanamivir (*n* (%))**	***p***	**Placebo (*n* (%))**	**Zanamivir (*n* (%))**	***p***	**Placebo (*n* (%))**	**Zanamivir (*n* (%))**	***p***	**Placebo (*n* (%))**	**Zanamivir (*n* (%))**	***p***
IPP	56 (37%)	52 (33%)	0.52	20 (13%)	20 (13%)	1.00	40 (26%)	37 (23%)	0.63	0	0	
ITTP	99 (38%)	92 (35%)	0.61	39 (15%)	41 (16%)	0.89	69 (26%)	63 (24%)	0.63	2 (< 1%)	1 (< 1%)	
Complications requiring antibiotics (IPP)	32 (21%)	25 (16%)	0.29	14 (9%)	10 (6%)	0.45	19 (12%)	18 (11%)	0.88	0	0	
Complications requiring antibiotics (ITTP)	61 (23%)	48 (18%)	0.20	28 (11%)	24 (9%)	0.67	40 (15%)	31 (12%)	0.32	2 (< 1%)	1 (< 1%)	

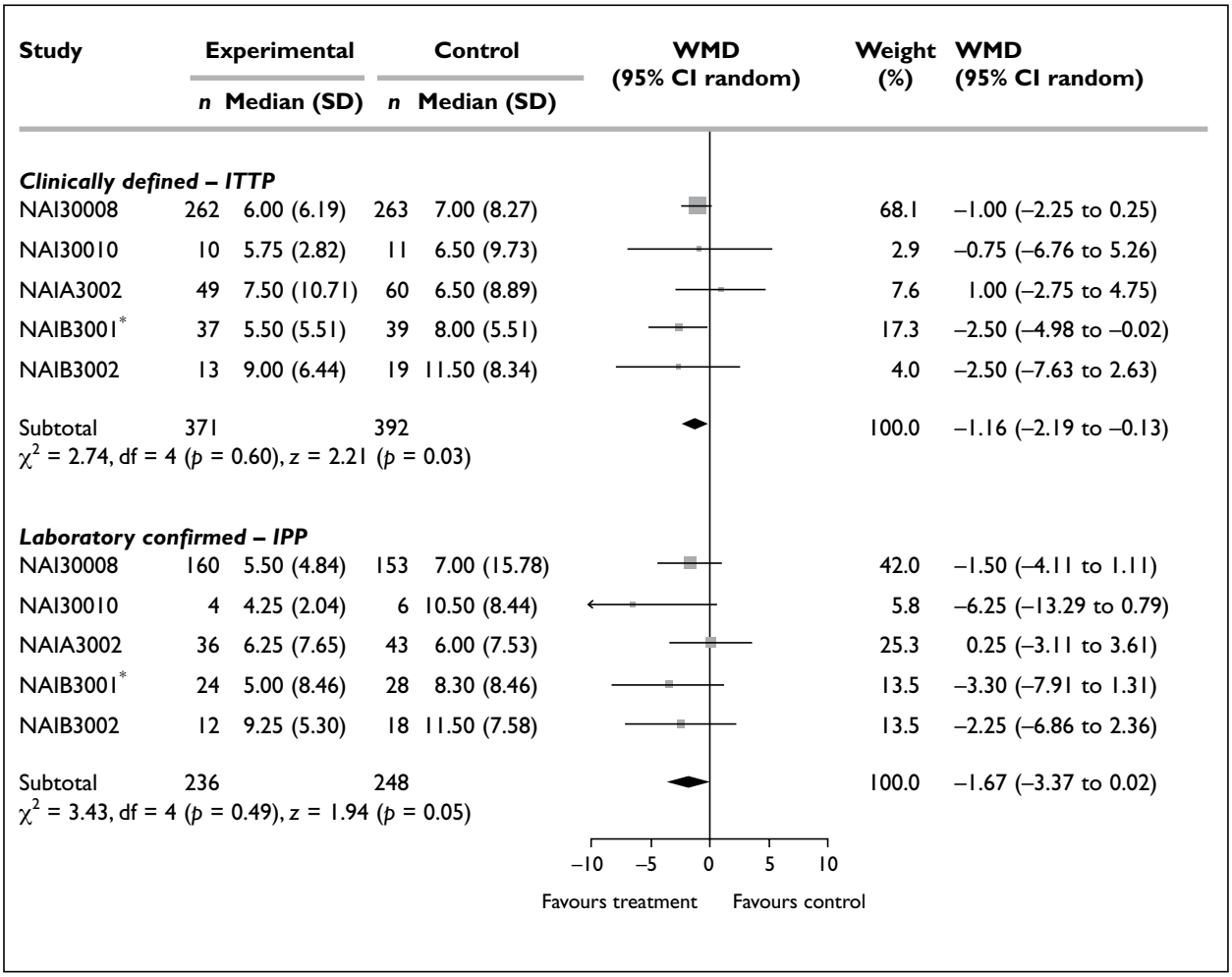

FIGURE 11 *Median time to alleviation of symptoms for at-risk population treated with 10 mg zanamivir twice daily for 5 days*

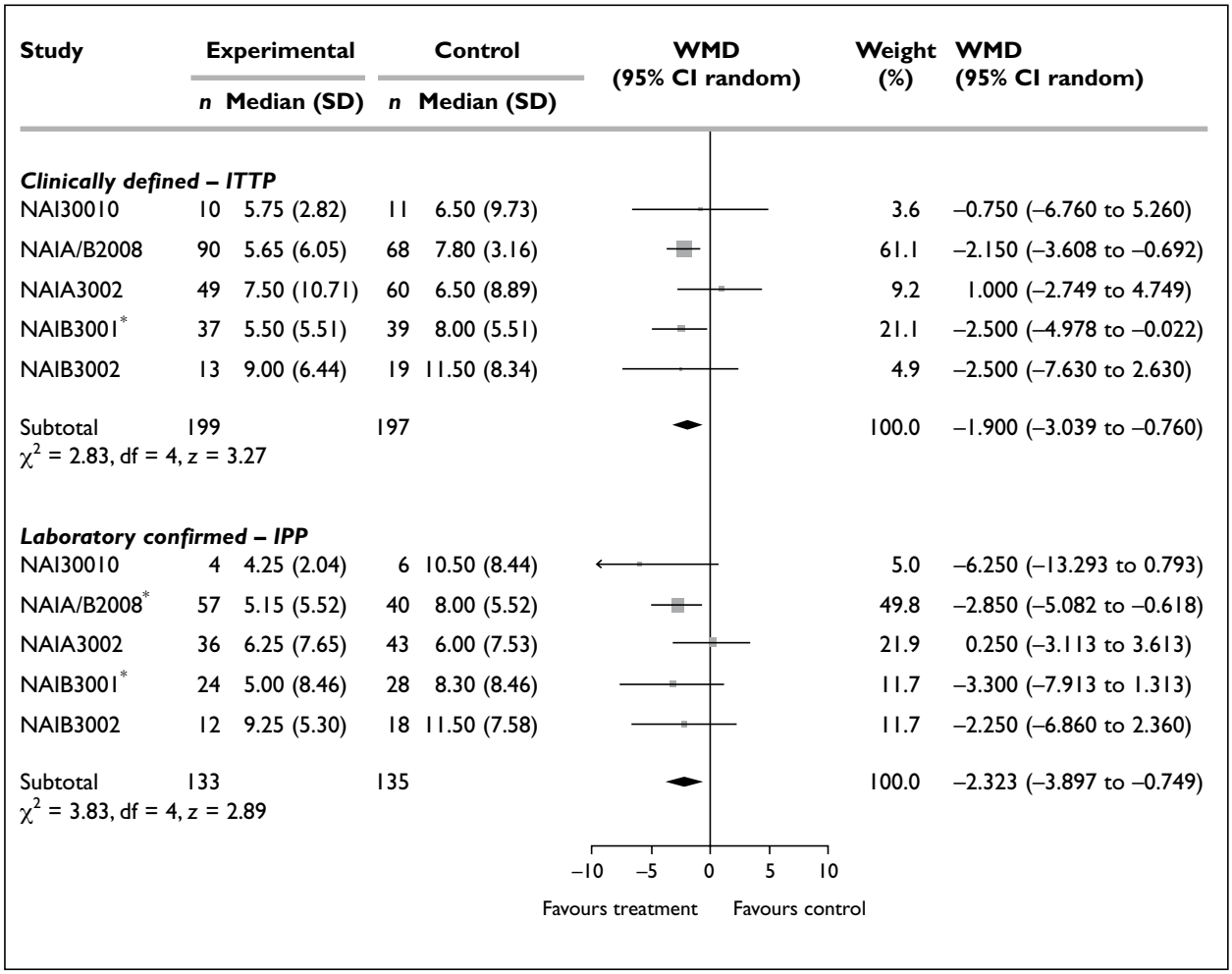

FIGURE 12 *Pooled analysis for at-risk population for time to alleviation of symptoms – all zanamivir treatment arms versus placebo*

TABLE 7 *Antibiotic use*

Study*†	Arm	ITTP	IPP	At-risk ITTP	At-risk IPP
NAIA30008	Zanamivir	–	–	48 (*n* = 262)	25 (*n* = 160)
	Placebo	–	–	61 (*n* = 263)	32 (*n* = 153)
NAIA3002	Zanamivir	52 (*n* = 412)	34 (*n* = 312)	13 (*n* = 49)	9 (*n* = 36)
	Placebo	58 (*n* = 365)	39 (*n* = 257)	9 (*n* = 60)	5 (*n* = 43)
NAIA30010	Zanamivir	7 (*n* = 78)	7 (*n* = 78)	–	–
(index cases)	Placebo	7 (*n* = 87)	7 (*n* = 87)	–	–
NAIB2007	Zanamivir 10 mg	22 (*n* = 188)	13 (*n* = 113)	–	–
	Placebo	38 (*n* = 183)	24 (*n* = 118)	–	–
NAIB3001	Zanamivir	45 (*n* = 227)	36 (*n* = 161)	5 (*n* = 37)	–
	Placebo	52 (*n* = 228)	41 (*n* = 160)	15 (*n* = 39)	–
NAIB3002	Zanamivir	21 (*n* = 174)	15 (*n* = 136)	0 (*n* = 13)	0 (*n* = 12)
	Placebo	32 (*n* = 182)	24 (*n* = 141)	5 (*n* = 19)	5 (*n* = 18)
Total	Zanamivir	147 (*n* = 1079; 13.6%)	105 (*n* = 800; 13.1%)	–	–
	Placebo	187 (*n* = 1045; 17.9%)	135 (*n* = 763; 17.7%)	–	–

* *See appendix 3 for references for each study*
† *No data available for studies JNAI-01, NAIA1001–4, NAIA2005, NAIB2005, NAIA3005 and NAIA/B2008*

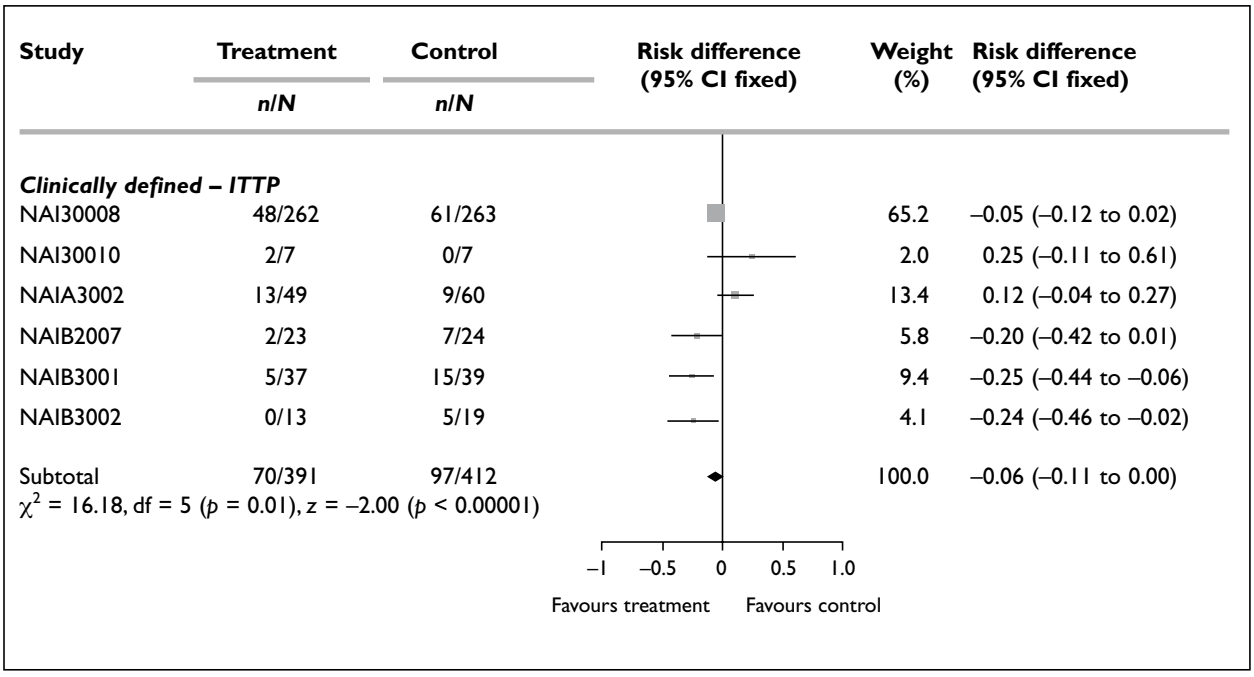

FIGURE 13 *Complications requiring antibiotic use for at-risk population using a fixed-effects model – 10 mg zanamivir versus placebo*

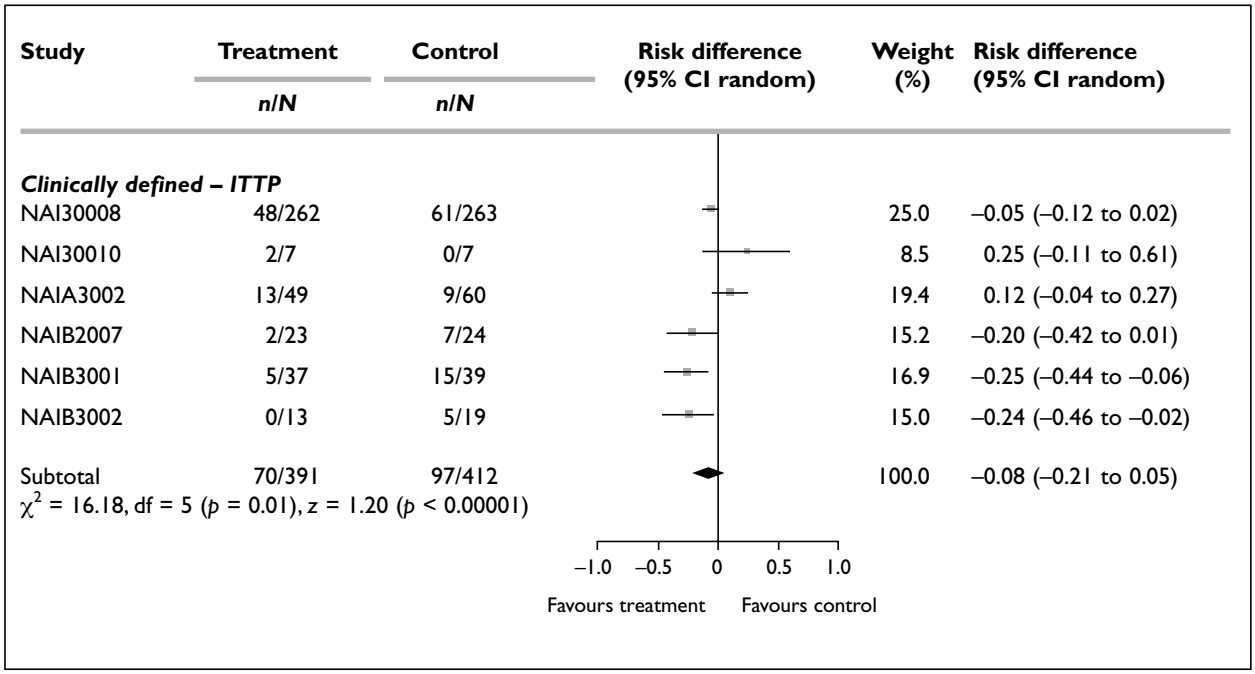

FIGURE 14 *Complications requiring antibiotic use for at-risk population using a random-effects model – 10 mg zanamivir versus placebo*

TABLE 8 *Combined adverse events for placebo arms versus control arms in included studies*

Combined arms of all trials	Nausea and vomiting	Other gastrointestinal	Respiratory	Skin	Any adverse event
Placebo (*n* = 1980)	About 4%	*n* = 196 (10%)	*n* = 254 (13%)	*n* = 60 (3%)	*n* = 828 (42%)
Zanamivir (*n* = 2789)	About 3%	*n* = 256 (9%)	*n* = 230 (8%)	*n* = 65 (2%)	*n* = 1002 (36%)

Chapter 4

Economic evaluation

Cost

The cost of a 5-day course of 10 mg zanamivir twice daily together with a diskhaler device is £24.[19]

Existing economic evaluations

One economic evaluation was found in the published literature,[76] which reported the cost-effectiveness of zanamivir for the treatment of influenza in an at-risk population in Australia. It was a modelling study based on the data from one trial, NAIB3001,[‡] with some of the parameters derived from other sources.

It takes a broader perspective than the health service, for example, including the costs of OTC medications, but does not incorporate social costs/savings, such as absence from work. Efficacy data from the clinical trial were used to populate a computer model designed to estimate the costs and health outcomes associated with alternative treatments for influenza and ILI. There was no specific alternative treatment in the comparison – it compared usual practice (mainly vaccination plus OTC medications for symptomatic relief) with usual practice plus zanamivir. The QoL data was based on assumptions, with the utility weight for a day with influenza symptoms being deduced from the Quality of Wellbeing Scale. Functional status on a day with influenza symptoms was assumed to be: mobility = in house; physical activity = walked with limitations; and social activity = limited in work, school or housework. This gave a utility of 0.5552. To this was added an additional tariff to account for other symptoms of influenza, giving a utility score for influenza of 0.5579. A utility of 1.0 was assumed for the health state of no influenza.

The study was based on a cost of a 5-day course of treatment of Aus$45 (£17.15). It reported an incremental cost of Aus$14.20 (£5.41) per day of symptoms avoided in the base case.

The cost per quality-adjusted life-year (QALY) gained was Aus$11,715 (£4466). The results were sensitive to several parameter values, including the influenza-positive rate and the impact of zanamivir on days to alleviate symptoms and hospitalisation. If this analysis is valid at a drug cost of £24 for a 5-day course of treatment, it would translate to an incremental cost/QALY of £6250.

The evaluation follows established methods. Nonetheless, we have serious reservations about this evaluation stemming from the information that was used to populate the model. We are concerned that:

- it was based on the data from only one trial
- the trial results were more optimistic than those from a pooled analysis of all trials
- it concerned only at-risk individuals
- it was based on very small numbers of at-risk patients (n = 37 in the treatment arm – this figure was derived for our data extraction, the authors do not mention sample size)
- no CIs were presented
- the data behind important parameters was questionable:
  - the prevalence of true influenza among ILI was assumed to be 0.7 and did not reflect the real clinical situation
  - the numbers of follow-up visits were not given in the source document referenced[77]
- it had the optimistic assumptions that all patients being treated presented within the appropriate time limit and that there was no change in the numbers of patients presenting with influenza because zanamivir was available
- the utility of the no-influenza health state would have a value below 1.0 in the general population.

For the above reasons, we have limited confidence in the results reported in this study and, therefore, proceeded to derive UK-based estimates of cost-effectiveness based on all data available.

[‡] See appendix 3 for the references for each study.

Birmingham cost-effectiveness analysis

The following cost-effectiveness analysis is from an NHS perspective. It does not take into account potential costs or savings to the individual from time off work or other costs of illness, including OTC medications. Two measures are calculated: incremental cost per day of symptom avoided and incremental cost/QALY gained. The decision tree on which it is based is shown in *Figure 15*. The tree represents the base case for the population who currently present to general practice. The patients who do not currently present to general practice but would if zanamivir were available are considered in sensitivity analyses. Analyses have been performed for otherwise healthy adults and at-risk adults. Basic effectiveness data is that for the IPP which is then modelled against different levels of prevalence of true influenza in patients presenting with ILI. This is because the ITTP does not reflect clinical practice as the proportion of influenza-positive patients is much higher.

Base-case values and parameters

The parameters used in the model together with the base values and the sources[9,19,27,75,76,78–82] from which these are derived are given in *Table 9*. The comparator in the base-case analysis considers the patient who, under current circumstances, would present to their GP with an ILI. It compares the benefit with and without zanamivir being prescribed. It assumes that the alternative is standard treatment, that is, symptomatic treatment alone with no influenza-specific treatment (amantadine, although available for treating influenza A, is rarely used in general practice).

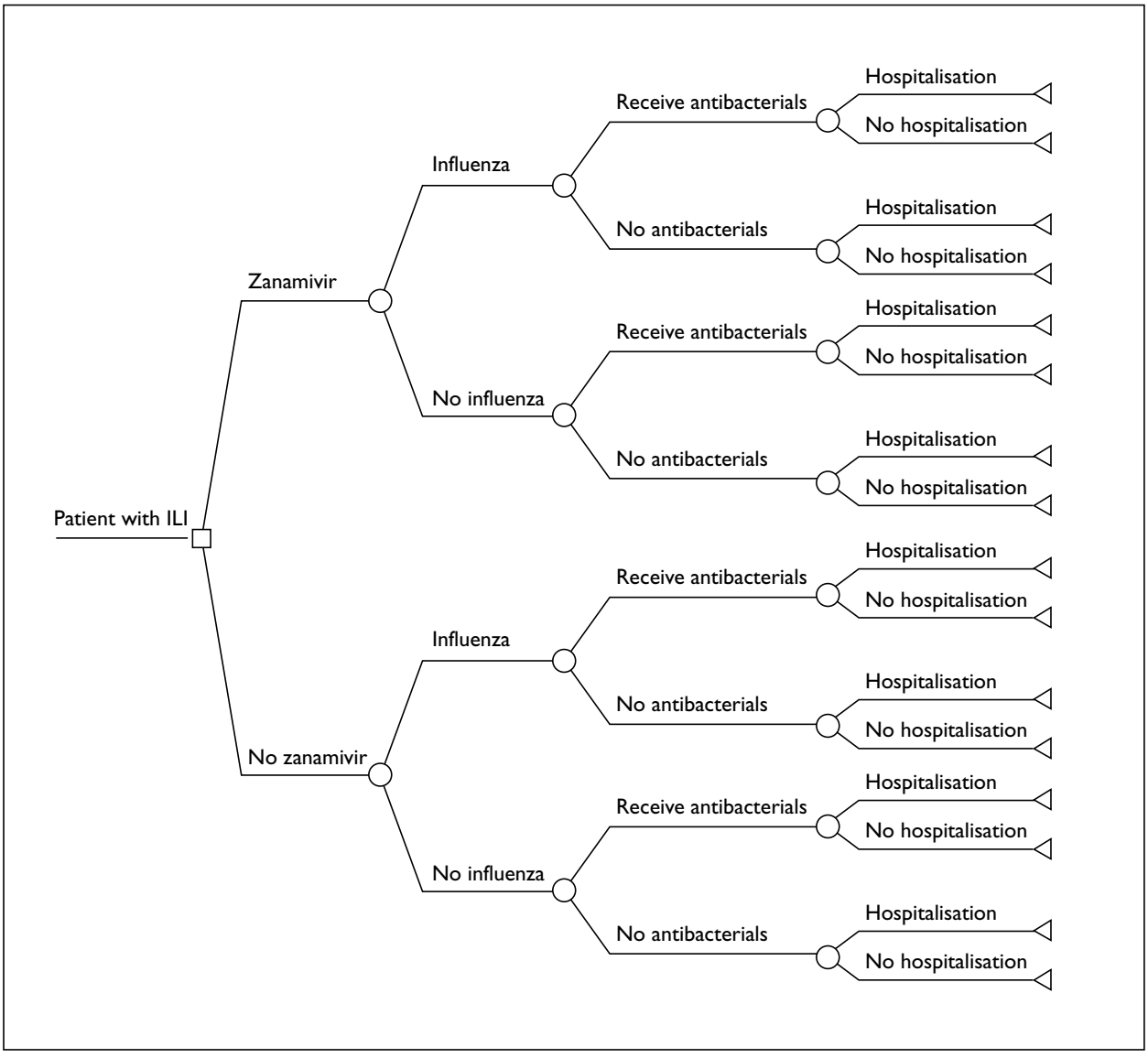

FIGURE 15 *Decision tree for Birmingham cost-effectiveness model*

TABLE 9 *Base-case values and sources for key parameters*

Resource-use parameters	Value	Source
Proportion of patients receiving medication (all adults)		
Zanamivir group		
Inhaled zanamivir	1.00	By definition
Antibacterials for respiratory infection	0.13	Kaiser *et al.*, 2000[75]
Standard therapy group		
Inhaled zanamivir	0.00	By definition
Antibacterials for respiratory infection	0.18	Kaiser *et al.*, 2000[75]
Proportion of patients receiving medication (at-risk adults)		
Zanamivir group		
Inhaled zanamivir	1.00	By definition
Antibacterials for respiratory infection	0.18	Birmingham meta-analysis
Standard therapy group		
Inhaled zanamivir	0.00	By definition
Antibacterials for respiratory infection	0.24	Birmingham meta-analysis
Length of hospital stay	8 days	Jefferson and Demicheli, 1998[9]
Effectiveness parameters	**Value**	**Source**
Reduction in days to alleviate major symptoms (all adults)	–1.384 (95% CI, –0.840 to –1.927)	Birmingham meta-analysis
Reduction in days to alleviate major symptoms (at-risk adults)	–1.670 (95% CI, –3.370 to 0.020)	Birmingham meta-analysis
Prevalence parameters	**Value**	**Source**
Prevalence of influenza among patients presenting with ILI		
All adults (average during influenza season)	14%	PHLS data[78,79]
All adults (when virus is circulating)	34%	Glaxo Wellcome UK Limited, 2000[27]
At-risk patients (when virus is circulating)	34%	Glaxo Wellcome UK Limited, 2000[27]
Health-related QoL with influenza (utility score)	0.516	Assumption based on EuroQol-5 dimensions
Health-related QoL without influenza (utility score)	0.8	Kind *et al.*, 1998[82]
Death rate from influenza in those ≥ 65 years (without zanamivir)	28.0/100,000	Simonsen *et al.*, 1998[80]
Death rate from influenza in those ≥ 65 years (with zanamivir)	26.3/100,000	Assuming a 6% reduction paralleling reduction in antibiotic use
Unit cost	**Value**	**Source**
Cost/GP consultation	£18	Netton and Dennett, 1998[81]
Cost/hospital day	£222	Netton and Dennett, 1998[81]
Cost/prescription of zanamivir	£24	British National Formulary, 2000[19]
Cost/prescription of antibacterials	£5	Mauskopf *et al.*, 2000[76]

Resource-use parameters

We assume that all patients in the zanamivir group receive zanamivir and none of the patients in the standard therapy group receive zanamivir.

The figures in the base case for the use of antibacterials have been taken from meta-analyses of trial data. These data provide an indication of the relative rate of prescribing of antibiotics in the zanamivir and standard therapy populations. However, the rate of prescribing of antibiotics in the clinical trials was much lower than that seen in actual clinical practice. (Note, it has been suggested that much of the prescribing of antibiotics to patients with influenza in general practice is inappropriate.[70])

The estimate of the mean number of GP visits per patient has been taken from the study by Meier and colleagues.[12] We have assumed that

the same rate of consultation will be seen in both the zanamivir and standard therapy groups as there is as yet no evidence to suggest otherwise.

The all-hospitalisation rates seen in the clinical trials suggest hospitalisation rates much lower than used in our base-case scenario, which was based on data from the Meier and co-workers study.[12] However, this latter study is a high-quality study and uses real data from primary care and we believe more accurately reflects the true clinical situation. It is probable that the lower rates of hospitalisation seen in the trials are due to selection of participants and raises concern over the external validity of the results.

Effectiveness and prevalence parameters

Effectiveness data is taken from the meta-analyses in this report for the IPP. The prevalence of influenza in ILI changes throughout the year and from season to season. The estimate for the base-case prevalence for influenza-positive patients presenting with ILI was derived from several national studies. The Public Health Laboratory Service (PHLS) Collaborative Virological Surveillance collect combined nose and throat swabs from patients presenting within 5 days of onset of ILI symptoms (defined as an acute respiratory tract infection with fever or complaint of feverishness) at 17 public health laboratories. From 505 specimens collected in 1998–1999, 13% tested positive for influenza A or B.[83] (In the preceding year, 14% tested positive in the same exercise.[84]) In the 1998–1999 RCGP/Enteric and Respiratory Virus Laboratory (ERVL) Virological Surveillance, 11% were positive for influenza A and 1.89% for influenza B from 742 samples submitted.[83] (The 1997–1998 RCGP/ERVL virological surveillance reported 15% positive for influenza A from 793 specimens submitted.[84]) Using this data we have applied a base-case prevalence for influenza-positive patients presenting with ILI of 14%.

There was no published empirical data on measures of utility in influenza. For the calculation of QALYs, we have assumed that, on the five dimensions of health that the EuroQol-5 dimensions (EQ-5D) covers (mobility, self care, usual activity, pain/discomfort and anxiety/depression), someone with influenza scores 2 on a scale of 1–3 (1 = no problem, 2 = some problem and 3 = extreme problem). This gives a health-related QoL score of 0.516.[85] This is very similar to the estimate of 0.5579 used by Mauskopf and colleagues.[76] We assume that not having influenza has an average QoL score of 0.8 based on the estimate of Kind and co-workers[82] from a UK national survey.

Model results

Table 10 presents the incremental cost-effectiveness ratio (ICER) results when realistic prevalence rates are used and the effectiveness derived from the IPP applied.

Key points from the base-case analysis are as follows.

1. The difference in expected costs for both groups (i.e. all adults and those at risk) reflects differences in medication usage only.

TABLE 10 *Base-case incremental cost-effectiveness analysis results*

Parameter	Value
Expected cost per patient (all adults)	
Zanamivir group	£78.11
Standard therapy group	£54.36
Expected cost per patient (at-risk adults)	
Zanamivir group	£96.12
Standard therapy group	£72.42
Incremental cost/day of symptom avoided	
All adults (prevalence over influenza season)	£123
All adults (prevalence when influenza circulating)	£50
At-risk adults (prevalence when influenza circulating)	£42
Incremental cost/QALY gained	
All adults (prevalence over influenza season)	£158,000
All adults (prevalence when influenza circulating)	£65,000
At-risk adults (prevalence when influenza circulating)	£54,000

2. The higher expected costs of at-risk patients reflects higher hospitalisation rates compared to all adults.

Sensitivity analyses

In the sensitivity analyses, we varied those parameters identified by Mauskopf and colleagues[76] as important to the results of their model plus a number of other parameters of our own. These are listed in *Table 11*.

Glaxo Wellcome, in their second submission to NICE,[87] have used a model similar to that used by Birmingham. Their estimate of cost/QALY of using zanamivir for the treatment of influenza in at-risk adults is £13,000. In the main, they have used the same assumptions as we did in our model. The difference between Glaxo Wellcome's estimate and ours is driven by the following.

- The fact that they assume a higher prevalence of influenza-positive individuals amongst those visiting their GPs with influenza (50%) based on an estimate half-way between the rate observed in practice (34%) and the rate observed in trials (64%). They believe that could be achieved with an educational programme and improved communication.
- They assume a higher gain in utility for the difference between influenza and no influenza. This figure is derived from a small retrospective study of 21 patients, which estimated a day with influenza to produce a state worse than death (–0.66). Our estimate has no empirical data informing it.

We believe that there is genuine uncertainty about these parameters.

Other potentially important considerations

The fact that zanamivir reduces complications requiring antibiotics does not directly inform the model on the benefits side – it only feeds into the costs. Clearly, the benefit of not acquiring a secondary bacterial infection will indirectly influence the estimate of time to alleviation of symptoms, but it may also have other benefits. In particular, it is possible that it may reduce hospital admission and save lives.

Assuming that hospital admission rates are reduced by 6%, in parallel with the more conservative estimate of the reduction in antibiotic use, produces a cost/QALY of £48,000 for the base case or £28,000 if a utility of 1.0 is used for no influenza in the at-risk population.

As death from influenza is relatively rare (there is measurable mortality from influenza each year because influenza is so common), clinical trials are not powered to demonstrate saving of life. However, it seems reasonable to suppose that if we can prevent 6% of the at-risk population from needing antibiotics, it is possible that we may also prevent some deaths.

We have thus sought estimates of death rates from influenza in the at-risk population from the epidemiological literature. It is difficult to obtain the death rate for those with influenza from routine statistics. Macro-estimates suggest an excess death rate of 3000 to 4000 people per annum in the UK due to influenza, but routine hospital statistics only have influenza recorded as the cause of death for a fraction of these. In England and Wales in 1997, 694 deaths were recorded for the International Classification of Diseases (ICD) 9 codes 487–487.1 (reference details not available). A study of age-specific excess mortality related to influenza A in the USA from 1968 to 1995 showed that nearly all deaths in current influenza epidemics occurred among the elderly.[63] Estimates of the excess mortality in people aged ≥ 65 years in different years varied from 2.8 to 85/100,000 with a mean of 28/100,000.[80] The relative risk of death in those aged ≥ 65 years compared to those < 65 years varied from 7:1 to 281:1 depending on the strain of influenza.[80] Studies of at-risk individuals < 65 years of age suggest at least as high a death rate.[86] Using the estimate of 28/100,000 as a baseline death rate for influenza in the at-risk population and assuming that zanamivir would produce a parallel 6% reduction in this rate, an estimate of 1.68 deaths prevented per 100,000 treated is reached. This would reduce the cost/QALY.

Sensitivity of diagnostic tests for influenza

An important consideration when considering influenza-positive rates is the fact that diagnostic tests are not 100% sensitive. The sensitivity changes, for example, with education of doctors about how, when and in whom to take a sample. It also changes with the laboratory methods and techniques used. The PHLS have undertaken educational exercises with laboratories and GPs and have increased virus isolation rates dramatically from 1–2% to > 30% in some cases (Laidler P, PHLS, London: personal communication, June 2000). The sensitivity of a test also varies with the strain of the virus. Thus at the start of the influenza season sensitivity will be less than at the end when methods of culture have been adapted to the circulating strain. Since there

TABLE 11 *Parameters varied in the sensitivity analyses together with the results*

Parameter	Variation explored	Source	Cost/QALY		
			All adults (influenza season)	**All adults (circulating influenza)**	**At-risk adults (circulating influenza)**
Base case			£158,000	£65,000	£54,000
Use of antibiotics	*Proportion of patients receiving antibiotics:* Zanamivir = 0.3 Standard therapy = 0.452	Assumes: – antibiotics used at rates found in Meier *et al.*, in press – relative risk of use with zanamivir derived from clinical trials[70]	£154,000	£63,000	£53,000
Proportion of patients hospitalised (in at-risk population)	Reduced by 6% (same proportion as reduction in complications requiring antibiotic use)	Assumption from the Birmingham meta-analysis	£147,000	£61,000	£48,000
Number of follow-up visits per patient	Zanamivir = 0.46 Standard therapy = 0.72	Mauskopf *et al.*, 2000[76]	£126,000	£52,000	£43,000
Prevalence of influenza in patients presenting with ILI	Continuous across the range	NA	As shown in *Figure 16*		
Proportion of false-negatives in ILI population (and assuming they would also respond to treatment)	10 and 20%	Assuming influenza diagnostic test sensitivity of 80 and 90% (Laidler P, PHLS, London: personal communication, 2000)	As shown in *Figure 17*		
ITTP effectiveness and influenza prevalence observed in trials	*Reduction in days to alleviation of symptoms in ITTP:* All adults = 1.071 At-risk adults = 1.15 (with influenza prevalence of 60% seen in trials)	Current review	NA*	£30,000	£24,000
Reduction in number of days to alleviation of symptoms	*All adults:* Lower limit = 0.840 Upper limit = 1.927 *At-risk adults:* Lower limit = –0.02 Upper limit = 3.37	From 95% CI in current review	Lower limit = £260,000 Upper limit = £113,000	Lower limit = £107,000 Upper limit = £47,000	Lower limit dominated by placebo Upper limit = £27,000
Calculation of incremental cost for patients who would otherwise have stayed at home had treament not been available	*Standard therapy:* Antibiotic use = 0 GP visits = 0 Hospitalisations = base case *Zanamivir:* Antibiotic use = base case GP visits = base case Hospitalisations = base case	Assumptions	£341,000	£141,000	£117,000
Health-related QoL scores	Utility of influenza = 0.0 Utility of no influenza = 0.8	All optimistic assumptions	£56,000	£23,000	£19,000
	Utility of influenza = 0.516 Utility of no influenza = 1.0		£92,000	£38,000	£31,500
	Utility of influenza = 0.0 Utility of no influenza = 1.0		£45,000	£18,000	£15,000
Price	£8	Price of 5-day course of treatment in France[85]	£51,000	£21,000	£17,000

* *Trials undertaken when influenza was circulating*

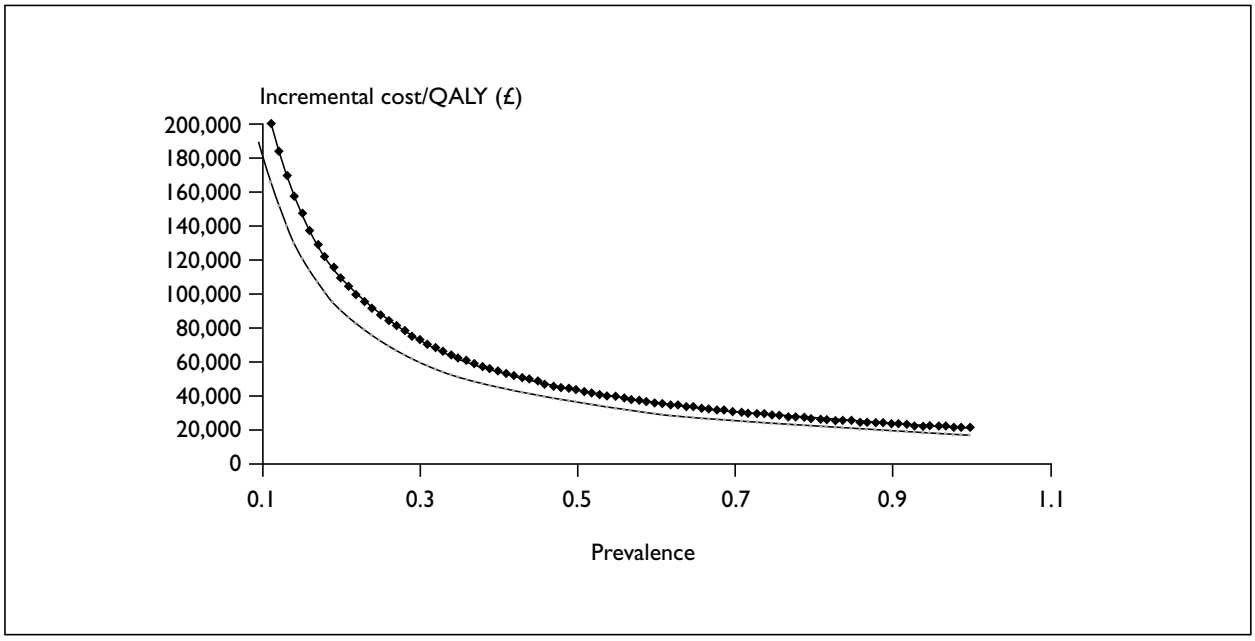

FIGURE 16 *ICER for zanamivir by prevalence of true influenza in all adults (–◆–) and at-risk adults (–▲–)*

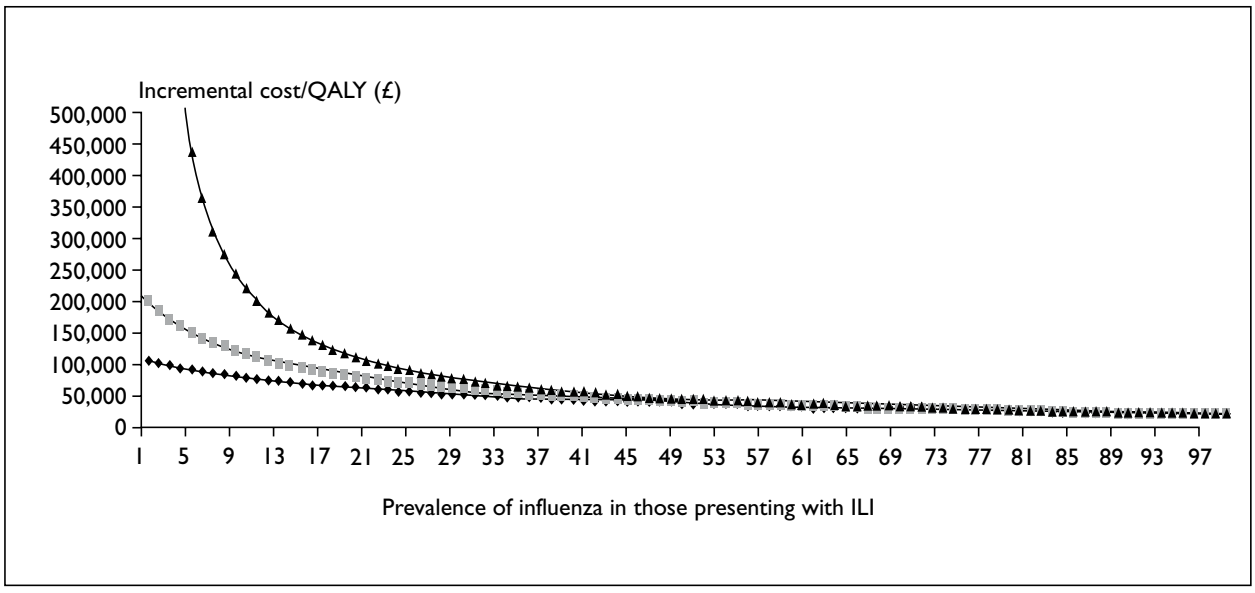

FIGURE 17 *ICER for the baseline prevalence of influenza in those with ILI during influenza season (–▲–) and when prevalence is adjusted for false-negative rates of diagnosis of 20% (–◆–) and 10% (–■–)*

is no 'gold standard' against which to measure the performance of the tests, it is not possible to be certain about their sensitivity. The PHLS estimate that somewhere between 10 and 20% of patients may have false-negative results overall. This is consistent with the findings of a greater effectiveness in the ITTP in the clinical trials than would have been accounted for by applying the IPP effectiveness data to this group (although this difference was not statistically significant). These are the percentages that have been applied in *Figure 17*.

Key points from the sensitivity analysis are as follows.

1. The ICER is highly sensitive to a number of parameters and varies from £15,000 to £341,000, that is, from reasonable to very poor value for money.
2. The ICER is highly sensitive to assumptions about the utility scores associated with the health state of influenza (and varies from £15,000 to £158,000/QALY). This is important because there is no published empirical data available to inform this.

3. *Figure 16* shows that the ICER is highly sensitive to variation in prevalence rate. This confirms that the trial-based economic analysis such as that presented by Mauskopf and colleagues[76] can be very misleading. At more realistic estimates of prevalence, such as the 34% used in our base-case analysis, the ICER was £47,000 for the at-risk group.
4. The base case has the optimistic assumption that there is no off-indication prescribing (for example, using zanamivir for patients presenting with a symptom duration of > 48 hours or without the classic symptom complex for influenza). Off-indication prescribing will mean that the prevalence rate of influenza at a treatable stage of the illness is reduced and the implications can be deduced from *Figure 16* by adjusting the true prevalence rate according to the anticipated rate of off-indication prescribing.
5. Price is very important in determining whether use of the drug represents good value for money: the cost/QALY dropped from £65,000/QALY to £21,000/QALY for all adults when influenza is circulating when the current price in France was used.
6. There has been concern expressed that the availability of zanamivir may, in fact, cause people who would not otherwise have presented to go to their GP. It is not possible to predict with certainty the extent to which the availability of zanamivir on the NHS would change presentation rates to GPs. We cannot tell from routinely collected statistics what percentage of people with ILI are currently staying at home. The Australian cost-effectiveness model[76] states that 60% do not go to the doctor in Australia (based on the Australian national health survey[88]). We found an estimate that, over a 20-year period in the UK, some 50% of patients with ILI do not present, but it was not clear how this estimate was derived.[89] The sensitivity analysis explores the ICER for patients with influenza who would not have presented to their GP had zanamivir not been available. In this situation, the ICER varied from £117,000 to £341,000. This suggests that concerns about the potential impact of increased presentation rates are justified.
7. In no scenario did the use of zanamivir for all adults in the general influenza season (when influenza virus was not known to be circulating) have an ICER that reflects what has been historically considered good value for money in the NHS. Even if the price dropped to one-third of the current cost, the ICER would be £51,000.
8. The proportion of patients with ILI who are prescribed antibiotics has negligible impact on the cost-effectiveness of zanamivir.
9. The assumptions about the true number of days to alleviation of symptoms has a significant impact on the ICER. This is potentially of most importance in the at-risk group for which the evidence base is likely to grow because trials are currently in progress for this group

Limitations of the model

Most patients present more than 48 hours after onset of symptoms, when treatment with zanamivir is no longer useful. In a Glaxo Wellcome study of influenza diagnosis in general practice, a total of 1792 acute respiratory infections were recorded. Of these, 31% were diagnosed as an ILI, of which only 12.5% presented within 48 hours.[27] These would all increase the incremental cost/QALY.

Chapter 5

Potential methodological strengths and weaknesses of the technology assessment

Strengths

This review has systematically used data from all published sources identified plus it incorporates unpublished information. It has used all existing data made available. It has been able to cross-check information from different sources.

Potential weaknesses

Publication bias

Publication bias is always a potential problem when interpreting the results of a systematic review.

- We cannot be sure we have identified all smaller trials. A comment in one paper supplied in confidence mentions two Japanese trials. Glaxo Wellcome had no Japanese trials listed on their clinical trials register as at 1st June 2000. (We identified one through the published literature.)
- There are a number of prophylaxis trials that have time to alleviation of symptoms as the primary outcome with a total $n = 330$ – this is perplexing and they are not published in sufficient detail to exclude a treatment arm.
- We have not been able to retrieve data for some unpublished trials that potentially meet the inclusion criteria for treatment trials (NAIA1005, NAIB2001 and NAIB2003[‡]). These involved a total of 187 patients. (However, if all three of these trials showed a null effect, this would not be sufficient to alter the general conclusion that the treatment shows a statistically significant effect in reducing the duration of symptoms of influenza.)

Missing information

For some trials, there were limited data.

- Where CIs were not given, we were obliged to estimate the uncertainty surrounding the medians in order to be able to weight studies in a pooled analysis.
- We did not have enough information to be able to do this for all outcomes for all trials. Therefore, there is information absent from the meta-analyses, even for the primary outcome time to alleviation of symptoms.
- Data was often truncated at day 10 in the presented results, despite having been collected over a much longer period. Sometimes over one-third of patients had not recovered by this time. Unless the complete distribution of the data is reported for the period collected, we cannot exclude the possibility that any apparent benefit is not diminished or lost later. The outcomes measured are, in the main, survival data and, in this situation, a hazard ratio would have provided a more appropriate summary of the relative benefits across the entire period of follow-up. Means, where given, were also biased because they had been calculated with all truncated data counted as day 10.
- Although QoL data was collected, it was not available. A firm cost–utility model requires patient-level health-related QoL data.
- There was also limited information on hospitalisations, OTC drug use, absence from work, impact on severity of illness measures, complications and deaths. Therefore, conservative assumptions have been used for some parameters as there is little evidence to the contrary (e.g. hospitalisations due to flu and use of antibacterials).

Unknown parameters

The external validity of the trials is weak due to:

- the high prevalence of influenza in patients with ILI
- the low hospitalisation rates
- the low rate of antibiotic prescription.

These factors do not match normal clinical practice.

Moreover, it is uncertain how the population would respond were zanamivir made available on the NHS. If more people consulted their GP, believing there to be an effective treatment, the prevalence of influenza in those presenting might change.

[‡] See appendix 3 for the references for each study.

The estimation of the impact on primary care is necessarily speculative.

The methodological uncertainty regarding combining medians

See chapter 2 for the discussion concerning this.

Limitations of the rapid review process

NICE works to a structured schedule with very fast turnaround times. The schedule allows only 4–6 weeks for the authors of a review to read and data extract from the industry submissions. Of the order of 6000 pages of detailed text and tables were provided by the industry. We cannot exclude the possibility that relevant information has been overlooked. There was not time for the pharmaceutical industry to supply requested missing information.

Important issues not addressed by this technology assessment

Key issues which this assessment did not encompass include the following.

- We have not considered the effectiveness, potential impact and costs of near-patient diagnostic tests for influenza A and B. These could be relevant because the cost-effectiveness of zanamivir increases as the proportion of people treated with zanamivir who truly have influenza A or B increases.
- We have not considered the effectiveness and cost-effectiveness of zanamivir in children < 12 years of age as this is currently not a licensed indication in the UK.
- We have not compared the cost-effectiveness of zanamivir against amantadine.
- There are other NIs that will come onto the market in the near future, in particular, oseltamivir. These have not been considered in this report.
- NIs have a potential use in the prophylaxis of influenza. While this is not currently a licensed indication for zanamivir, it will require assessment in the future should GlaxoSmithKline obtain a licence in Europe.

Chapter 6

Discussion and conclusions

Implications of the assessment findings

NHS

Zanamivir is an effective treatment for influenza. The evidence base for the effectiveness in at-risk adults is significantly larger than when this was first reviewed by NICE and it is now clear that zanamivir is effective in this group. However, even for at-risk adults, influenza remains a self-limiting illness for most. Results of other trials assessing the treatment of at-risk adults with zanamivir may shed more light on and give more precision to the estimates of the degree to which symptoms are reduced and, more importantly, whether zanamivir can reduce complications, hospitalisation or death rates in these groups.

Patients and carers

Individuals with influenza can expect to gain about a 1-day reduction in illness if they take zanamivir within 48 hours of the onset of influenza symptoms. Although the drug is relatively well tolerated, it is important that patients should know that there will be no benefit if taken later and that no medication is without some risk. People need to be aware of the symptoms of influenza: only a small percentage of acute respiratory infections meet the criteria for ILI (most importantly, the combined presence of abrupt onset, cough and fever). Moreover, patients should know that only one in seven people who experience this symptom complex in the influenza season will actually have influenza A or B and will gain from taking the drug.

Society

The economic evaluation did not take into account the costs to society of absence from work due to influenza or costs of OTC medications. The drug would appear more cost-effective were these other direct and indirect costs and savings taken into account.

Research in progress

We know of four treatment trials in adults (and there are other trials in progress examining the effectiveness in children and the prevention of influenza) that were ongoing or completed but not yet reported at the time of the review (see *Table 12*). Two of these address the important area of the effectiveness of zanamivir in at-risk groups.

TABLE 12 *Ongoing treatment trials of zanamivir at the time of the review*

Study ID* and title	Expected completion date	Planned number of patients	Country
NAI30011 – A randomized, double-blind, placebo-controlled study to evaluate the impact of inhaled zanamivir treatment on workplace attendance due to influenza A and B infections	Completed but not reported at the time of searching	Planned 500, recruited 340	USA
NAI30012 – A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for five days in the treatment of symptomatic influenza A and B viral infections in subjects aged greater or equal to 65 years	2001	500	Worldwide
NAI30015 – A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of zanamivir 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B virus infections in armed services personnel	Not known at the time of searching	500	Finland
NAI30020 – A double-blind, randomized, placebo-controlled, parallel-group, multicenter 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 high risk patients	2001	450	UK and Germany

* *See appendix 3 for references for each study*

Implications for future research

Zanamivir has the potential to be a useful drug, especially in the at-risk population. It is, therefore, important for the NHS to continue to collaborate in research in this area. It will be especially important to look at impact on hospitalisations, complications and death rates. As NICE has recommended its use in at-risk patients, it is important that pragmatic research or evaluation in a realistic primary care setting be undertaken to assess the true benefits, harms and costs in the real world situation. This should take into account such variables as the prevalence of influenza among those with ILI, the number of people with influenza visiting their GP when they would otherwise not have done so, referral rates, time after onset of symptoms when patients present, off-indication prescribing, use of other medications, complications, hopitalisations and death rates, which were not representative of general practice in the current trials of zanamivir.

There remains useful evidence in already existing research that we were unable to exploit in this review because of the way trials have been reported or due to missing information. Meta-analysis of individual patient data from the original data to allow a proper survival analysis and true comparison of the IPP and influenza-negative population using hazard ratios might give us better evidence about the treatment effect, size and precision.

We have used a simple economic model. The economic modelling could be extended to incorporate stochastic components. Ideally, empirical patient-level QoL data should be obtained to inform the model.

Amantadine is a much cheaper drug. There have been no head-to-head trials to demonstrate the relative effectiveness of amantadine versus zanamivir.

Amantadine and zanamivir have different mechanisms of action. It could be that their effect is additive. An RCT of combined therapy in at-risk adults might be warranted.

Oseltamivir or other NIs will almost certainly come onto the market in the very near future, and there needs to be a systematic review of their effectiveness and cost-effectiveness. We know of no head-to-head trials comparing oseltamivir and zanamivir. Again, it would be important for trials to directly compare the effectiveness of these drugs because the prevalence of influenza within the trials, and other sources of heterogeneity between trials, confound indirect comparisons of effect size.

It is important for emerging new evidence to be systematically reviewed in the context of existing information.

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Amanda Burls was the main author. She designed the protocol and piloted and modified the forms used for assessment of eligibility, validity and data extraction. She undertook searches for studies, contacted the authors for further information and liaised with content experts in the field to obtain background information and support. She also assessed studies for eligibility and validity, extracted, collated and summarised the data from the studies, and contributed to the economic evaluation. Wendy Clark helped identify studies and handsearched *Scrip*. She undertook the assessment of studies for validity and independently extracted the data from them. She also read and commented on the draft report. Tony Stewart assessed studies for their eligibility and validity and independently extracted the data from them, and read and commented on the draft report. Stirling Bryan worked on the economic evaluation, and read and commented on parts of the draft report. Carrol Preston provided statistical advice and undertook data extraction for the effectiveness results of most of the trials included in this review. She helped produce summary statistics and read and commented on the draft report. Tom Jefferson helped devise the protocol for the review, contributed to the background and epidemiology section and read and commented on the draft report. Anne Fry-Smith advised on the search strategy and undertook searches of electronic databases.

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88. Australian Bureau of Statistics. Australian national health survey. Sydney: ABS; 1995.

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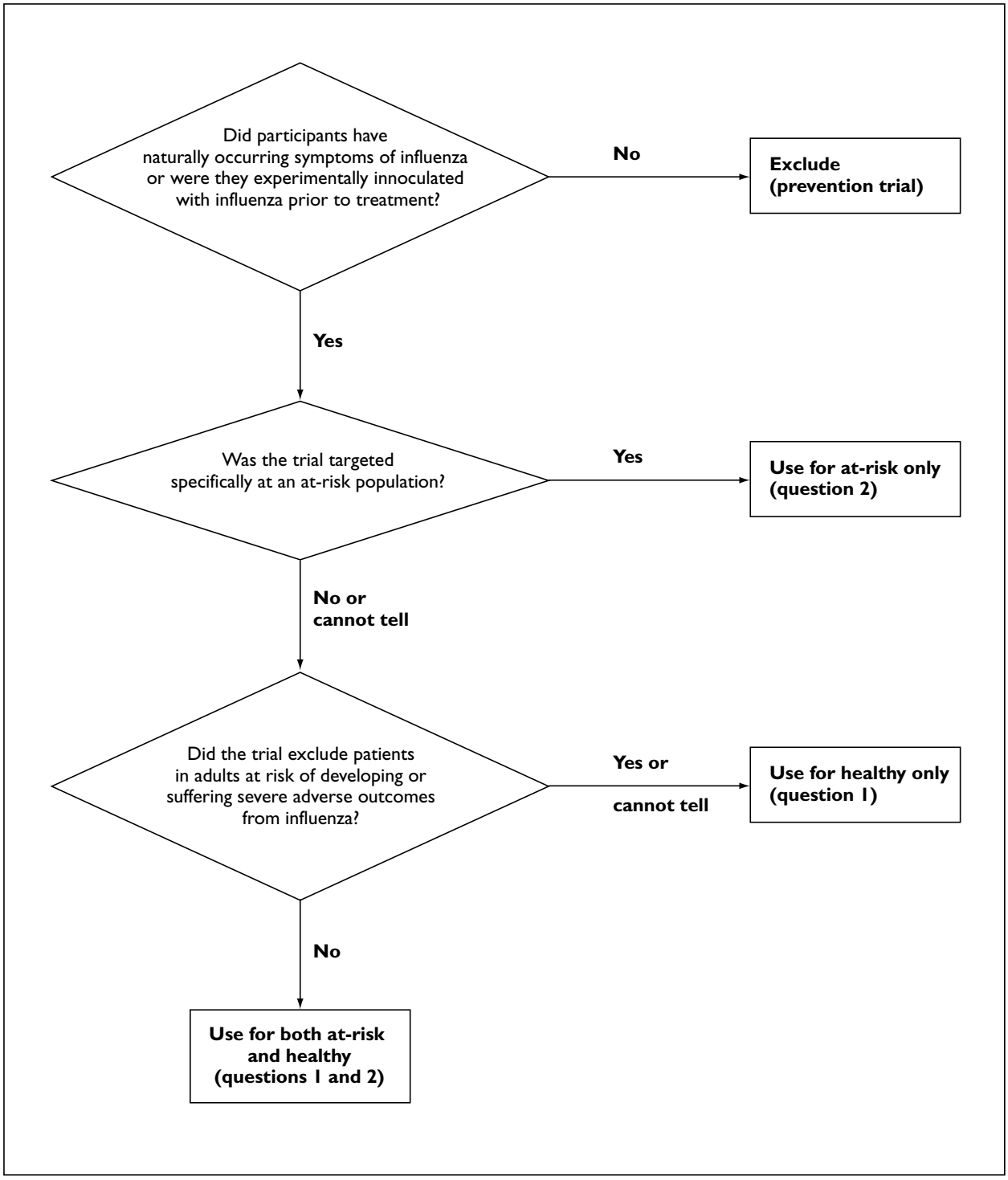
Appendix 1

Decision flow chart for eligibility of data from trials for inclusion in each question



Appendix 2

Method for pooling medians

Pooling continuous data: methods for skewed data

Preston C, Deeks J, Altman D. Pooling continuous data: methods for skewed data. Poster presented at the 8th International Cochrane Colloquium; October 2000; Cape Town, South Africa.

Abstract

Many continuous biomedical outcome measures have naturally skewed distributions. Current methodologies for pooling continuous data are limited to methods for combining differences in means or standardised differences in means. These approaches assume normality of the data, and require arithmetic means and SDs to be available for each arm of the study. However, skewed outcomes are most appropriately summarised using medians or geometric means. Meta-analyses of skewed outcomes, therefore, typically necessarily exclude studies that report the most appropriate summary (medians) whilst including studies that use potentially misleading summaries (arithmetic means).

It is possible to pool any summary statistic using inverse variance weights if a standard error of the summary statistic is available. Whilst there is no formula for calculating the standard error of a difference in medians, estimates of a pseudo standard error may be obtained from measures of uncertainty and statistical significance that may be obtained from measures of uncertainty, which may be presented in conjunction with the medians.

Through simulation, we are investigating the relationships between sample size, the degree of skew and:

- the bias and performance of arithmetic means for summarising skewed continuous data
- the bias and performance of methods of pooling medians using alternative estimates of standard error.

Introduction

- Weighted mean difference (WMD) and standardised mean difference are two methods used to combine continuous data.
- Standardised mean difference is used in preference to WMD when different scales have been used to measure the same outcome and is the difference in means divided by the pooled SD.
- Both methods require means, SDs and sample sizes to be reported and use an inverse weighted method.
- The underlying assumption behind the use of these methods is that the data are normally distributed. Reporting means and SDs as summary statistics also relies on an assumption of normality.
- If the underlying data of the individual trials is not symmetrically distributed but is positively skewed, what implications does this have for:
  – the results of a single trial
  – the results of a meta-analysis combining these single trials?
- If the data has a symmetrical shape then estimates of the mean and median will be approximately equivalent. If the data are positively skewed estimates of means and medians separate such that estimates of the mean are greater than the median. The mean is strongly affected by skew, and is not a good measure of central tendency.
- *Figure 18* illustrates that as the level of skewness increases the mean can over-estimate the treatment effect by up to 120% relative to the median.

How can you tell if the aggregate data from the trials for meta-analysis might be positively skewed?

- If your data are naturally bounded at zero and the mean/SD < 1.64 then the data might be positively skewed.
- If the SDs of the trials increase with estimates of the means then this may indicate that the data have a log-normal distribution. This is because the formula for the SD of the log-normal distribution is given by $m(w^2 - w)^{1/2}$ where m is the median, $w = \exp(s^2)$ and s^2 is the variance of the log-transformed data. Hence, the SD increases with increasing medians.
- Although the spread of the data is controlled by the magnitude of the median, the shape or the skew of the data is determined by $(w^2 - w)^{1/2}$. The larger this quantity, the more positively skewed the data.

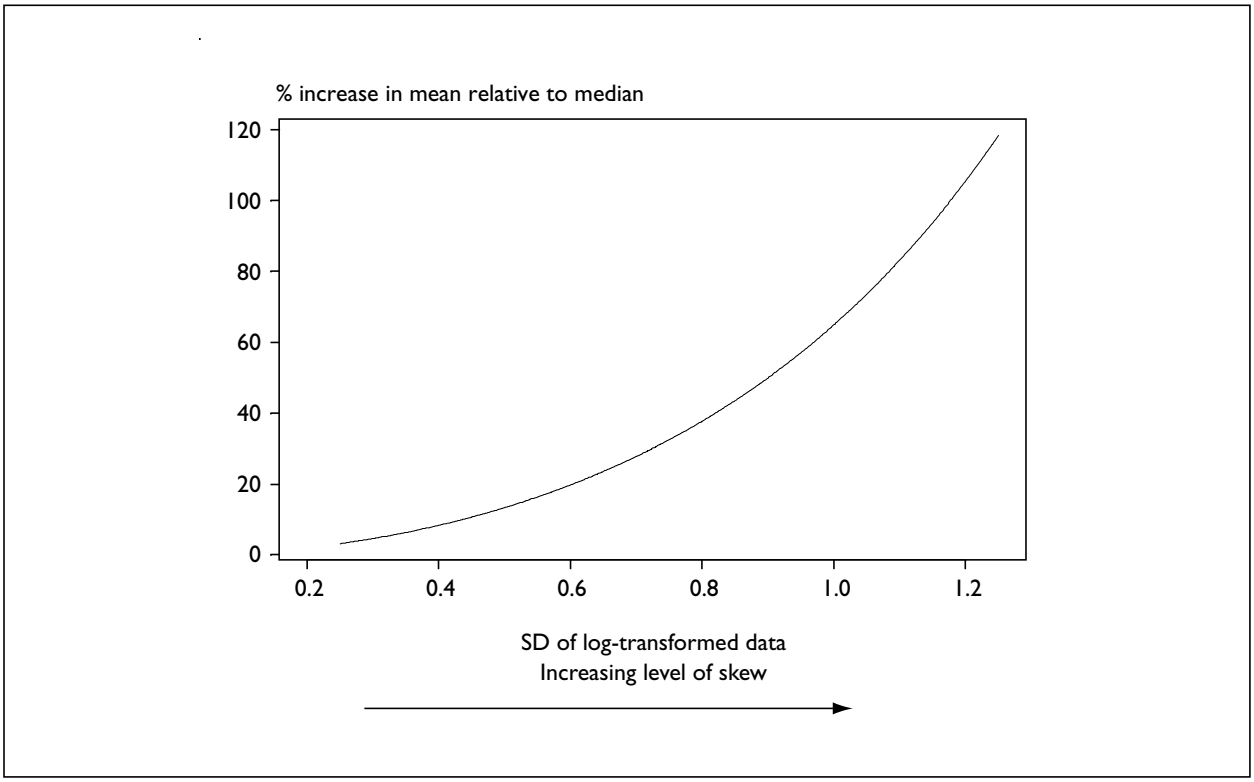


FIGURE 18 *Graph showing that as the level of skewness increases, the mean can overestimate the treatment effect by up to 120% relative to the median*

- Transforming the data by taking natural logs stabilises the variance and gives the transformed data a symmetrical shape. Back-transformation of means calculated on the transformed scale gives geometric means.

What are the implications of summarising positively skewed data from a single trial using means and SDs?

Aim

To consider the robustness of summarising positively skewed data from a single trial using means and SDs.

Methods

Using the log-normal distribution, 5000 trials were simulated for each treatment difference of 0, 10, 20, 50 and 100% at each of the log-transformed SDs 0.25, 0.5, 0.75, 1.0 and 1.25. The skewness of the simulated data increases as the log-transformed SD increases. As the treatment difference increases, assumptions of equal variance in each trial arm become increasingly invalid. Calculations of 95% CIs were made for each of the simulated trials using their means and SDs. The number of CIs not containing the true treatment difference and the number not containing zero were recorded.

Results

We would expect about 5% of the CIs not to contain true treatment value. *Figure 19* suggests that:

- single trial coverage is fairly robust even when the data is skewed, however, this deteriorates as sample size and treatment difference increase
- if the data are strongly positively skewed, the sample size in each trial arm large and there is a large treatment difference, up to 80% of CIs may exclude the true treatment difference.

Conclusions

If data are positively skewed then the arithmetic mean provides an inflated measure of central tendency, which is better estimated using the median. The larger the sample size, the more closely the mean is estimated increasing the probability that the true central measure is excluded. Where true treatment difference is excluded, this is frequently due to the lower end of the CI being greater than the median.

How does this translate for meta-analyses?

Aim

To determine the robustness of meta-analyses using estimated means and SDs from trials with positively skewed data.

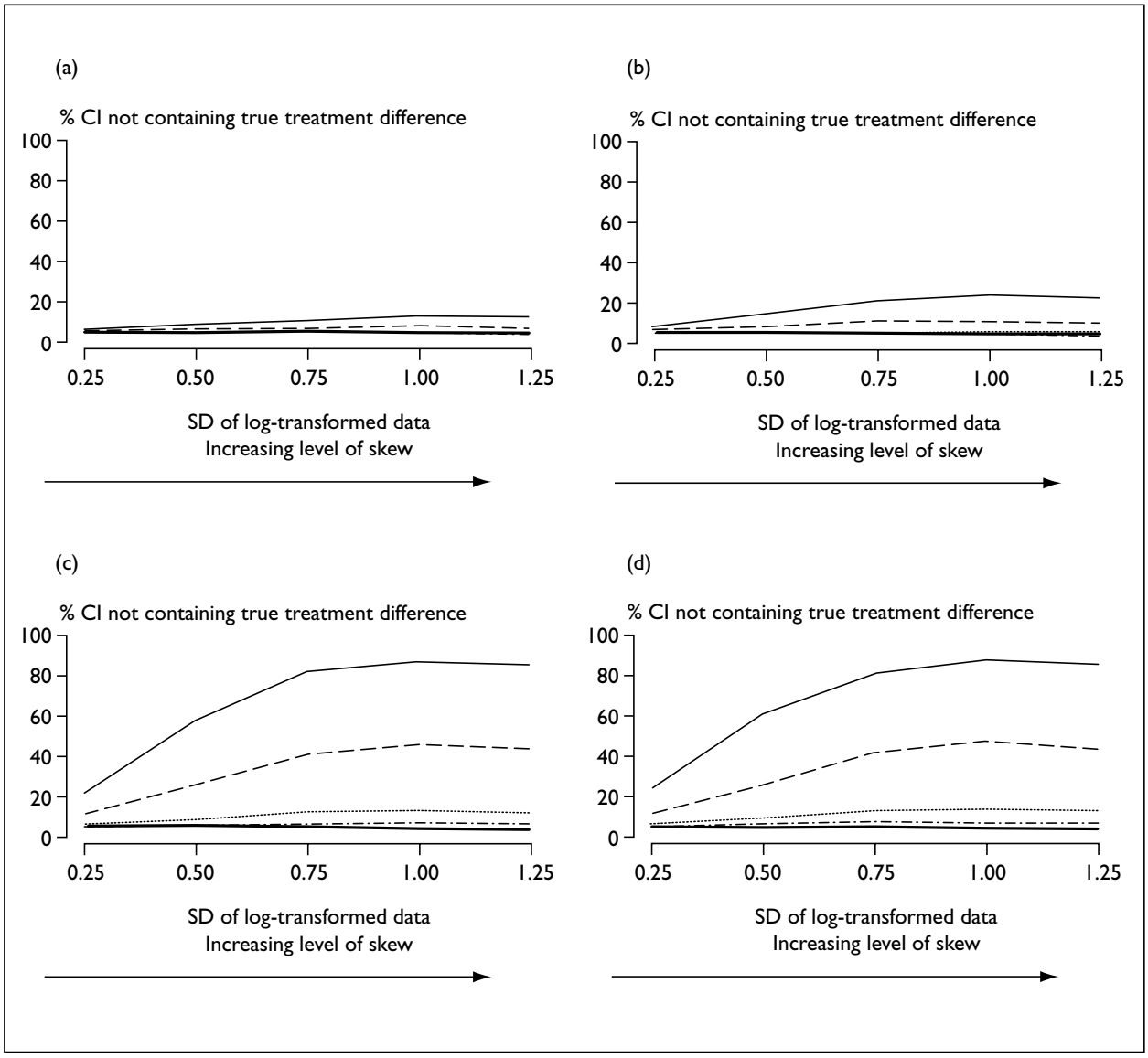


FIGURE 19 *CI coverage of a single trial with positively skewed data for (a) 50, (b) 100, (c) 500 and (d) 1000 observations in each trial arm with a 0% (——), 10% (· – · – ·), 20% (·····), 50% (– – – –) and 100% (——) treatment difference*

Methods

The simulations generated to investigate robustness of a single trial were used again. The 5000 trials generated for each treatment difference and level of skew were grouped to give 1000 metaanalyses each containing five trials. The number of CIs not containing the true treatment value were recorded and are presented in *Figure 20*.

Results

Figure 20 shows that even if data are only slightly skewed but there is a large treatment difference, then approximately 50% of CIs will not contain the true treatment value, and as the sample size increases this can reach almost 100%. This shows that while summarising the results from a single trial with means and SDs is fairly robust, even when the data is strongly positively skewed, meta-analyses of trials in which the data are only slightly skewed are not.

Conclusions

Current methods for combining the results from trials of continuous data are inadequate when the data are positively skewed. This highlights the necessity of work in this area to develop new methods to improve the robustness of meta-analyses of skewed data.

Method for combining differences in medians

Aim

To evaluate a method to combine medians.

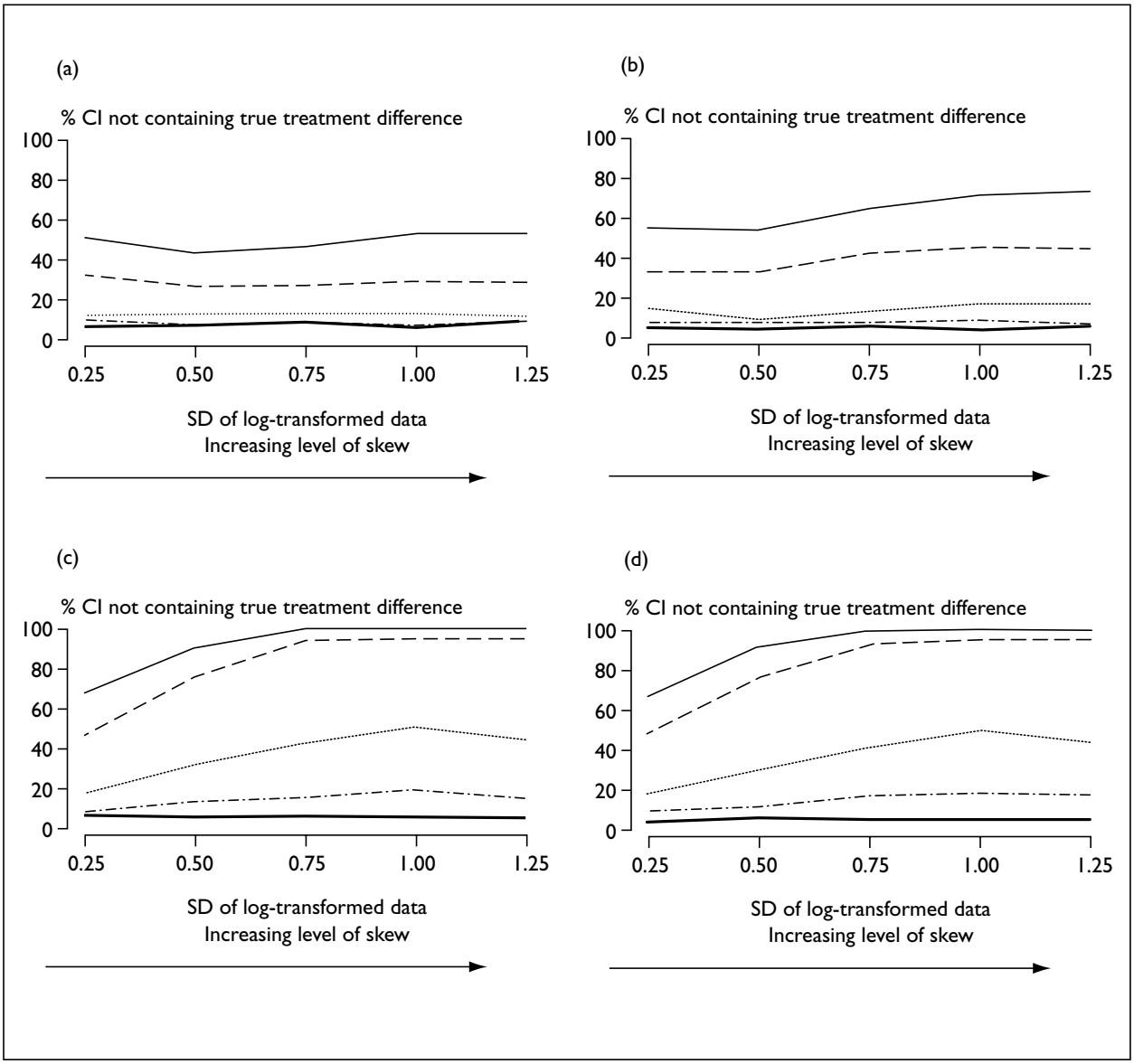


FIGURE 20 *CI coverage of meta-analyses of five trials with positively skewed data for (a) 50, (b) 100, (c) 500 and (d) 1000 observations in each trial arm with a 10% (· – – · ·), 20% (·····), 50% (– – – –) and 100% (——) treatment difference*

Methods

The simulations used to evaluate CI coverage of skewed data for single trials and meta-analyses of five trials were used again. Estimates of medians and 95% CIs about the medians were calculated for each trial arm. The 5000 trials generated for each treatment difference and level of skew were grouped to give 1000 meta-analyses each containing five trials. The number of CIs not containing the true treatment value were recorded and are presented in *Figure 21*.

- The results show that meta-analyses of trials with skewed data based on means and SDs give poor CI coverage.
- Single trials in which the data is positively skewed may not report means and SDs, but, more appropriately, medians and CIs around the medians.
- The following suggested method aims to provide a way to combine data from trials that report medians with their 95% CIs for each trial arm.
- If means and 95% CIs are available, the SD would be estimated by:

$$lci = m - 1.96 \times \frac{\text{SD}}{\sqrt{n}}$$

$$uci = m + 1.96 \times \frac{\text{SD}}{\sqrt{n}}$$

$$uci - lci = 2 \times 1.96 \times \frac{\text{SD}}{\sqrt{n}}$$

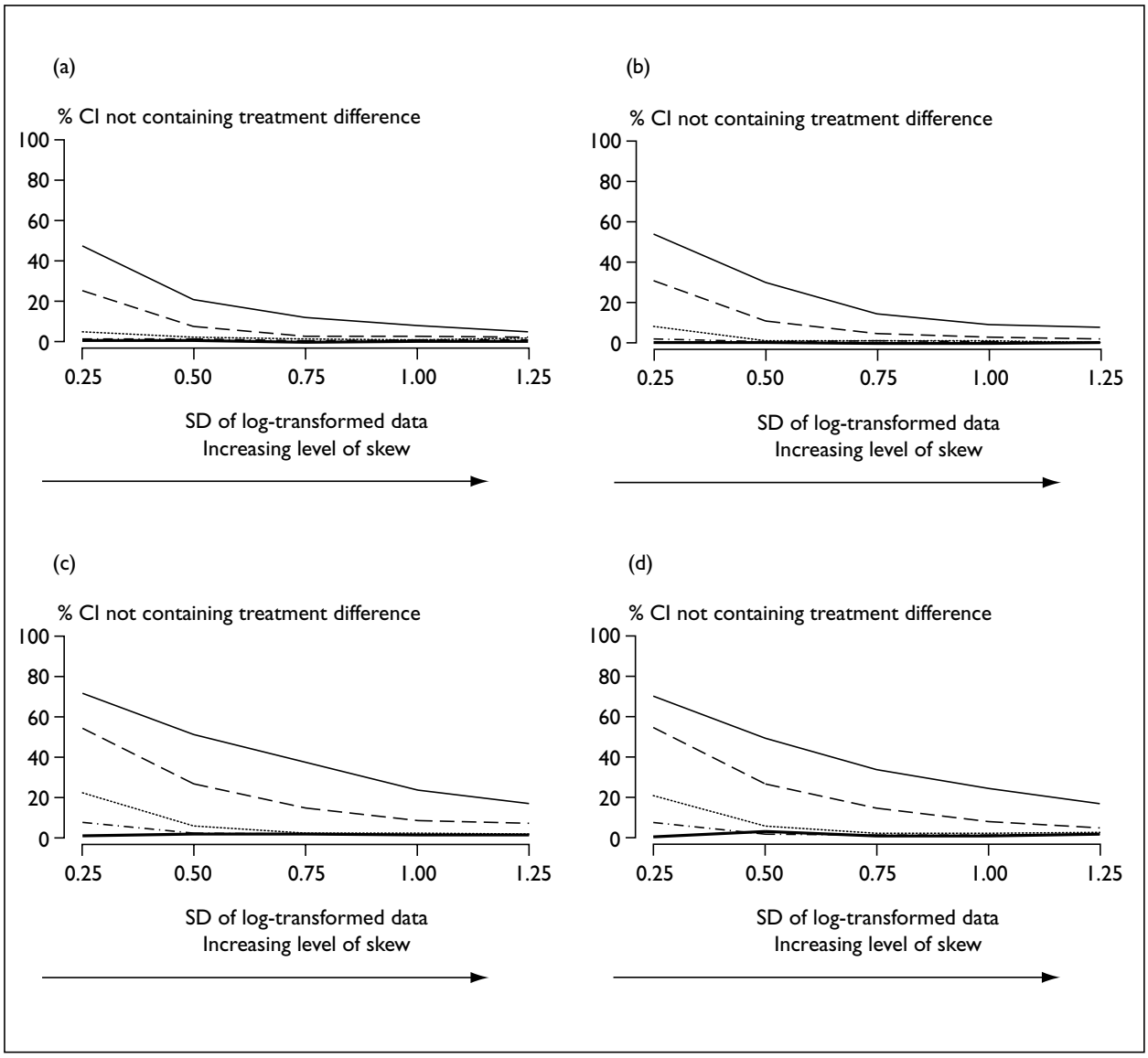


FIGURE 21 *CI coverage of meta-analyses of five trials with positively skewed data for (a) 50, (b) 100, (c) 500 and (d) 1000 observations in each trial arm using a method to combine medians with a 0% (——), 10% (· – · – ·), 20% (·····), 50% (– – – –) and 100% (——) treatment difference*

- This formula can then be rearranged to give an estimate of the SD. If medians and their CIs are available, a pseudo SD could be estimated using the same formula.

Results

Figure 21 shows that when the data are only slightly skewed this method has poorer CI coverage than the traditional method of meta-analysis of continuous data. As the skew of the data increases, the coverage using this method improves but this is affected by the number of observations in each trial and the magnitude of the treatment difference. For heavily skewed data, this method performs better than the traditional method by containing the true treatment value more often. This is because the combined CI width is approximately twice the width of the traditional method, however, this also means that the method of medians has lower power than the method of means.

Conclusions

Use of medians and their CIs provides an alternative method of combining the results of trials with positively skewed data. This method only provides benefit when the data are heavily skewed but has lower power than the methods using means.

- This method:
  - gives a way of scaling CI widths around estimates of the median which allows trials with the

smallest CI widths and the largest sample sizes to be given the most weight in a meta-analysis
  - does not take into account the asymmetry of the CI around the median
  - relies on normal distribution theory.

Summary of conclusions

- Traditional methods of meta-analysis of continuous data are not robust when the data of the individual trials are positively skewed.
- A method for combining medians has been proposed and while this gives more appropriate CIs it has low power when data are heavily skewed.
- One additional drawback of the evaluated method is that it requires CIs for medians, which are not often available.

Further work

- Alternative methods of pooling skewed data need to be developed and evaluated.
- Method development could be based on medians and consider allowing for asymmetry of CIs, or be based on means and make adjustments to allow for observed skewness.
- Reporting of primary studies needs to be evaluated to ascertain which summary statistics are most commonly presented.
- Simulations have shown that using SD/mean provides a way to measure the skewness of the data within trials that can be related back to the original shape of the data. This assumes that the data follow a log-normal distribution. By estimating skewness in this way, it may be possible to scale down the estimate of the mean to bring it closer in line with the median to allow improved CI coverage.
- Results show that meta-analyses of trials with skewed data based on means and SDs give poor CI coverage.

Appendix 3

All zanamivir studies identified

Study ID	Title	Public domain data sources
JNAI-01	Inhaled and intranasal GG167 in the treatment of influenza A and B in Japan	Matsumoto *et al*., 1996[30] Matsumoto and Ogawa, 1999[31]
NAI10901	A double-blind, randomized, placebo-controlled study to evaluate the effect of inhaled zanamivir 10 mg o.d. for 28 days on anti-haemagglutinin trivalent antibody production (HAI Titre) following co-administration with fluvirin influenza vaccine in healthy subjects	FDA Center for Drug Evaluation and Research, 1999[32] Glaxo Wellcome, 2000[33]
NAI10902	An open-label, randomized, evaluation of the direct measurement of zanamivir concentrations in respiratory secretions following a single dose inhalation of 10 mg Relenza via diskhaler in healthy volunteers	Glaxo Wellcome, 2000[33]
NAI30008	A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of influenza in patients 12 years or over with asthma or chronic obstructive pulmonary disease (COPD)	Glaxo Wellcome, 2000[33]
NAI30009	A double-blind, randomized, placebo-controlled, parallel-group multicenter study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered by inhalation twice daily for five days in the treatment of symptomatic influenza A and B viral infections in children ages 5–12	Glaxo Wellcome, 2000[33] Hedrick *et al*., 2000[34]
NAI30010	A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within families	Glaxo Wellcome, 2000[33] Hayden *et al*., 2000[35]
NAI30011	A randomized, double-blind, placebo-controlled study to evaluate the impact of inhaled zanamivir treatment on workplace attendance due to influenza A and B infections	Glaxo Wellcome, 2000[33]
NAI30012	A double-blind, randomized, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered twice daily for five days in the treatment of symptomatic influenza A and B viral infections in subjects aged greater or equal to 65 years	Glaxo Wellcome, 2000[33]
NAI30015	A double-blind, randomized, placebo-controlled, parallel-group, multicenter 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 virus infections in armed services personnel	Glaxo Wellcome, 2000[33]
NAI30020	A double-blind, randomized, placebo-controlled, parallel-group, multicenter 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 virus infections in high risk patients	Glaxo Wellcome, 2000[33]
NAI30028	A double-blind, randomized, placebo-controlled, parallel-group, multicenter 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 virus infections in children	Glaxo Wellcome, 2000[33]
NAI40003	A prospective study of consumer comprehension of the patient instructional leaflet for Relenza (zanamivir for inhalation)	Glaxo Wellcome, 2000[33]
NAI40004	An open-label study evaluating the lung deposition of ^{99}mTc-zanamivir following orally inhaled administration via diskhaler in subjects with asthma and healthy volunteers	Glaxo Wellcome, 2000[33]
NAI40012	An open-label, multicenter study of the patient instructional leaflet for Relenza	Glaxo Wellcome, 2000[33]
NAI40015	A study to evaluate the practicability and potential cost-effectiveness of providing a Relenza influenza treatment programme for employees through occupational health at UK Glaxo Wellcome sites	Glaxo Wellcome, 2000[33]

continued

continued

Study ID	Title	Public domain data sources
NAIA1001	A study to investigate the effect of intranasal GR121167X on infection rates in healthy male volunteers when experimentally inoculated with influenza A/ Texas/91 (H1N1) virus	Glaxo Wellcome, 2000[33] Hayden *et al*., 1996[36] Hayden *et al*., 1996[37]
NAIA1002	A study to investigate the effect of intranasal GG167 initiated at various intervals post inoculation on infection in healthy volunteers when experimentally inoculated with influenza A/Texas/91 (H1N1) virus	Glaxo Wellcome, 2000[33] Hayden *et al*., 1996[36] Hayden *et al*., 1996[37]
NAIA1003	A study to investigate the effect of intranasal GG167 at various dosing frequencies on infection in healthy volunteers when experimentally inoculated with influenza A/Texas/91 (H1N1) virus	Glaxo Wellcome, 2000[33] Hayden *et al*., 1996[36] Hayden *et al*., 1996[37]
NAIA1004	A study to investigate the effect of intranasal GG167 as nasal drops and nasal spray on infection in healthy volunteers experimentally inoculated with influenza A/Texas/91 (H1N1) virus	Glaxo Wellcome, 2000[33] Hayden *et al*., 1996[36] Hayden *et al*., 1996[37]
NAIA1005	A study to investigate the effect of intranasal GG167 on infection in healthy volunteers experimentally inoculated with influenza B/Yamagata/16/88 virus	Glaxo Wellcome, 2000[33] Walker *et al*., 1997[38]
NAIA1006	A study to investigate the effect of intranasal GG167 on prevention of infection in healthy volunteers experimentally inoculated with influenza B/Yamagata/ 16/88 virus	Glaxo Wellcome, 2000[33] Hayden *et al*., 1996[37]
NAIA1008	Evaluation of reduced frequency of GG167 dosing in the intranasal challenge model in healthy volunteers inoculated with influenza A/Texas/91 (H1N1) virus	Calfee and Peng, 1999[39] Glaxo Wellcome, 2000[33]
NAIA1009	Pharmacokinetics of zanamivir (GG167) following inhaled administration in pediatric volunteers with signs and symptoms of respiratory illness	Glaxo Wellcome, 2000[33]
NAIA1010	Efficacy of zanamivir administered intravenously as repeated doses to healthy male volunteers inoculated with influenza A/Texas/91 (H1N1) virus	Calfee and Peng, 1999[40] Glaxo Wellcome, 2000[33]
NAIA2005	A double-blind, randomised, placebo-controlled, multicenter study to investigate the efficacy and safety of GG167 in the treatment of influenza A and B viral infection	FDA Center for Drug Evaluation and Research, 1999[41] Glaxo Wellcome, 2000[33] Hayden *et al*., 1997[42]
NAIA2006	A double-blind, randomized, placebo-controlled multicenter study to investigate the efficacy and safety of GG167 (zanamivir) therapy in the prevention of progression of influenza A and B viral infections	Glaxo Wellcome, 2000[33]
NAIA2008	A double-blind, randomised, placebo-controlled, multicentre, parallel-group study to investigate the efficacy and safety of GG167 administered twice or four times a day for the treatment of influenza A and B viral infections	Aoki *et al.,* 1997[43] FDA Center for Drug Eva1uation and Research, 1999[44] Glaxo Wellcome, 2000[33] Monto *et al*., 1999[45] Monto *et al*., 1999[46] Osterhaus *et al*., 1998[47]
NAIA2009	A double-blind, randomized, placebo-controlled, multicenter, parallel-group study to investigate the efficacy and safety of GG167 in the prevention and/or progression of influenza A and B viral infections	Glaxo Wellcome, 2000[33] Kaiser *et al*., 2000[48]
NAIA2010	Efficacy of zanamivir (GG167) in controlling nursing home influenza outbreaks	FDA Centre for Drug Evaluation and Research, 1999[49] Glaxo Wellcome, 2000[33] Schilling *et al*., 1998[50]
NAIA3002	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults	Boivin *et al*., 1999[51] FDA Center for Drug Evaluation and Research, 1999[52] Glaxo Wellcome, 2000[33] Lalezari *et al*., 1999[53] Lalezari *et al*., 1999[54] Monto *et al.,* 1999[45] Osterhaus *et al*., 1999[55]
NAIA3003	A double-blind, randomized, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day compared to the standard of care in controlling nursing home influenza outbreaks	Glaxo Wellcome, 2000[33]
NAIA3004	A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir 10 mg administered once a day in controlling nursing home influenza outbreaks	Glaxo Wellcome, 2000[33]

continued

continued

Study ID	Title	Public domain data sources
NAIA3005	A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered by inhalation once a day for 28 days in the prevention of symptomatic influenza A and B viral infections in community-dwelling adults	FDA Center for Drug Evaluation and Research, 1999[56] Glaxo Wellcome, 2000[33] Monto *et al.,* 1998[57] Monto *et al*., 1999[58] Monto *et al*., 1999[59]
NAIB1001	Pharmacoscintigraphic evaluation of lung deposition of GG167 inhaled from the diskhaler and the free flow powder system (FFPS) in healthy volunteers	Glaxo Wellcome, 2000[33]
NAIB1002	A study to evaluate the effect of repeat doses of GG167 dry powder on pulmonary function and bronchial hyper-responsiveness in asthmatic subjects	Glaxo Wellcome, 2000[33]
NAIB1003	A study to investigate the pharmacokinetics of GG167 in subjects with impaired renal function	Glaxo Wellcome, 2000[33]
NAIB1004	A positron emission tomography study to determine the deposition and disposition of 11C-zanamivir following administration as an intranasal spray	Glaxo Wellcome, 2000[33]
NAIB1005	A positron emission tomography study to determine the deposition and disposition of 11C-GG167 following administration as a dry powder using the free flow powder system (FFPS)	Glaxo Wellcome, 2000[33]
NAIB1007	A GG167 pharmacokinetic study to select a regimen for prophylaxis	Glaxo Wellcome, 2000[33]
NAIB1008	A study to evaluate the safety, tolerability and pharmacokinetics of GG167 administered intravenously and orally to healthy volunteers	Glaxo Wellcome, 2000[33]
NAIB1009	A study to evaluate the safety, tolerability and pharmacokinetics of zanamivir administered intravenously as repeated doses	Glaxo Wellcome, 2000[33]
NAIB2001	A double-blind, randomised, comparative, multicentre study to investigate the efficacy and safety of zanamivir (GR121167) administered by the inhaled and inhaled plus intranasal routes versus placebo in the treatment of adults with influenza	Glaxo Wellcome, 2000[33]
NAIB2002	A double-blind, randomised, comparative, multicentre study to investigate the efficacy and safety of zanamivir administered intranasally versus placebo in the prophylaxis of influenza	Glaxo Wellcome, 2000[33]
NAIB2003	Double-blind, randomised, comparative, multicentre study to investigate the efficacy and safety of GR121167 administered by inhaled and inhaled plus intranasal route versus placebo in the treatment of adults with influenza	Glaxo Wellcome, 2000[33]
NAIB2004	A double-blind, randomised, comparative, multicentre study to investigate the efficacy and safety of zanamivir administered intranasally versus placebo in the prophylaxis of influenza in adults	Glaxo Wellcome, 2000[33]
NAIB2005	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled and intranasal GG167 in the treatment of influenza A and B viral infections	Barnett *et al*., 2000[60] FDA Center for Drug Evaluation and Research, 1999[61] Glaxo Wellcome, 2000[33] Hayden *et al*., 1997[42] Monto *et al*., 1999[45] Osterhaus *et al*., 1999[55]
NAIB2006	Double-blind, randomised, placebo-controlled, multicentre study to investigate the efficacy and safety of inhaled zanamivir in preventing progression of influenza	Glaxo Wellcome, 2000[33]
NAIB2007	Double-blind, randomised, placebo-controlled, multicentre study to investigate the efficacy and safety of inhaled and inhaled plus intranasal GG167 in the treatment of influenza A and B viral infections	FDA Center for Drug Evaluation and Research, 1999[62] Glaxo Wellcome, 2000[33] Lalezari *et al*., 1999[53] Monto *et al*., 1999[45] Osterhaus *et al*., 1999[55]
NAIB2008	A double-blind, randomised, placebo-controlled, multicentre, parallel-group study to investigate the efficacy and safety of GG167 administered twice or four times a day for the treatment of influenza A and B viral infections	Aoki *et al.,* 1997[43] Barnett *et al*., 2000[60] FDA Center for Drug Evaluation and Research, 1999[44] Glaxo Wellcome, 2000[33] Monto *et al*., 1999[45] Monto *et al*., 1999[46] Osterhaus *et al*., 1998[47]

continued

continued

Study ID	Title	Public domain data sources
NAIB2009	A double-blind, randomized, placebo-controlled, multicenter, parallel-group study to investigate the efficacy and safety of GG167 in the prevention and/or progression of influenza A and B viral infections	Glaxo Wellcome, 2000[33] Kaiser *et al*., 2000[48]
NAIB3001	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) administered twice daily in the treatment of influenza A and B viral infections in adults	FDA Center for Drug Evaluation and Research, 1999[63] Glaxo Wellcome, 2000[33] Lalezari *et al*., 1999[53] Monto *et al*., 1999[45] Osterhaus *et al*., 1999[55] Silagy for the MIST Study Group, 1998[64] Silagy *et al*., 1998[65]
NAIB3002	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults	FDA center for Drug Evaluation and Research, 1999[66] Fleming, 1998[67] Glaxo Wellcome, 2000[33] Lalezari *et al*., 1999[53] Mäkelä *et al*., 2000[68] Monto *et al*., 1999[45] Osterhaus *et al.,* 1999[55]

o.d., once daily

Appendix 4

Publications mapped to studies reported

Reference	Studies reported
Aoki FY, Fleming DM, Lacey L, Keene O, Keech M, MacLeod P. Impact of treatment of influenza with zanamivir on patients' health status, sleep quality, productivity and healthcare use. In: Proceedings of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1997 Sept 28–Oct 1; Toronto, Canada. p. 384[43]	NAIA/B2008
Barnett JM, Cadman A, Gor D, Dempsey M, Walters M, Candlin A, *et al*. Zanamivir susceptibility monitoring and characterization of influenza virus clinical isolates obtained during Phase III clinical efficacy studies. *Antimicrob Agents Chemother* 2000;**44**:78–87[60]	NAIB2005, NAIB2008
Boivin G, Goyette N, Hardy I, Aoki F, Wagner A, Trottier S. Rapid antiviral effect of inhaled zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults. *J Infect Dis* 2000;**181**:1471–4[51]	NAIA3002 (subset)
Calfee DP, Peng A. Safety and efficacy of once daily intranasal zanamivir in preventing experimental human influenza A infection. *Antiviral Ther* 1999;**4**:143–9[39]	NAIA1008
Calfee DP, Peng A. Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 1999;**43**:1616–20[40]	NAIA1010
Fleming D. High risk and otherwise healthy patients demonstrate alleviation of influenza symptoms 2.5 days earlier following inhaled zanamivir treatment. In: Proceedings of the 36th Meeting of the IDSA; 1998 Nov 12–15; Denver, CO, USA. Abstract 78[67]	NAIB3002
Freund B, Gravenstein S, Elliott M, Miller I. Zanamivir: a review of clinical safety. *Drug Safety* 1999;**21**:267–81[69]	None
Hayden FG, Gubareva L, Klein T, Elliott M, Hammond J, Ossi M, *et al*. Inhaled zanamivir for preventing transmission of influenza in families. *N Engl J Med* 2000;**343**:1282–9[35]	NAI30010
Hayden FG, Lobo M, Hussey EK, Eason CU. Efficacy of intranasal GG167 in experimental human influenza A and B virus infection. In: Brown L, Hampson A, Webster R, editors. Options for the control of Influenza III. Amsterdam: Elsevier Science; 1996. p. 718–25[37]	NAIA1001–4, NAIA1006
Hayden FG, Osterhaus AD, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, *et al*. Efficacy and safety of the new neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Engl J Med* 1997;**337**:874–80[42]	NAIA2005, NAIB2005
Hayden FG, Treanor JJ, Betts RF, Lobo M, Esinhart JD, Hussey EK. Safety and efficacy of the neuraminidase inhibitor GG167 in experimental human influenza. *JAMA* 1996;**275**:295–9[36]	NAIA1001–4
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Appendix 5

Studies meeting the inclusion criteria for the all-adults review

Study ID*	Title	Phase	Influenza type
NAIA1001†	A study to investigate the effect of intranasal GR121167X on infection rates in healthy male volunteers when experimentally inoculated with influenza A/Texas/91 (H1N1) virus	I	Experimental
NAIA1002†	A study to investigate the effect of intranasal GG167 initiated at various intervals post inoculation on infection in healthy volunteers when experimentally inoculated with influenza A/Texas/91 (H1N1) virus	I	Experimental
NAIA1003†	A study to investigate the effect of intranasal GG167 at various dosing frequencies on infection in healthy volunteers when experimentally inoculated with influenza A/Texas/91 (H1N1) virus	I	Experimental
NAIA1004†	A study to investigate the effect of intranasal GG167 as nasal drops and nasal spray on infection in healthy volunteers experimentally inoculated with influenza A/Texas/91 (H1N1) virus	I	Experimental
NAIA1005‡	A study to investigate the effect of intranasal GG167 on infection in healthy volunteers experimentally inoculated with influenza B/Yamagata/16/88 virus	I	Experimental
JNAI-01	Inhaled and intranasal GG167 in the treatment of influenza A and B in Japan	II	Natural
NAIA2005	A double-blind, randomised, placebo-controlled, multicentre study to investigate the efficacy and safety of GG167 in the treatment of influenza A and B viral infection	II	Natural
NAIA/B2008	A double blind, randomised, placebo controlled, multicenter, parallel-group study to investigate the efficacy and safety of GG167 administered twice or four times a day for the treatment of influenza A and B viral infections	II	Natural
NAIB2001	A double-blind, randomised, comparative, multicentre study to investigate the efficacy and safety of zanamivir (GR121167) administered by the inhaled and inhaled plus intranasal routes versus placebo in the treatment of adults with influenza	II	Natural
NAIB2003	Double-blind, randomised, comparative, multicentre study to investigate the efficacy and safety of GR121167administered by inhaled and inhaled plus intranasal route versus placebo in the treatment of adults with influenza	II	Natural
NAIB2005	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled and intranasal GG167 in the treatment of influenza A and B viral infections	II	Natural
NAIB2007	Double-blind, randomised, placebo-controlled, multicentre study to investigate the efficacy and safety of inhaled and inhaled plus intranasal GG167 in the treatment of influenza A and B viral infections	II	Natural
NAI30010	A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within families (Note: data from index cases included for treatment review)	III	Natural
NAIA3002	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults	III	Natural
NAIB3001	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) administered twice daily in the treatment of influenza A and B viral infections in adults	III	Natural
NAIB3002	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults	III	Natural

* *See appendix 3 for references for each study*
† *These trials are treated as one study for the purpose of this review*
‡ *Although these trials appeared to meet the inclusion criteria, the results were not available in published or unpublished form and data from them are not included in the review*

Appendix 6

Included studies for the at-risk adults review

Study ID*	Title	Phase	Influenza type
NAIA/B2008	A double-blind, randomised, placebo-controlled, multicentre, parallel-group study to investigate the efficacy and safety of GG167 administered twice or four times a day for the treatment of influenza A and B viral infections	II	Natural
NAIB2007	Double-blind, randomised, placebo-controlled, multicentre study to investigate the efficacy and safety of inhaled and inhaled plus intranasal GG167 in the treatment of influenza A and B viral infections	II	Natural
NAI30008	A double-blind, randomized, placebo-controlled, parallel group, multicenter study to investigate the efficacy and safety of zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of influenza in patients 12 years or over with asthma or chronic obstructive pulmonary disease (COPD)	III	Natural
NAI30010	A double-blind, randomized, placebo-controlled, parallel-group, multicenter study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered once a day for 10 days in the prevention of transmission of symptomatic influenza A and B viral infections within families (Note: data from at-risk index cases included for treatment review)	III	Natural
NAIA3002	A double blind, randomised, placebo-controlled, parallel group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults	III	Natural
NAIB3001	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) administered twice daily in the treatment of influenza A and B viral infections in adults	III	Natural
NAIB3002	A double-blind, randomised, placebo-controlled, parallel-group, multicentre study to investigate the efficacy and safety of inhaled zanamivir (GG167) 10 mg administered twice a day for five days in the treatment of symptomatic influenza A and B viral infections in adolescents and adults	III	Natural

* *See appendix 3 for references for each study*

Appendix 7

Excluded studies with reason for exclusion

Study ID*	Reason for exclusion
NAI10901	No relevant outcomes (Phase I)
NAI10902	No relevant outcomes (Phase I)
NAI30009	Paediatric trial
NAI30011	Not completed at 31st March 2000
NAI30012	Not completed at 31st March 2000
NAI30015	Not completed at 31st March 2000
NAI30020	Not completed at 31st March 2000
NAI30028	Paediatric trial (not completed at 31st March 2000)
NAI40003	Not a clinical trial
NAI40004	Not a controlled trial (Phase I)
NAI40012	Not a clinical trial
NAI40015	Not completed at 31st March 2000
NAIA1005	No information about results of trial available
NAIA1006	Prevention trial
NAIA1008	Prevention trial
NAIA1009	Paediatric trial
NAIA1010	Prevention trial
NAIA2006	Prevention trial? (title states that it is about "preventing progression" of influenza.[71] No published or unpublished data was made available to confirm this was not a treatment trial. One of the main outcomes was time to alleviation of symptoms; *n* = 16)
NAIA2009	Prevention trial
NAIA2010	Prevention trial
NAIA3003	Prevention trial
NAIA3004	Prevention trial
NAIA3005	Prevention trial
NAIB1001	Not a controlled trial (Phase I)
NAIB1002	No relevant outcomes (Phase I)
NAIB1003	No relevant outcomes (Phase I)
NAIB1004	Not a controlled trial (Phase I)
NAIB1005	Not a controlled trial (Phase I)
NAIB1007	No relevant outcomes (Phase I)
NAIB1008	No relevant outcomes (Phase I)
NAIB1009	No relevant outcomes (Phase I)
NAIB2001	No information about results of trial available
NAIB2002	Prevention trial (title implies it is a prophylaxis trial, however, the main outcome was time to alleviation of symptoms.[72] No published or unpublished data about this trial was made available to confirm that there was not a treatment arm; *n* = 100)
NAIB2003	No information about results of trial available
NAIB2004	Prevention trial (title implies it is a prophylaxis trial, however, the main outcome was time to alleviation of symptoms.[73] No published or unpublished data about this trial was made available to confirm that there was not a treatment arm; *n* = 167)
NAIB2006	Prevention trial (title states that it is about "preventing progression" of influenza.[71] No published or unpublished data was made available to confirm this was not a treatment trial; *n* = 63)
NAIB2009	Prevention trial

* *See appendix 3 for references for each study*

Appendix 8

Validity of included RCTs

Study ID*	Truly random allocation	Was concealment adequate?	Was treatment allocation masked for:			Significant differences in completion rates between arms?	Jadad score
			Participants	Investigators	Assessors		
JNAI-01	Yes	Yes	Yes	Unclear	Unclear	No	4
NAI30010	Yes	Yes	Yes	Yes	Yes	No	5
NAIA1001–4	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	2
NAIA1005	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	2
NAIA2005	Yes	Yes	Yes	Yes	Yes	No	5
NAIA3002	Yes	Yes	Yes	Yes	Yes	No	5
NAI30008	Yes	Yes	Yes	Yes	Yes	No	5
NAIA/B2008	Yes	Yes	Yes	Yes	Yes	No	5
NAIB2001	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	2
NAIB2003	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	2
NAIB2005	Yes	Yes	Yes	Yes	Yes	No	5
NAIB2007	Yes	Yes	Yes	Yes	Yes	No	5
NAIB3001	Yes	Yes	Yes	Yes	Yes	No	5
NAIB3002	Yes	Yes	Yes	Yes	Yes	No	5

* *See appendix 3 for references for each study*

Appendix 9

Dosages and formulations used in included treatment trials of healthy adults

Study ID*	Total number of patients	Total number receiving zanamivir	Number receiving zanamivir					Number receiving placebo
			10 mg inhaled b.d. for 5 days	10 mg inhaled + 6.4 mg i.n. b.d for 5 days	10 mg inhaled + 6.4 mg i.n. q.d. for 5 days	16 mg inhaled six times daily for 4 days	16 mg inhaled b.d. for 4 days	
JNAI-01	116	77	37	40	NA	NA	NA	39
NAI30010	321	163	163	NA	NA	NA	NA	158
NAIA1001–4	57† (IPP)	31† (IPP)	NA	NA	NA	20	11	26
NAIA2005	220	139	68	71	NA	NA	NA	81
NAIA3002	777	412	412	NA	NA	NA	NA	365
NAIA/B2008	1256	834	NA	419	415	NA	NA	422
NAIB2005	197	134	64	70	NA	NA	NA	63
NAIB2007	554	371	188	183	NA	NA	NA	183
NAIB3001	455	227	227	NA	NA	NA	NA	228
NAIB3002	356	174	174	NA	NA	NA	NA	182
Total	4309	2562	1333	783	415	20	11	1747

* *See appendix 3 for references for each study*
† *Number receiving treatment < 48 hours after onset of symptoms. Data only available for the influenza-positive participants*
i.n., intranasal/intranasally; q.d., four times daily

Appendix 10

Key characteristics of the RCTs meeting the inclusion criteria

Study ID*	Formulation	*n*	Patient characteristics	Treatment arms and number recruited	Treatment duration	Follow-up	Comments
JNAI-01	Inhaled and i.n.	116	Previously healthy adults aged 16–65 years presenting with ILI for < 36 hours in an area where an epidemic was judged to have broken out	Placebo (*n* = 39) Zanamivir 10 mg inhaled b.d. (*n* = 37) Zanamivir 10 mg inhaled b.d. + 6.4 mg i.n. b.d. (*n* = 40)	5 days	28 days	Naturally acquired influenza
NAI30008	Inhaled	525	People aged ≥ 12 years with underlying asthma and COPD presenting with ILI of < 36 hours	Placebo (*n* = 263) Zanamivir 10 mg inhaled b.d. (*n* = 262)	5 days	28 days	Naturally acquired influenza
NAI30010 (index case data only)	Inhaled	321	Subjects had to be aged > 5 years and able to take the first dose of medication within 36 hours of ILI symptom onset in index cases. ILI was defined as the presence of ≥ two of the following: fever ≥ 37.8°C, cough, headache, sore throat, myalgia or feverishness. In some centres, only index cases confirmed to be influenza-positive were enrolled in the study	Placebo b.d. (*n* = 158) Zanamivir 10 mg inhaled b.d. (*n* = 163)	5 days	14 days	Naturally acquired influenza. An RCT to investigate the efficacy and safety of inhaled zanamivir 10 mg o.d. for 10 days in the prevention of transmission of influenza A and B within families. Data from treatment of index cases were included in the review. Families had to have two to five members living at home for the duration of the study, with ≥ one adult (aged ≥ 18 years) and one child (aged 5–17 years)
NAIA1001–4	i.n. drops	103 (69 IPP)	Healthy young adults susceptible to challenge virus inoculated with influenza A (H1N1) by nasal drops	Placebo (*n* = 26 IPP) Zanamivir 16 mg i.n. six times daily (*n* = 20 IPP) Zanamivir 16 mg i.n. b.d. commencing 26 or 32 hours after inoculation (*n* = 11 IPP) Zanamivir 16 mg i.n. six times daily commencing 50 hours after inoculation (*n* = 12 IPP)	4 days	8 days	Four trials reported together examining both treatment and prevention in experimental influenza in healthy susceptible volunteers. Compared i.n. zanamivir when begun as early or delayed treatment following viral inoculation. Reports results for IPP only. Baseline characteristics are compared across both treatment and prevention trials combined
NAIA1005	i.n. drops	32	Healthy adults	Placebo b.d. (*n* = not available) Zanamivir 3.2 mg i.n. b.d. (*n* = not available) Zanamivir 6.4 mg i.n. b.d. (*n* = not available)	Not available	Not available	No information on outcomes found in publications and no unpublished data made available
NAIA2005	i.n. spray and inhaler	417	Previously healthy adults (aged ≥ 13 years) with ILI of ≤ 48 hours duration during documented influenza virus circulation in the community	Placebo (*n* = 81) Zanamivir 10 mg inhaled b.d. (*n* = 68) Zanamivir 10 mg inhaled b.d. + 6.4 mg i.n. b.d. (*n* = 71)	5 days	28 days	Naturally acquired influenza
NAIA3002	Inhaled	777	ILI ≤ 48 hours duration	Placebo (*n* = 365) Zanamivir 10 mg inhaled b.d. (*n* = 412)	5 days	28 days	Naturally acquired influenza

continued

Study ID*	Formulation	*n*	Patient characteristics	Treatment arms and number recruited	Treatment duration	Follow-up	Comments
NAIA/B2008	i.n. spray + inhaled	1256	Patients with ILI for < 48 hours	Placebo (*n* = 422) Zanamivir 10 mg inhaled b.d. + 6.4 mg i.n. b.d. (*n* = 419) Zanamivir 10 mg inhaled q.d. + 6.4 mg i.n. q.d. (*n* = 415)	5 days	21 days	Naturally acquired influenza. Compared the efficacy of b.d. to q.d. regimens in treating acute influenza
NAIB2001	i.n. and i.n. + inhaled	22	Not available	Not available	Not available	Not available	No publication of results and no unpublished data made available
NAIB2003	i.n. and i.n. + inhaled	133	Not available	Not available	Not available	Not available	No publication of results and no unpublished data made available
NAIB2005	i.n. spray and inhaler	417	ILI of ≤ 48 hours duration	Placebo (*n* = 63) Zanamivir 10 mg inhaled b.d. (*n* = 64) Zanamivir 10 mg inhaled b.d. + 6.4 mg i.n. b.d. (*n* = 70)	5 days	28 days	Naturally acquired influenza
NAIB2007	i.n. inhaler	554	Patients aged ≥ 13 years with symptoms of feverishness and ≥ two of the following for ≤ 48 hours duration: headache, myalgia, cough or sore throat	Placebo (*n* = 183) Zanamivir 10 mg inhaled b.d. (*n* = 188) Zanamivir 10 mg inhaled b.d. + 6.4 mg i.n. b.d. (*n* = 183)	5 days	5 days	Naturally acquired influenza
NAIB3001	Inhaled	455	Previously healthy individuals aged > 12 years presenting with ILI of ≤ 36 hours duration when influenza activity seen to be increasing in the community	Placebo (n = 228) Zanamivir 10 mg inhaled b.d. (n = 227)	5 days	14 days	Naturally acquired influenza
NAIB3002	Inhaled	356	ILI of ≤ 48 hours duration	Placebo (*n* = 182) Zanamivir 10 mg inhaled b.d. (*n* = 174)	5 days	28 days	Naturally acquired influenza

* *See appendix 3 for references for each study*

Appendix 11

Common adverse events

Study ID*		Adverse event† (*n* (%))				
		Nausea and vomiting	Other gastrointestinal	Respiratory	Skin	Any adverse event
JNAI-01	Placebo (*n* = 39)	NA	NA	NA	NA	8 (21%)
	Zanamivir (*n* = 77)	NA	NA	NA	NA	15 (19%)
NAI30008	Placebo (*n* = 261)	Nausea = 15; vomiting = 7	39	79	14	159 (61%)
	Zanamivir (*n* = 263)	Nausea = 6; Vomiting = 3	31	77	10	157 (60%)
NAI30010	Placebo (*n* = 160)	Nausea = 5; vomiting = 3	11	8	3	84 (53%)
	Zanamivir (*n* = 161)	Nausea = 1; vomiting = 1	11	6	5	72 (45%)
NAIA1001–4	Placebo	NA	NA	NA	NA	NA
	Zanamivir	NA	NA	NA	NA	NA
NAIA2005	Placebo (*n* = 81)	11	17	8	0	51 (63%)
	Zanamivir (*n* = 138)	30	38	20	6	99 (72%)
NAIA3002	Placebo (*n* = 365)	19	42	37	12	136 (37%)
	Zanamivir (*n* = 412)	12	42	32	10	126 (31%)
NAIA/B2008	Placebo (*n* = 422)	14	Any GI event = 38	29	14	139 (33%)
	Zanamivir (*n* = 834)	20	Any GI event = 62	29	15	239 (29%)
NAIB2005	Placebo (*n* = 62)	5	Any GI event = 6	3	1	25 (40%)
	Zanamivir (*n* = 134)	2	Any GI event = 13	3	1	37 (28%)
NAIB2007	Placebo (*n* = 180)	2	Any GI event = 8	20	5	65 (36%)
	Zanamivir (*n* = 369)	11	Any GI event = 36	26	9	130 (35%)
NAIB3001	Placebo (*n* = 228)	8	Any GI event = 20	50	7	98 (43%)
	Zanamivir (*n* = 227)	4	Any GI event = 11	29	5	83 (37%)
NAIB3002	Placebo (*n* = 182)	5	15	20	4	63 (35%)
	Zanamivir (*n* = 174)	4	12	8	4	44 (25%)
Combined	Placebo (*n* = 1980)	–	196 (10%)	254 (13%)	60 (3%)	828 (42%)
	Zanamivir (*n* = 2789)	–	256 (9%)	230 (8%)	65 (2%)	1002 (36%)

* *See appendix 3 for references for each study*

† *Adverse events are reported by safety population (i.e. by those actually receiving the treatment) so that the denominators may vary from those recorded for the ITT analysis for effectiveness*

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We look forward to hearing from you.

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