

Antiviral drugs for the treatment of influenza: A Systematic Review and Economic Evaluation

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1 List of abbreviations

CDSC	Communicable Disease Surveillance Centre
CDC	Centre for Disease Control and Prevention
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHE	Centre for Health Economics
CI	Confidence interval
CNS	Central nervous system
COA(P)D	Chronic obstructive airways (pulmonary) disease
CRD	Centre for Reviews and Dissemination
CrI	Credibility interval
CRISP	Computer Retrieval of Information on Scientific Projects
DARE	Database of Abstract of Reviews of Effects
DIC	Deviance Information Criterion
DoH	Department of Health
ECDC	European Centre for Disease Prevention and Control
EISS	European Influenza Surveillance Scheme
EQ-5D	EuroQoL 5-dimension measure of health-related quality of life
FDA	Food and drug administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GP	General practice/practitioner
GPRD	General Practice Research Database
GSK	GlaxoSmithKline
H1,2 or 3	Haemagglutinin subtype 1, 2 or 3
HPA	Health Protection Agency
HRG	Health Resource Group

HRQoL	Health related quality of life
HTA	Health Technology Assessment
HUI-3	Health Utilities Index Mark 3
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ILI	Influenza-like illness
ITU	Intensive therapy unit
ITT	Intention to treat
ITTI	Intention to treat, infected (those with confirmed influenza)
LRTI	Lower respiratory tract infection
MCMC	Markov Chain Monte Carlo
MeSH	Medical subject headings in the MEDLINE thesaurus
MOSA	Medical Officers of Schools Association
MVH	Measurement and Valuation of Health study
N1 or 2	Neuraminidase subtype 1 or 2
N/A	Not available
NAMCS	National Ambulatory Medical Care Survey
NHS	National Health Service
NI	Neuraminidase inhibitor
NIC	National Influenza Centre
NICE	National Institute for Health and Clinical Excellence
NPHS	National Public Health Service
NR	Not reported
NRR	National Research Register
OR	Odds ratio
OTC	Over the counter
PPV	Positive predictive value
QALD	Quality-adjusted life days

QALY	Quality-adjusted life year
QoL	Quality of Life
RCGP	Royal College of General Practitioners
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RSV	Respiratory Syncytial Virus
RTI	Respiratory tract infection
SARS	Severe acute respiratory syndrome
SAVE	Simulating Anti-influenza Value and Effectiveness model
ScHARR	Sheffield School of Health and Related Research
SD	Standard deviation
SE	Standard error
SPC	Summary of Product Characteristics
TA58	Technology Assessment No. 58
TTO	Time Trade Off
UK	United Kingdom
URTI	Upper respiratory tract infection
US(A)	United States (of America)
VAS	Visual analogue scale
WHO	World Health Organisation
WMD	Weighted median difference
WRS	Weekly Returns Service

2 Executive summary

2.1 Background

Influenza is a viral infection of the respiratory tract causing an acute, febrile illness. Outbreaks follow a seasonal pattern, concentrated in winter, and vary in distribution and severity between years. Symptoms include fever, cough, nasal congestion, headache, sore throat, fatigue, and joint and muscle aches. In otherwise healthy populations, symptoms are usually self-limiting.

However, in vulnerable populations such as the elderly, chronically ill, or immunocompromised, the illness may be prolonged and the development of serious complications more common. In England and Wales, influenza is thought to be responsible for over 10,000 deaths from respiratory disease annually.

For periods in which influenza is reported to be ‘circulating in the community’, existing NICE guidance recommends the use of antiviral treatment (either oseltamivir or zanamivir) only in ‘at risk’ populations as defined by the Department of Health Green Book. Since this guidance was issued, the marketing authorisation for zanamivir has been extended to include children aged 5 years and over. This review provides an updated assessment of new and existing evidence for the clinical and cost-effectiveness of antivirals (oseltamivir, zanamivir and amantadine) for the treatment of influenza.

2.2 Objectives

The objective of this review is to evaluate the clinical effectiveness (including adverse events) and cost-effectiveness of antivirals for the treatment of naturally acquired influenza. Where appropriate, this evaluation also considers these issues for the separate ‘at risk’ and otherwise healthy populations.

2.3 Methods

Systematic reviews of the evidence on the clinical and cost-effectiveness of antivirals for the treatment of influenza were undertaken. In addition, an independent decision model was developed to evaluate the cost-effectiveness of antiviral treatment from the perspective of the National Health Service. Data for the review were sought systematically from eleven electronic databases, including those specific to adverse event data, and the grey literature. In addition, trial reports and extra data were provided by GlaxoSmithKline (zanamivir) and Roche (oseltamivir).

Randomised controlled trials (RCTs) comparing antivirals with each other, placebo, or best symptomatic care were included in the evaluation of clinical effectiveness in patients presenting with an influenza-like illness (ILI). Where appropriate, standard meta-analytic techniques were applied to data stratified by the following patient groups: otherwise healthy adults, ‘at risk’, the elderly, children, and the overall population. The primary outcomes considered were measures of symptom duration (median time to alleviation of symptoms and median time to return to normal activity). Incidence of complications, mortality, hospitalisations, antibiotic use (as a surrogate for complications) and adverse events were also assessed. Pooled odds ratios or weighted median differences, with 95% confidence intervals, were estimated. Analyses were carried out for both the ITT (intention to treat) and ITTI (intention to treat, confirmed, influenza-infected) populations wherever possible.

In the absence of head-to-head evidence on the relative effectiveness of the alternative antiviral treatments, an indirect comparison was also undertaken using Bayesian approaches to characterise the joint distribution of the efficacy of the antiviral treatments in terms of symptom duration. These estimates were subsequently used to inform the independent economic model which provided an overall framework for combining data from the synthesis of symptom outcomes, with the wider data on complications and other relevant parameters required for cost-effectiveness considerations.

2.4 Results

Clinical effectiveness results

Literature searches yielded 1061 references and 100 potentially relevant full papers that were subsequently retrieved and screened. Amantadine was excluded at an early stage of the review owing to a lack of any new trials that met the inclusion criteria and the limitations of the existing evidence. The earlier review noted both the poor quality of amantadine trial data and its lack of comparability with other antiviral treatments; this was reflected in the previous NICE guidance which did not recommend amantadine for the treatment of influenza. This review therefore focussed on the neuraminidase inhibitors (NIs), oseltamivir and zanamivir.

Twenty nine RCTs were included in the final assessment of clinical effectiveness. Fourteen of these were additional to those considered in the previous review; six RCTs of zanamivir (three in healthy adults, one in the elderly, one in ‘at risk’ adults and one in children which included a minority of ‘at risk’ participants), and eight of oseltamivir (four in healthy adults, one in an ‘at risk’ population of undefined age, one in ‘at risk’ children and two in adult populations which included both healthy and ‘at risk’ individuals). The RCTs included were of variable quality and

the completeness of follow-up was an issue in many; despite the trials' short duration (up to 28 days) only half the studies achieved follow-up of at least 95% of the participants.

Both zanamivir and oseltamivir were found to be effective in reducing symptom duration, as measured by time to alleviation of symptoms and/or time to return to normal activity.

In healthy adults, zanamivir reduced the median duration of symptoms by between approximately 0.5 and 1 day, and oseltamivir by between 0.5 and 1.5 days; the median reduction in the time taken to return to normal activity was about 0.5 days with zanamivir and approximately 1.5 to 2.5 days with oseltamivir.

For the 'at risk' subgroups, effect sizes for differences in symptom duration were generally larger, and potentially more clinically significant, than those seen in healthy adults. However, there was greater uncertainty around these results with estimates often failing to reach statistical significance, although the direction of effect remained in favour of treatment with NIs. For the overall 'at risk' population, treatment reduced the median duration of symptoms by approximately 1 to 2 days with zanamivir, and by 0.5 to 0.75 days with oseltamivir. A similar pattern was seen in the time taken to return to normal activity, with the median time being between 1 and 2 days with zanamivir and 0.75 and 2.5 (data for 'at risk' adults only) days with oseltamivir.

As might be expected, estimates derived from ITTI populations generally produced greater reductions than those produced from ITT populations. Similarly, the time to return to normal activities was generally longer than that to resolution of symptoms.

Estimates of clinical effectiveness in reducing symptoms derived from the standard meta-analysis were broadly consistent with the results derived from the Bayesian synthesis. However, the "borrowing of strength" and consideration of the number still ill at end of follow up, increased the precision of the subsequent estimates of effect sizes derived from the multi-parameter synthesis model in particular populations (particularly 'at risk' populations). Across both symptom measures and populations, the probability that NI treatment was more effective than placebo was 100%. In otherwise healthy adults, oseltamivir consistently had a higher probability of being the better treatment. In 'at risk' populations, zanamivir consistently had a higher probability of being better. The results for the otherwise healthy children were more varied across the separate analyses due to more limited data available. However, the strength of these findings needs to be considered in relation to the indirect nature of these comparisons and the clinical (and biological) plausibility of these results.

Where data were available for adverse events and complication rates, there was little overall difference associated with the use of either zanamivir or oseltamivir when compared individually to placebo. However, data were reported for few trials, studies were not designed to detect changes in these outcomes and the numbers of events were generally very small. The most consistent data and strongest evidence related to antibiotic use, with both zanamivir and oseltamivir resulting in statistically significant reductions in antibiotic use.

Cost effectiveness results

The results from the cost-effectiveness model demonstrated important variation across the separate populations in terms of the cost-effectiveness estimates. In general, the estimates were more favourable in 'at risk' populations compared to the otherwise healthy populations. Within each of the separate 'at risk' populations considered, zanamivir appeared the optimal NI treatment based on cost-effectiveness considerations. In contrast, oseltamivir was considered the optimal NI treatment for healthy populations (both adults and children). However, the overall differences between the NIs, in terms of the absolute estimates of both costs and outcomes, were minor across all populations.

The overall conclusions and cost-effectiveness estimates in the 'at risk' populations appeared remarkably robust to a wider range of alternative assumptions. The cost-effectiveness results for the otherwise healthy populations were less robust to these alternative assumptions with many scenarios reporting incremental cost-effectiveness estimates over £20,000 per QALY.

2.5 Discussion

The clinical effectiveness data for population subgroups, used to inform the multi-parameter evidence synthesis and cost-effectiveness modelling, were, in places, limited and this should be borne in mind when interpreting the findings of this review. Trials were often not designed to determine clinical effectiveness in population subgroups and hence, though the direction of effect was clear, estimates of differences in symptom duration tended to be subject to greater uncertainty in subgroups. This limitation was more apparent for data on the rates of complications; studies whose sample size and duration were not designed to detect these outcomes resulted in low event rates and relatively weak evidence, even when available data were combined in meta-analyses. However, despite these concerns, the use of NIs in 'at risk' populations appeared a cost-effective approach for the treatment of influenza.

The main areas of outstanding uncertainty are:

- The impact of NI treatments on the rates of complications, hospitalisation and mortality associated with influenza.
- The uncertainty surrounding the effect size of antiviral drugs in ‘at risk’ populations.
- The relative effectiveness of the separate NIs.
- The probability that a patient presenting to a healthcare provider has true influenza as opposed to other ILI and the impact of this upon clinical and cost-effectiveness of NIs.
- The impact on quality of life of influenza symptoms and the relative effect of NI treatments on this aspect.

A well-designed, adequately powered head-to-head trial (with a placebo arm), in a representative ‘at risk’ population (with sufficient follow-up time to also evaluate complications) would reduce the uncertainty around the estimates of clinical effectiveness of antiviral drugs in this population. However, the conduct of such a trial would need to be carefully assessed in terms of the cost-effectiveness of the research itself, as well as the potential feasibility and ethical issues (i.e. the inclusion of a placebo arm) which may arise. Well-designed observational studies might also be considered to evaluate the impact of NI treatments on complications, hospitalisation and mortality as well as quality of life.

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3 Background

3.1 Description of health problem

3.1.1 The influenza virus

The influenza virus is a single-stranded ribonucleic acid (RNA) virus of the family Orthomyxoviridae. There are three types of influenza virus that are classified according to their core proteins;¹ types A, B and C. Only A and B cause the large outbreaks that are familiar during the winter season,² with influenza A occurring more frequently, and being more virulent, than influenza B.³ Type C influenza is poorly understood and tends to cause sporadic subclinical infection,¹ therefore the review will concentrate on types A and B. Influenza A and B viruses have two surface glycoproteins, haemagglutinin and neuraminidase, which stimulate an immune response and are used to classify influenza viruses into subtypes.¹ Neuraminidase inhibition is the mode of action of the antiviral drugs most commonly used to treat influenza. There are 15 subtypes of the influenza A haemagglutinin and nine subtypes of the neuraminidase; of these, three haemagglutinin (H1/2/3) and two neuraminidase (N1/2) subtypes have formed stable lineages in humans.² There is only one subtype of influenza B.² Three subtypes of influenza A which do not normally use humans as a natural host, H5N1, H7N7 and H9N2, have recently caused outbreaks of 'bird flu' in humans.² The influenza virus frequently mutates at antibody binding sites, producing new strains that can evade the body's immune system (antigenic drift).⁴ Antigenic drift occurs in all strains of influenza A and B, although the rate at which it occurs varies depending on the strain.⁴ Influenza A is also subject to antigenic shift, where there is genetic recombination in which the haemagglutinin, and sometimes the neuraminidase, subtype is replaced with a new subtype; this can result in pandemics of the new strain, and potentially substantial increases in influenza-related deaths world-wide.⁴

3.1.2 Clinical presentation and diagnosis

Influenza can cause annual outbreaks of varying distribution and degrees of severity. The period of heightened surveillance activity in the UK is from week 40 to week 20 of the calendar year (October to May).⁵ Influenza outbreaks have tended to have a sudden onset, peaking rapidly over a period of a few weeks, and disappearing gradually over several months.¹ More recently, the increase in activity has been slower, with low peaks of activity. In England and Wales, nine of the 11 years from 1990 to 2000 have seen significant outbreaks of influenza A, and four outbreaks of influenza B; two years had outbreaks of both influenza A and B. Since 1990, approximately 74% of influenza has been caused by type A, with the seasonal rates varying between 20% to 97%.³

The most commonly reported symptoms of influenza are cough and/or fever,^{2,6,7} with nasal congestion, headache, sore throat, fatigue, joint and muscle aches also common.⁶ The incubation period of influenza ranges from 1 to 7 days, but most commonly lasts for 2 to 3 days.^{1,3,6} In healthy adults, the symptoms usually last for up to 8 days and resolve without treatment.⁶ For the elderly and people with comorbid conditions or who are immunocompromised, the illness may be more prolonged, and influenza-related complications (for example pneumonia) more likely to occur.⁶ There are a number of case definitions that assist in the identification of influenza-like illnesses from presenting symptoms (examples are given in Box 1), however, it is difficult to give a positive diagnosis of influenza based on these alone. For example, one study showed that of 207 hospitalised patients who tested positive for influenza, only 51% would have passed the Centre for Disease Control and Prevention (CDC) case definition for an influenza-like illness (ILI).⁷ A second study showed that of 79 patients that passed the NIVEL criteria, 52% were confirmed with influenza A, and of 72 patients that passed the ICHPPC-2 criteria, 54% had influenza A. In contrast, 76% of the patients with influenza A were correctly diagnosed by the GP's opinion of the aetiology of the illness.⁸

There are a range of rapid diagnostic tests for influenza that can provide results within 30 minutes. These either: detect influenza but do not distinguish between types; detect one or other influenza type; or can distinguish between influenza A and B. Most rapid tests are immunoassays, which detect influenza viral antigen, but Z-Stat Flu detects viral neuraminidase activity. According to the CDC, the sensitivity and specificity of rapid tests compared with viral culture vary, with median sensitivities of approximately 70-75%, and specificities approximately 90-95%, however, these values may be less in the elderly where viral shedding may be lower.⁹

Laboratory tests include enzyme-linked immunosorbant assay (ELISA), direct immunofluorescence (DIF), viral culture, polymerase chain reaction (PCR) and serologic testing. Each laboratory technique has advantages and disadvantages. ELISA is frequently used as it is fairly simple and rapid (up to 2 hours), but does not provide information about the type of influenza. Viral culture has high specificity and sensitivity, and is identified by the CDC as the reference standard, but takes up to 7 days for a diagnosis to be made.⁹ Some PCR methods can be rapid (giving results within 2 to 4 hours, although feedback of the results to a GP may take longer) and is more sensitive than cell culture, particularly in the elderly where viral shedding may be lower, but it is expensive and requires specialised laboratory equipment and personnel. Serologic testing is used for epidemiological evaluation but clinical application is limited as the diagnosis takes at least two weeks. DIF is not used routinely as it requires skilled technicians to

undertake the processing required. PCR is the standard test for influenza in reference laboratories in the UK.

Box 1. Case definitions for influenza-like illnesses

Netherlands Institute of Primary Health Care (NIVEL)

Acute onset (a prodromal stage of no more than 4 days)

Rectal temperature of at least 38°C

and at least one of the following symptoms:

Cough

Coryza (inflamed mucus membranes)

Sore throat

Frontal headache

Retrosternal pain

Myalgia

**Classification Committee of the World Organisation of Family Doctors (WONCA),
ICHPPC-2**

Either:

Influenza epidemic present

plus 4 of the following 9 criteria:

Sudden onset (within 12 hours)

Cough

Rigors and chills

Fever

Prostration and weakness

Headache

Myalgia

Widespread aches and pain

No significant physical signs other than redness of nasal mucous membrane and throat

Influenza in close contact

Or:

The absence of an influenza epidemic, plus any 6 of the above 9 criteria.

Centre for Disease Control and Prevention (CDC)

Temperature of 37.8C

plus either a cough or sore throat.

3.1.3 Mode of transmission

Secretions expelled during coughing and sneezing that are heavily laden with the influenza virus are the primary mode of transmission.^{1,10} This means that transmission is most rapid and effective in crowded areas or where ventilation is poor. Viral shedding peaks and remains high for approximately 24 to 72 hours after the onset of symptoms, decreasing to low values by day 5, in otherwise healthy adults.² Children and immunocompromised patients may show prolonged viral shedding, beyond the seven days normally considered the time of infectivity, therefore potentially increasing the time over which influenza can be transmitted.^{2,11}

3.1.4 Burden of influenza on the NHS

A recent study by Pitman and colleagues (2006) used data from the Health Protection Agency (HPA) Centre for Infections, the General Practice Research Database (GPRD), Hospital Episodes Statistics (HES), and the Office for National Statistics in a multiple linear regression analysis to determine the burden of influenza in terms of general practice and hospital admissions in England and Wales.¹² The results of this study estimated that 585,000 (95% CI: $\pm 169,000$) general practice consultations, 19,000 (95% CI: ± 5000) hospital admissions and 9700 (95% CI: ± 800) deaths from respiratory disease can be attributed to influenza A annually.¹² The burden of influenza B was lower, estimated to cause 194,000 (95% CI: $\pm 89,000$) general practice consultations and 800 (95% CI: ± 300) deaths from respiratory disease, annually.¹² Although most of the burden of influenza was in those under 45 years of age, most of the hospitalisations were in the elderly.¹² Table 3.1 gives the frequency of hospitalisations as reported in the current NICE guidance, and clearly shows the increased hospitalisation rates for people aged 65 years and over, particularly those at higher risk due to co-morbid conditions.³ Influenza B primarily affects school-age children, and therefore when influenza B is the predominant virus circulating in the community, excess hospital admissions in the elderly tend to be lower, compared to years when influenza A is circulating.¹³

Table 3.1: The frequency of hospital admissions for different age and risk groups as reported in the NICE guidance³

Risk/age group	Frequency of hospital admissions
High-risk patients aged 75 years or more	1 in 24 people with influenza (4.2%)
Low-risk patients aged 75 or more	1 in 89 (1.1%)
High-risk patients aged 65 to 75 years	1 in 42 (2.4%)
Low-risk patients aged 65 to 75 years	1 in 230 (0.4%)
High-risk patients aged 16 to 64 years	1 in 250 (0.4%)
Low-risk patients aged 16 to 64 years	1 in 4000 (0.03%)

A different strategy to assess the impact of influenza is to compare the general practice consultation and complication rates recorded during the weeks when influenza is circulating in the community, to a baseline rate calculated from averaging the weekly rates over a nine year period when influenza was not circulating. Using this method on data from the weekly returns service (WRS) of the Royal College of General Practitioners (RCGP), proportionate excesses in general practitioner visits as a result of influenza were 400% in 1989, 300% in 1993 and 150% in 1995.¹⁴ Excess pneumonia cases ranged from 2200 in 1995 to 12,500 in 1989, and acute bronchitis from 200,000 in 1989 and 1995 to 403,00 in 1993.¹⁴ There was also a minimum excess of 25% of people, primarily children, presenting with otitis media.¹⁴

A large population-based study using the GRPD (141,293 people with ILI-related physician visits) aimed to quantify clinical complications of, and risks associated with, influenza in all age groups from 1991 to 1996.¹⁵ They reported higher 30-day mortality rates in ‘at risk’ groups compared to otherwise healthy populations, particularly in patients aged 65 years and older. These results refer to patients presenting with ILI who are not necessarily infected with the influenza virus. A second study explored mortality in patients with confirmed influenza or respiratory syncytial virus infections using US national mortality and viral surveillance data for the 1976/7 to 1998/9 influenza seasons.¹⁶ This study reported that on average influenza virus infections were associated with 3 times as many deaths as respiratory syncytial virus infections. Together, the findings of these studies suggest that the risk of premature mortality from secondary complications of influenza, may vary according to age and risk groups.

In a recent review of data from NHS Direct to determine the increase in enquiries as a result of respiratory pathogens, and found that 601,454 calls over a two-year period related to four respiratory syndromes. Of these 45% of calls were classified as being about fever, 32% cough, 13% difficulty breathing, and 10% cold and flu.¹⁷ The proportion of calls attributed to influenza were estimated at 13% in the fever category, 15% in the cough category, and 22% in the cold and flu category.¹⁷ The mean annual incidence of NHS Direct respiratory calls in these three categories attributed to influenza was estimated as 72.6 per 100,000 population.¹⁷

3.2 Surveillance

The World Health Organisation (WHO)¹⁸ provides a global surveillance network which, as of May 2007, comprised four Collaborating Centres (UK, USA, Japan, Australia), and 118 National Influenza Centres (NICs) in 89 countries.¹⁹ The NICs conduct seasonal influenza surveillance, which assists in determining the annual vaccine composition, and defining when influenza is circulating in a country.¹⁹ In the UK, there are four NICs based in London, Glasgow, Belfast and Aberdeen.

The European Influenza Surveillance Scheme (EISS)²⁰ collects clinical and virological data, exchanges information on influenza activity and contributes to the annual determination of the influenza vaccine content. Twenty-six European Union member states, Norway, Serbia, Switzerland and Ukraine participate in the EISS, which is funded by the European Centre for Disease Prevention and Control (ECDC).²¹ The UK is represented by the four surveillance networks England, Northern Ireland, Scotland and Wales. EISS publishes weekly surveillance

reports on influenza activity in the 30 member countries. The reports are based on data reported by 25,750 sentinel physicians and cover a total population of 498 million people.

UK surveillance of influenza is co-ordinated and collated by the Health Protection Agency (HPA) Colindale Surveillance of Influenza Group, based at the London NIC centre.²² The HPA monitors and records the incidence of seasonal influenza in the UK and uptake of seasonal influenza vaccine in England, and releases data on a weekly basis to the WHO.²²

The RCGP²³ uses a network of 100 general practices located throughout England and Wales to collect information on every consultation and new episode of illness diagnosed in general practice, particularly the incidence of ILIs and other common respiratory conditions, as part of the Weekly Returns Service (WRS). The population covered by the WRS is approximately 900,000 across three regions; the North, Central and South Reporting Areas.²² A study using Geographical Information Systems techniques compared the population covered by the RCGP WRS with the national population, to give an indication of its representativeness.²⁴ The RCGP WRS population was found to be less deprived than the general population, with the most deprived wards in London not being represented.²⁴ However, at the time of this study, the RCGP WRS had 78 GPs providing data across England and Wales; there are currently 100 practices following a recruitment drive in 2005 in areas where the WRS was under-representative.²⁴ The Birmingham Research Unit is the Records and Statistical Unit of the RCGP, and provides weekly reports of the data for respiratory tract infections which can be downloaded from the RCGP website.²³

Other surveillance schemes which report weekly information on influenza activity are provided by the National Public Health Service (NPHS) for Wales, Health Protection Scotland (HPS) and the Communicable Disease Surveillance Centre (CDSC) Northern Ireland. The data in these schemes are collected mainly from networks of sentinel GP practices. A further surveillance scheme is undertaken by the Department of Primary Care at Nottingham University. It is called Qsurveillance® (previously know as Q-FLU) and utilises approximately 3,300 GP practices, covering a population of almost 22 million, which makes it the largest scheme of its kind in Europe. Data from ILI consultations are automatically extracted from participating practices and made immediately available for analysis.

NHS Direct offers a 24-hour nurse-led telephone service that covers England and Wales. Algorithms from clinical decision support systems are utilised so that symptom-based advice can be given to callers. The collected syndromic surveillance data are analysed by the West Midlands Regional Surveillance Unit. In another scheme, the Medical Officers of Schools Association

(MOSA) collects information about influenza activity in approximately 12,000 school children at 42 boarding schools. During the school terms MOSA sends weekly reports to the centre for infections. Most of the schools participating in this scheme are located in southern England, with pupils aged between 5 and 18 years, the majority, however, are boys aged from 13 to 18 years.

Up until 2003, the threshold for influenza circulating in the community was 50 consultations for ILI per 100,000 population. However, over the period between 1997 and 2003, influenza activity was at such a low level that the threshold for circulating in the community was reduced in 2003 to 30 per 100,000.⁵

3.3 Management of disease

3.3.1 Vaccination

Vulnerable groups can be protected from influenza to some degree by vaccination. Live, whole viruses are grown in fertile hens' eggs, and then chemically inactivated, treated and purified.^{2, 10} There are three types of vaccine which are equal in terms of efficacy and adverse events:¹⁰

- 'Split virion, inactivated' or 'disrupted virus' vaccines containing virus components prepared by treating whole viruses with organic solvents or detergents.¹⁰
- 'Surface antigen, inactivated' vaccines containing highly purified haemagglutinin and neuraminidase antigens prepared from disrupted virus particles.¹⁰
- 'Surface antigen, inactivated, virosome' vaccines containing highly purified haemagglutinin and neuraminidase antigens prepared from disrupted virus particles reconstituted into virosomes with phospholipids.¹⁰

Influenza immunisation to protect people at a higher risk of serious morbidity and mortality has been recommended in the UK since the late 1960s; in 2000 the policy was extended to include all people aged 65 years or over.¹⁰ Uptake was limited, even in the elderly, until the 1990s. The influenza vaccine is also offered to health professionals and carers, although uptake in this group is poor.¹⁰ The effectiveness of influenza vaccination has been evaluated in a systematic review of prophylaxis by the Sheffield School of Health and Related Research (SchARR), and is therefore not being evaluated in the current review.²⁵

3.3.2 Antiviral drugs

The first step in the replication of influenza virus is mediated by attachment of the virus haemagglutinin to sialic acid (neuraminic)-acid receptors on the cell surface of the respiratory epithelium,²⁶ thereby initiating virus penetration and fusion of viral and cellular membranes.^{2, 27} The virus is hence engulfed by the cell membrane and enters the cell (endocytosis) where it replicates.²⁶ Following viral replication, progeny virions accumulate at the cell surface and are released from the cell by the action of viral neuraminidase. Neuraminidase also aids the movement of influenza virus from sites of infection in the respiratory tract.^{2, 27, 28} Antiviral drugs used for the management of influenza two different modes of action; inhibition of M2 membrane protein, or inhibition of the neuraminidase surface glycoprotein.

3.3.2.1 Treatment

M2 membrane protein inhibitors

The anti-influenza action of amantadine (Lysovir, symmetrel syrup; Alliance Pharmaceuticals) was recognised in 1964, leading to the first license for antiviral treatment for influenza.²⁹ Rimantadine (Flumadine; Forest Pharmaceuticals) is a derivative of amantadine, and was first approved for use in 1993. Both amantadine and rimantadine inhibit the M2 membrane protein ion-channel activity of influenza A, but have no effect on influenza B.^{2, 3} The blocking of the proton pump of the M2 protein stops the virus uncoating and inactivates newly synthesised viral haemagglutinin. Rimantadine is not licensed for use in the UK.²⁹ Amantadine is licensed for treatment of influenza A in people over the age of 10 years for whom complications could be expected.

Neuraminidase inhibitors

The first sialic acid analogue, Neu5Ac2en, was developed in 1969.^{27, 30} However, this early analogue had low potency and poor specificity.²⁷ Subsequent development, led to the production of zanamivir (first trialed in 1994), and oseltamivir (first described in 1997).²⁷ Zanamivir and oseltamivir are effective against both influenza A and B.^{2, 3, 27}

Zanamivir (GG167, Relenza; Biota/GlaxoSmithKline)

Zanamivir is a second generation neuraminidase inhibitor. It is poorly absorbed via the gastrointestinal tract, and is therefore most commonly administered via inhalation, (it can also be administered intravenously).²⁶ Zanamivir is licensed for treatment of both influenza A and B in adults and children (5 years or over) who present with symptoms typical of influenza when

influenza is circulating in the community.³¹ The recommended dose of zanamivir in this population is two inhalations (10 mg) twice daily for five days.^{31,32} Treatment should begin within 48 hours of onset of symptoms for adults, and within 36 hours of onset of symptoms for children.³¹ As zanamivir contains lactose, its use is contra-indicated in patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.³¹ Use of zanamivir is not recommended during pregnancy or in mothers who are breast-feeding.³¹

Oseltamivir (GS4104, Tamiflu; Gilead/Hoffmann-La Roche)³¹

Oseltamivir is a third generation neuraminidase inhibitor that is readily absorbed from the gastrointestinal tract and is therefore administered orally.²⁶ Oseltamivir is licensed for treatment of influenza A and B in people over the age of 1 year if given within 48 hours of the onset of symptoms, only when influenza is circulating.^{3,31} The recommended dose of oseltamivir is 75 mg twice daily for 5 days, with a reduction to 75 mg once daily in patients with impaired creatinine clearance.³³ For children aged between 1 and 12 years, there are recommended doses of oseltamivir oral suspension based on weight (Table 3.2).³¹ Treatment should be initiated as soon as possible within the first two days of onset of symptoms of influenza.³¹ Use of oseltamivir is not recommended during pregnancy or in mothers who are breast-feeding.³¹

Table 3.2: The recommended weight-adjusted dosing regimens for oseltamivir³¹

Body Weight	Recommended dose for 5 days
<= 15 kg	30 mg twice daily
> 15 kg to 23 kg	45 mg twice daily
> 23 kg to 40 kg	60 mg twice daily
> 40 kg	75 mg twice daily

Other neuraminidase inhibitors

Two neuraminidase inhibitors are currently under development; peramivir (BCX-1812, RWJ-270201; Biocryst Pharmaceuticals)³⁴ and A-315675 (Abbott Laboratories).^{35,36} As both of these drugs are still in the development phase, they are not considered in this review.

3.3.2.2 Prophylaxis

Oseltamivir and amantadine are both licensed for use as prophylaxis against influenza. The current NICE guidance states that oseltamivir is recommended for the post-exposure prophylaxis of influenza in ‘at risk’ people aged 13 years or over who are not effectively protected by vaccination, or if prophylaxis can begin within 48 hours in people in residential care, who have

been exposed to the illness; oseltamivir is not recommended for post-exposure use in healthy adults aged 65 years or under.³⁷ Amantadine is licensed for seasonal and post-exposure prophylaxis of influenza A, particularly in ‘at risk’ patients, however, NICE guidance states that amantadine is not recommended for either post-exposure or seasonal prophylaxis of influenza.³⁷ The review of effectiveness of drugs as prophylaxis against influenza has been undertaken separately, and is therefore not evaluated in the current review.²⁵

3.3.3 Resistance to antiviral drugs

The emergence of viral resistance is a potential problem where the use of antiviral drugs becomes widespread. An increase in resistance to amantadine (first noted in 1981^{2,29}) has been observed in Asia and the USA since 2003.^{29,38}

To date, there has been a single reported case of resistance to zanamivir in an immunocompromised child who had a prolonged influenza infection who received treatment for 15 days.^{29,39} Until recently, the rate of resistance to oseltamivir has generally been low. Two reviews reported incidences of naturally occurring resistance to oseltamivir of 0.32%⁴⁰ and 1-4%²⁹ in adults, and 4.1%⁴⁰ and 5-6%²⁹ in children. A third review published in 2007 stated that resistance was reported in up to 2% of oseltamivir treated patients in trials, rising to 18% in children in two small studies in Japan which used a dosing system not based on the child’s weight.^{28,40} Over the 2007/8 influenza season, surveillance of the antiviral susceptibility of influenza viruses has shown a substantial increase in the rate of resistance of the H1N1 subtype of type A influenza to oseltamivir across Europe, including the UK (H1N1-H247Y).^{21,41-43} This resistance is a result of an amino-acid mutation of the neuraminidase protein.^{21,41} The rate of resistance has been as high as 70% in Norway.⁴¹ According to the last HPA weekly bulletin of the 2007/8 influenza season, 11% of H1N1 viruses have shown resistance to oseltamivir in the UK.^{42,44} There was no concomitant increase in the rate of resistance to zanamivir. The difference between oseltamivir and zanamivir has been attributed to the differences in the way they bind at the neuraminidase catalytic site, with resistance more likely with oseltamivir.²⁸

Data were provided by the HPA regarding the number of samples that were identified for each subtype of influenza for the last six influenza seasons in England and Wales (Table 3.4). Not all influenza A (H1 and H3) viruses are sub-typed for the neuraminidase gene (N1 or N2). It can be seen from these data that the 2007/8 influenza season had a [REDACTED] incidence of H1N1 than in the previous five years. Of the samples taken in 2007/8 (excluding those H1 that were not sub-typed for N1 or N2), [REDACTED] of the swabs collected by GPs and [REDACTED] of all samples obtained from both GPs and hospitals, were confirmed as the H1N1 subtype. With a resistant rate

of 11% in only H1N1, the proportion of viruses that were resistant in 2007/8, would be [redacted] for swabs collected by GPs and [redacted] for those obtained from both GPs and hospitals. Using the total numbers of samples (excluding those H1 that were not sub-typed for N1 or N2) and applying these rates, [redacted] collected by GPs and [redacted] from GPs and hospitals, would be expected to show resistance. It is unclear whether the 2007/8 levels of H1N1 are [redacted], as in the previous 5 years, H1N1 was [redacted], and the proportion of samples confirmed as H1N1 was, at most, [redacted] for swabs collected by GPs and [redacted] for samples obtained from both GPs and hospitals (2004/5). If the rate of resistance was 11%, the overall proportion of viruses resistant to oseltamivir in 2004/5, would have been [redacted] for swabs collected by GPs and [redacted] for samples obtained from both GPs and hospitals.

Table 3.3: The number samples confirmed for each subgroup of influenza virus. Only a proportion of influenza A (H1 and H3) viruses are sub-typed for the neuraminidase gene (N1 or N2). Data in this table are AIC (provided by the HPA)

Season	Swabs obtained from GPs							Swabs from GPs plus hospital samples						
	Influenza A H1 (not sub-typed)	Influenza A H1N1	Influenza A H1N2	Influenza A H3	Influenza A H3N2	Influenza B	% H1N1 (excluding H1 not sub-typed)	Influenza A H1 (not sub-typed)	Influenza A H1N1	Influenza A H1N2	Influenza A H3	Influenza A H3N2	Influenza B	% H1N1 (excluding H1 not sub-typed)
2007-2008	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2006-2007	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2005-2006	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2004-2005	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2003-2004	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2002-2003	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Resistance has, to date, only been observed in the H1N1 subtype of type A influenza. Given the early stage of investigation of this new subtype, some caution must be observed when considering its potential impact. The information is from a relatively small number of isolates, and continued surveillance is required to detect any trend in the rate of resistance. In addition, H1N1 viruses are often associated with milder illness than other influenza subtypes and the oseltamivir-resistant subtypes remain sensitive to zanamivir.^{21,28} WHO are collecting global data and producing a summary table which is being updated on a regular basis as reports become available.⁴²

3.3.4 Anticipated costs associated with intervention

According to the current British National Formulary (BNF; March 2008) the net price for 5 disks of dry powder zanamivir for inhalation with Diskhaler® device is £24.55.⁴⁵ This covers the recommended dose for both adults and children of 10 mg twice daily over a 5 day course of treatment. However, a reduction in the price of zanamivir has recently been agreed with the DoH. This will lower the price of zanamivir to the same as oseltamivir (£16.36 for a course of treatment). The net prices for oseltamivir are £16.36 for capsules (45 mg or 75 mg in 10 cap-packs) as well as for oral suspension (75 mL with 60 mg/5 mL) and £8.18 for capsules (30 mg in 10 cap-pack).⁴⁵

3.3.5 Current NICE guidance

Certain groups of people are considered more likely to develop influenza-related complications, and therefore ‘at risk’, and immunisation is recommended in these groups. Current NICE guidance states that zanamivir and oseltamivir are only recommended for the treatment of influenza in children and adults who are ‘at risk’. The use of amantadine is not recommended. ‘At risk’ populations are defined in the DoH ‘The Green Book’ as those aged 65 years and over, and all those aged 6 months and over in clinically ‘at risk’ groups (Table 3.6).^{3,10} The effectiveness and safety of oseltamivir and zanamivir will be investigated in these subgroups where sufficient data are presented. In addition, immunisation is provided to reduce the transmission of influenza within health and social-care premises, to contribute to the protection of individuals who may have a suboptimal response to their own immunisations, or to avoid disruption to services that provide their care.

Annual immunisation is recommended for:

- Health and social care staff directly involved in patient care
- Those living in long-stay residential care homes or other long-stay care facilities where rapid spread is likely to follow introduction of infection and cause high morbidity and mortality (this does not include prisons, young offender institutions, university halls of residence etc.)
- Those who are the main carer for an elderly or disabled person whose welfare may be ‘at risk’ if their carer falls ill. Vaccination should be given at the GP’s discretion.

Table 3.4: Clinical groups deemed to be ‘at risk’ of developing influenza-related complications

Clinical risk category	Examples
Chronic respiratory disease, including asthma	<p>Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, and such conditions as bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD)</p> <p>Asthma requiring continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission</p> <p>Children who have previously been admitted to hospital for lower respiratory tract disease</p>
Chronic heart disease	<p>Congenital heart disease</p> <p>Hypertension with cardiac complications</p> <p>Chronic heart failure</p> <p>Individuals requiring regular medication and/or follow-up for ischaemic heart disease</p>
Chronic renal disease	<p>Nephrotic syndrome</p> <p>Chronic renal failure</p> <p>Renal transplantation</p>
Chronic liver disease	<p>Cirrhosis</p> <p>Biliary atresia</p> <p>Chronic hepatitis</p>
Diabetes requiring insulin or oral hypoglycaemic drugs	<p>Type 1 diabetes,</p> <p>Type 2 diabetes requiring oral hypoglycaemic drugs</p>
Immunosuppression	<p>Due to disease or treatment</p> <p>Asplenia or splenic dysfunction</p> <p>Human immunodeficiency virus (HIV) infection at all stages.</p> <p>Patients undergoing chemotherapy leading to immunosuppression.</p> <p>Individuals on or likely to be on systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age) or for children under 20kg a dose of 1mg or more per kg per day.</p> <p>Some immunocompromised patients may have a suboptimal immunological response to the vaccine</p>

4 Definition of decision problem

4.1 Decision problem

Treatment with antivirals has the potential to reduce the duration of symptoms in influenza, and hence facilitate return to normal activities. Treatment may also reduce the incidence of influenza-related complications, hospitalisations and mortality. These potential effects are of particular interest in patient groups considered to be 'at risk' from influenza (the elderly, chronically ill, or immunocompromised), in whom the duration of illness is generally longer and the incidence of complications, hospitalisations and mortality higher.

A previous technology appraisal by Turner (2003),⁴⁶ which helped inform the current NICE guidelines (TA58), concluded that zanamivir and oseltamivir reduce the length of influenza illness by similar durations when compared, separately, with placebo and/or symptom relief. However, no comparison of clinical effectiveness was made between the two drugs. Uncertainties also remain regarding relative effectiveness in 'at risk' patients, and impact on the incidence of influenza-related complications, hospitalisations, and mortality. In addition, since the previous appraisal, new trials have been reported, and the license of zanamivir has been extended to include children.

An expansion of the previous appraisal is therefore needed, to incorporate new evidence and, where possible, to address the outstanding questions.

4.2 Overall aims and objectives of the assessment

The aim of this review is to inform the update of NICE guidance (TA58) using currently available data from RCTs on the clinical effectiveness. Data on antiviral drugs, compared to each other, placebo, or symptomatic care, will be synthesised using standard meta-analytic methods. Where direct comparisons between interventions are not available, indirect comparisons will be made through the development of a Bayesian multi-parameter evidence synthesis. The outcomes considered will be duration of influenza symptoms/time to return to normal activities, incidence of influenza-related complications, incidence of hospitalisations, mortality, adverse effects of treatment and health related quality of life. Analysis of clinically important subgroups will be undertaken where sufficient data are available. The results from these analyses will inform an economic model, which will consider the clinical and cost outcomes from the NHS and Personal Social Services Perspective.

5 Assessment of Clinical Effectiveness

5.1 Methods for Reviewing Clinical Effectiveness

5.1.1 Search strategy

5.1.1.1 Resources Searched

Studies were identified by searching the following databases: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Pascal, Science Citation Index (SCI), BIOSIS, Latin American and Caribbean Health Sciences (LILACS), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment Database (HTA). TOXLINE was also searched for studies with adverse event data. In addition, information on studies in progress, unpublished research and research reported in the grey literature was identified by searching Inside Conferences, Dissertation Abstracts, ClinicalTrials.gov, Current Controlled Trials, ClinicalStudyResults.org, Clinical Trial Results, World Health Organization International Clinical Trials Registry Platform (ICTRP), GlaxoSmithKline Clinical Trials Register, and Roche Clinical Trial Protocol Registry and Results Database. A methodological search filter was used to help identify randomised controlled trials. The searches updated those undertaken for the original guidance and so were run from October 2001 to the present. Trial reports and additional data were provided by GlaxoSmithKline (zanamivir) and Roche (oseltamivir); no additional data were provided for amantadine (Alliance Pharmaceuticals).

Searches for economic evaluations were undertaken in the databases listed above, replacing the randomised controlled trials search filter with an economic/cost methodological search filter. In addition, searches of NHS EED and HEED were carried out, alongside a search of the Economics Working Papers archive (IDEAS). Searches for health-related quality of life studies were also undertaken.

Internet searches were carried out using the specialist search gateways intute (www.intute.ac.uk) and MedlinePlus (<http://www.nlm.nih.gov/medlineplus/>) to identify relevant resources. Relevant websites were identified and searched included the British Lung Foundation, US National Institute of Allergy and Infectious Diseases, and US Centers for Disease Control and Prevention. Websites of regulatory agencies the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) were also searched. The full search strategies, dates and results of all searches are provided in Appendix 10.1.

A supplementary search was undertaken to retrieve studies about drug resistance during the 2007/8 influenza season. This consisted of brief searches in MEDLINE and EMBASE, and the following disease surveillance websites: Health Protection Agency, World Health Organization Epidemic and Pandemic Alert and Response programme, and the European Centre for Disease Prevention and Control.

5.1.2 Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any studies thought to be potentially relevant by either reviewer were obtained. The relevance of each study was assessed by two independent reviewers according to the criteria stated below. Any discrepancies were resolved by consensus, or where consensus could not be reached, a third reviewer was consulted. Non-English language papers were screened by one reviewer with a native speaker. Details of included studies are provided in Appendix 10.2 and a list excluded of studies and the reasons for their exclusion in Appendix 10.3. For studies retrieved only as an abstract, authors were contacted to request additional information. Where additional information was not obtained, abstracts were included only if sufficient outcome data were available. Studies written in any language were included.

5.1.2.1 Study designs

Only randomised controlled trials were included in the review of clinical effectiveness.

5.1.2.2 Interventions and comparators

Studies of treatment with antiviral drugs compared to each other, to placebo, or to best symptomatic care were included. Only licensed antiviral doses and durations of use were included (Appendix 4). Studies of prophylaxis were excluded, as were studies of intravenous and nebulised zanamivir as these are not licensed modes of administration.

5.1.2.3 Population

Studies of adults and/or children (in the age ranges indicated by the relevant licenses) who presented with symptoms typical of influenza were included, whether influenza was reported as circulating in the community or not. Studies reporting the efficacy of treatments during a pandemic, or a widespread epidemic of a new strain of influenza, were excluded as these

situations will not be covered by the new guidance. Studies of healthy volunteers with experimentally-induced influenza were also excluded. Subgroups as specified above in Section 3.3.5 were planned, conditional upon the availability of data.

5.1.2.4 Outcomes

The outcome measures were: time to alleviation of symptoms (composite of five or more symptoms); time to return to normal activity (encompassing varying definitions: able to perform usual daily activities, return to work or school, return to normal health and return to feeling as before illness); time to alleviation of fever; adverse events (overall, serious, minor and drug-related); and the incidence of influenza-related complications (overall, serious, antibiotic use, pneumonia, bronchitis and otitis media in children), hospitalisation and mortality. The numbers still with symptoms at final follow-up were extracted or calculated where possible.

5.1.3 Data extraction strategy

Data relating to both study content and quality were extracted by one reviewer, using a standardised data extraction form, and checked by a second reviewer. Discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Non-English language studies were extracted by one reviewer with a native speaker. Attempts were made to contact authors and pharmaceutical companies for missing data. Additional data were provided by the manufacturers, GlaxoSmithKline (zanamivir) and Roche (oseltamivir). There was no company submission for amantadine (Alliance Pharmaceuticals). Data from multiple publications of the same study were extracted and reported as a single study unless there was no overlap in the outcomes reported. Where overlap did occur, results from the largest population were extracted. Extraction included data on: study characteristics (e.g. study ID, author, year, location, duration of follow up, time from onset of symptoms to initiation of treatment, whether the study was reported as being conducted while influenza was circulating in community), patient characteristics (e.g. age, gender, number of participants and withdrawals, subgroups reported), interventions (dose and frequency of administration), comparators (placebo, symptomatic relief, or active comparator), study quality, and reported outcomes as specified in Section 5.1.2.4.

5.1.4 Quality assessment strategy

The quality of the individual studies was assessed by one reviewer and independently checked for agreement by a second reviewer. Any disagreements were resolved by consensus and, if

necessary, a third reviewer was consulted. The quality of the RCTs was assessed using standard checklists⁴⁷ which were adapted to incorporate topic-specific quality issues (Appendix 10.5).

5.1.5 Data analysis

Studies were analysed within the following categories: otherwise healthy adults, 'at risk', elderly, children. Analyses of all trials, including those with mixed populations where data could not be subdivided according to the above categories, were also undertaken. Analyses were carried out for both the ITT (intention to treat; representative of the entire population recruited in the trials) and ITTI (intention to treat, confirmed, influenza positive) populations wherever possible.

Odd ratios (OR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes. For continuous outcomes (time to event data), median differences and 95% CI were calculated. Where standard errors (SEs) were not available in publications or supplied by the companies for each arm of the trial, SEs around the medians were estimated from CI using the delta method,⁴⁸ or from standard deviations (SD). Where a SE, SD, or a CI were not provided, SEs were calculated using percentiles extrapolated from Kaplan-Meier graphs wherever possible, using the method reported by Collet (2003).⁴⁹

Median differences and 95% CI were pooled to produce a weighted median difference (WMD). A random effects model was used, unless there were four or fewer studies included in the analysis, in which case a fixed effect model was used, as the estimate of the heterogeneity parameter is likely to be unreliable with small numbers of trials.⁵⁰ All meta-analyses were conducted in RevMan 4.2.9 (Cochrane Collaboration). The impact of using the number of patients randomised (N) in the analyses of continuous outcomes rather than the number with alleviated symptoms (r) (as used in the previous review by Turner (2003)⁴⁶) was assessed by re-analysing the data from the previous review using N, and comparing these to the original results where 'r' was used.

Heterogeneity was assessed using the Chi² test and I² statistic. Where the results of the tests for heterogeneity were statistically significant (p<0.1), the potential sources of the heterogeneity, such as patient population, different durations of symptoms prior to treatment, vaccination status, and quality criteria, were identified. For the binary outcomes sensitivity analyses were conducted to explore the impact of the extent of loss to follow-up, where the overall drop-out rate was 10% or more. This could not be investigated for the continuous outcomes, as these were reported as medians, and individual patient data were unavailable for most trials.

As there were no direct head-to-head studies comparing zanamivir with oseltamivir that provided data for the outcomes being evaluated, an indirect comparison was undertaken using placebo as the common comparator, enabling indirect evidence to be utilised;^{51, 52} this is described and reported in Section 6.

5.2 Results of Review of Clinical Effectiveness

The scope and protocol of this review included amantadine hydrochloride, as well as the neuraminidase inhibitors, oseltamivir and zanamivir, as interventions. Amantadine was not considered a relevant comparator as current NICE guidance does not recommend its use for the treatment of influenza.

The current NICE guidance, that amantadine is not recommend for the treatment of influenza, was informed by the previous report by Turner *et al.* (2003)⁴⁶ which extended a Cochrane review on the effectiveness of amantadine⁵³ to include children and the elderly. It included two studies in children by Kitamoto (1968, 1971)^{54, 55} with 104 patients overall, who had a confirmed influenza diagnosis. No treatment trials in the elderly were identified. For data on the effectiveness of amantadine in otherwise healthy adults, Turner *et al.* (2003)⁴⁶ referred to an earlier version of the Cochrane review by Jefferson (2006)⁵⁶ published in the year 2000. This review, in its current version, includes 8 studies assessing the effectiveness of amantadine for influenza treatment (all published between 1968 and 1981), and concludes that amantadine should “be used only in emergency situations when all other measures fail.”⁵⁶

For the current review, studies of amantadine for the treatment of influenza, additional to those included in the Turner (2003) review, were sought. However, no new randomised controlled trials could be identified. There was no manufacturer submission for amantadine. The Turner (2003) review noted both the poor quality of amantadine trial data and its lack of comparability with other antiviral treatments and this was reflected in the previous NICE guidance. As no new data are available, this review focuses on determining the relative clinical and cost-effectiveness of zanamivir and oseltamivir and amantadine is not considered further.

5.2.1 Quantity and quality of research available

The electronic and hand searches retrieved 1061 references. Of these, 107 full papers were considered potentially relevant to the review of clinical effectiveness of zanamivir or oseltamivir; of which we were unable to locate seven.⁵⁷⁻⁶⁴ Two of these were only available as project details on the searchable database of US federally funded biomedical research projects (CRISP).^{59, 60}

One appears to be a commentary⁶¹ relating to an included study.⁶⁵ The remaining four were meeting abstracts,^{58, 62-64} one of which did not appear to have been published in the located proceedings.⁵⁸ Therefore 100 full papers and abstracts from these searches, along with 14 summary trial reports from company websites, seven trial reports of zanamivir submitted by GlaxoSmithKline, and one trial report of oseltamivir submitted by Roche, were screened for relevance. We included 34 trials, reported across 27 publications, nine trial summaries from company websites, five trial reports from a submission by GlaxoSmithKline, and one trial report from a submission by Roche (Table 5.1). Three trials were included where the primary source of data was published in a language other than English; two Chinese^{66, 67} and one Japanese.⁶⁸ Two further trials were published in English and Chinese;⁶⁹⁻⁷² data were extracted only from the English language papers.^{69, 71} Study details are available in Appendix 10.2.

Data for one study was originally only available from the previous HTA report (NAIB2007).⁴⁶ Further data from this trial were provided by the company, although this differed to that reported in the previous review in that the majority of patients were allocated an arbitrary day for alleviation of symptoms and time to return to normal activity (28 days) beyond the trial follow-up period (7 days). The data used in the previous report was included in the current meta-analysis for consistency. Five trials were published in a single paper, three recruiting an elderly population were combined (WV15819, WV15876, WV15978), and two recruiting an 'at risk' population were combined (WV15812, WV15873).⁷³ Data from these trials individually were only available from the previous HTA report.⁴⁶ Data from the NAIA2008 and NAIB2008 trials were combined and reported in two papers;^{74, 75} these papers reported different outcomes and are therefore presented separately. Data from the NAIA2005 and NAIB2005 trials were only available combined.⁷⁶ Data from the NV16871 trial was identified by Roche as being published in two sources, one reported results for children and adolescents (6 to 17 years of age)⁷⁷ and the other children only (6 to 12 years of age).⁷⁸ Where there was overlap in the reporting of outcomes, results were extracted for children only as this was the later publication, with a greater number of participants, and more complete reporting. Data for some outcomes from six RCTs were obtained from medical reviews by the Food and Drug Administration (FDA).^{79, 80}

The trial M76001 has been included in a number of previous reviews, often combined with data from three other trials (WV15670, WV15671, WV15730). However, the only published source of separate data for this trial was an abstract which contained insufficient information to be included in the analysis.⁸¹ Additional information was requested from the author, from the principal trial investigator and from Roche; Roche provided some outcome data which has been included in the review. A second abstract that met the inclusion criteria also contained insufficient information to be included in the analysis;⁸² this was identified as being related to the

WV15730 trial for which Roche subsequently submitted a trial report.⁸³ One study of zanamivir included in the treatment section of the last HTA report was excluded from the current review (NAI30010).⁸⁴ This trial was primarily a prophylactic trial, where households were randomised prior to an outbreak of influenza, and the entire household received either zanamivir or placebo once one household member contracted influenza. This trial therefore did not meet the inclusion criterion that participants were randomised at presentation of ILI.

Table 5.1: The sources of data for zanamivir utilised in the review

Trial	Population	Source
Matsumoto (1999)	Healthy adults	Full paper ⁸⁵
NAI30011	Healthy adults	Company submission ⁸⁶
NAI30015	Healthy adults	Puhakka (2003) ⁸⁷ Full paper Trial data from company website ⁸⁸ Company submission ⁸⁹
*NAIA2005	Healthy adults	Hayden (1997) ⁷⁶ Full paper
*NAIB2005		
*NAIB3001	Mixed population	MIST (1998) ⁹⁰ Full paper Trial data from company website ⁹¹ FDA medical review ⁷⁹ Additional data provided by GlaxoSmithKline
*NAIB2007	Mixed population	Data available from last HTA report ⁴⁶ Additional data provided by GlaxoSmithKline
*NAIA2008	Mixed population	Aoki (2000) ⁷⁴ Full paper Monto (1999) ⁷⁵ Full paper FDA medical review ⁷⁹
*NAIB2008	'At risk'	FDA medical review ⁷⁹
*NAIA3002	Mixed population 'At risk'	Boivin (2000) ⁹² Full paper Lalezari (1999) ⁹³ Abstract Trial data from company website ⁹⁴ FDA medical review ⁷⁹ Additional data provided by GlaxoSmithKline
*NAIB3002	Mixed population 'At risk'	Makela (2000) ⁹⁵ Full paper Trial data from company website ⁹⁶ FDA medical review ⁷⁹ Additional data provided by GlaxoSmithKline
*NAI30008	'At risk'	Murphy (2000) ⁹⁷ Full paper Additional data provided by GlaxoSmithKline
NAI30020	'At risk'	Trial data from company website ⁹⁸
*NAI30009	Children	Hedrick (2000) ⁹⁹ Full paper Trial data from company website ¹⁰⁰ Company submission ¹⁰¹
NAI30028	Children	Trial data from company website ¹⁰² Company submission ¹⁰³
NAI30012	Elderly	Trial data from company website ¹⁰⁴ Company submission ¹⁰⁵

Table 5.2: The sources of data for oseltamivir, and oseltamivir versus zanamivir, utilised in the review

Oseltamivir		
Trial	Population	Source
Deng (2004)	Healthy adults	Full paper published in Chinese ⁶⁶
Kashiwagi (2000)	Healthy adults	Full paper published in Japanese ⁶⁸
Li (2003)	Healthy adults	Full papers: one English, ⁶⁹ one Chinese ⁷⁰
Tan (2002)	Healthy adults	Full paper published in Chinese ⁶⁷
*WV15670	Healthy adults	Nicholson (2000) ¹⁰⁶ Full paper FDA medical review ⁸⁰ Additional data provided by Roche
*WV15671	Healthy adults	Treanor (2000) ⁶⁵ Full paper FDA medical review ⁸⁰ Additional data provided by Roche
*WV15730	Healthy adults	Company submission ⁸³ Robson (2000) Abstract ⁶² Last HTA report ⁴⁶
Markovski (2002)	Mixed population	Full paper ⁵⁷
M76001	Mixed population	Treanor (2000) ⁸¹ Abstract Additional data provided by Roche
Lin (2006)	'At risk'	Full papers: one English, ⁷¹ one Chinese ⁷² Abstract ¹⁰⁷
*WV15812	'At risk'	Martin (2001) ⁷³ Full paper, trials combined
*WV15872		Martin (2000) ¹⁰⁸ Abstract Individual trial data from previous HTA report ⁴⁶ Additional data provided by Roche
NV16871	Children (6-12 years)	Johnston (2005) Full paper ⁷⁸ Additional data provided by Roche
	Children and adolescents (6-17 years)	Trial data from company website ⁷⁷ Additional data provided by Roche
*WV15758	Children	Whitely (2001) ¹⁰⁹ Full paper
*WV15819	Elderly	Martin (2001) ⁷³ Full paper, trials combined Individual trial data from previous HTA report ⁴⁶
*WV15876		
*WV15978		
Trials of both zanamivir and oseltamivir		
Sato (2005)	Children	Full paper ¹¹⁰

*Trials included in the Turner (2003) review.

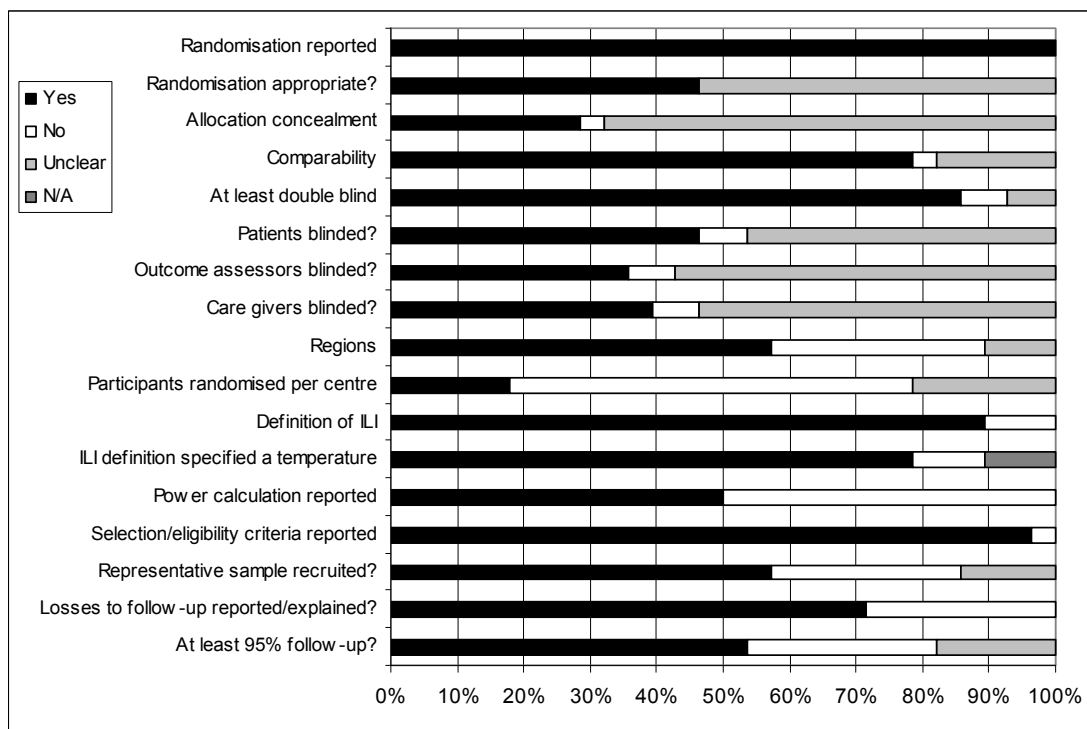
Six trials of zanamivir and eight of oseltamivir were not included in the Turner (2003) review and were therefore new to this review (Tables 5.1 and 5.2). One new trial comparing zanamivir with oseltamivir in children was identified, however, this did not provide usable outcome data.¹¹⁰

After accounting for duplicate publications, 29 trial reports underwent quality assessment. Summary results of the quality assessment are presented in Figure 5.1; full results are available in Appendix 10.5. All 29 reported being randomised, with 25 (86%) also reporting being double-

blind. An appropriate method of randomisation was explicitly reported in 13 (45%), allocation concealment in 8 (28%), patient blinding in 13 (45%), outcome assessor blinding in 10 (34%), and care giver blinding in 11 (38%). Two reports specified being open-label.^{66, 71} Eligibility criteria were reported in 28 (97%).

One factor identified specific to this review, and included in the quality assessment, was the number of participants recruited per centre, and whether centres were located across one or more continents. It has been suggested that a site's performance is a function of the number of patients enrolled, with studies that use fewer sites with greater numbers of patients at each site have more reliable results than those that use large numbers of sites with fewer patients per site.¹¹¹ Several included studies had a large number of recruiting centres, resulting in a very small mean number of participants recruited at any one centre. Only six reports (21%) recruited at least 15 participants at each centre taking part in the trial. Seventeen reports (59%) recruited participants from a single continent. Another review-specific criterion was the reporting of a case definition of influenza-like-illness (ILI). Twenty six reports (90%) provided such a definition; three did not specify a temperature as part of the definition.⁷⁴⁻⁷⁶

Figure 5.1: Proportion of trials with Yes, No, Unclear or Not Applicable (N/A) for each quality criterion



The rate of loss to follow-up depends upon a variety of factors, one of which is the duration of follow-up; trials of short duration would be expected to have lower rates of loss to follow-up than those of longer duration.¹¹² Given the short-term duration of the included studies (up to 28 days), it was disappointing to note that a large number of trials had losses to follow-up of greater than 5%. Only 15 (52%) reported 95% follow-up or over, with eight (28%) having a drop-out rate greater than 5%, and six (21%) not reporting on drop-outs. The highest overall drop-out rate across the trials was 9%.^{67, 78} Twenty trials (69%) reported the reasons for losses to follow-up.

5.2.2 Effectiveness in healthy adults

Eleven studies were restricted to healthy adults, four of zanamivir^{76, 85-89} and seven of oseltamivir.^{65-70, 83, 106, 113} Results for healthy adults from a further four zanamivir studies recruiting a mixed population were also available.^{46, 90-96} Three trials of zanamivir⁸⁵⁻⁸⁸ and four of oseltamivir⁶⁶⁻⁶⁹ were not included in Turner (2003) review.⁴⁶

The majority of the studies defined healthy adults as people aged between 18 and 65 years that were not otherwise 'at risk'.^{65, 67, 69, 70, 82, 83, 85, 90-95, 106} Four studies used recruited populations with age ranges different to the other studies, these were: aged 18 to 99 years;⁸⁶ aged 16 to 80 years;⁶⁸ a minimum of 13 years in the USA and 18 years in Europe with no upper age limit specified;⁷⁶ aged 17 to 29 years.⁸⁷⁻⁸⁹ One study reported a population with a mean age of 32 years (SD ±16 years).⁶⁶ Forest plots for pooled results are provided in Appendix 10.6.

5.2.2.1 Zanamivir compared to placebo

Symptoms

Seven trials of zanamivir in healthy adults reported the time to the alleviation of fever, all symptoms, or to return to normal activity.^{46, 76, 79, 86-88, 90-96} The follow-up period was 5 days in one trial,⁴⁶ 14 days in one trial,⁹²⁻⁹⁴ 21 days in one trial,⁸⁶ 28 days in three trials,^{87, 88, 90, 91, 95, 96} and between 21 and 28 days in one trial.⁷⁶ Three of the trials had a drop-out rate greater than 5%, but none greater than 10%.^{76, 86, 90, 91}

Treatment with zanamivir significantly reduced the time to the alleviation of all symptoms, but there was no clear evidence of an effect on the time to return to normal activity, in either the ITT (Table 5.3) or ITTI (Table 5.4) populations. Statistically significant heterogeneity was observed in the analyses of the time to return to normal activity in the ITT population. All the trials included in this analysis used the same outcome definition and there are no consistent differences

between the studies in terms of trial methodology or quality to account for the observed heterogeneity. One study reported the time to alleviation of fever, showing no difference between zanamivir and placebo in either the ITT or ITTI population.^{87, 88} This same study reported a time to the alleviation of symptoms that was shorter than the other studies, although this was not reflected in the time to return to normal activity.^{87, 88} This is most likely due to this study recruiting healthy young (17 to 29 years) men (99%), who were in the Finnish Defence Force, who may have recovered more quickly, but may not have returned to full duties immediately after symptoms had been relieved.^{87, 88}

Table 5.3: The median number of days to the alleviation of symptoms and return to normal activity in the ITT population of healthy adults treated with zanamivir (Zan.) or placebo (Pl.), with weighted median differences (WMD) and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zan.	Pl.			
ALLEVIATION OF SYMPTOMS					
*Boivin (2000) ⁹²⁻⁹⁴	363	305	5 (0.21)	5 (0.27)	0.0 (-0.69, 0.69)
GlaxoSmithKline NAI30011 ⁸⁶	229	237	4.5 (0.34)	4.5 (0.25)	0.0 (-0.84, 0.84)
*Hayden (1997) ⁷⁶	132	144	3.5 (0.28)	4.5 (0.28)	-1.00 (-1.78, -0.22)
*Makela (2000) ^{95, 96}	161	163	5 (0.35)	6.5 (0.61)	-1.50 (-2.88, -0.12)
*MIST (1998) ^{79, 90, 91}	190	189	5 (0.40)	6 (0.41)	-1.00 (-1.94, -0.06)
Puhakka (2003) ^{87, 88}	293	295	2.17 (0.89)	2.67 (0.23)	-0.50 (-2.30, 1.30)
Pooled result (Fig. 10.1)			WMD -0.57 (95% CI: -1.07, -0.08), p=0.02		
Heterogeneity			Chi ² =8.08; p=0.15; I ² =38.1%		
TIME TO NORMAL ACTIVITY					
GlaxoSmithKline NAI30011 ⁸⁶	229	237	2.1 (0.20)	2.2 (0.22)	-0.10 (-0.68, 0.48)
*Hayden (1997) ⁷⁶	132	144	3.5 (0.24)	3.5 (0.21)	0.0 (-0.63, 0.63)
*Boivin (2000) ⁹²⁻⁹⁴	363	305	6.5 (0.3)	6.5 (0.25)	0.0 (-0.77, 0.77)
*MIST (1998) ^{79, 90, 91}	190	189	7 (0.29)	8.5 (0.86)	-1.50 (-3.28, 0.28)
*Makela (2000) ^{95, 96}	161	163	6 (0.39)	8 (0.6)	-2.00 (-3.40, -0.60)
Puhakka (2003) ^{87, 88}	293	295	5 (0.48)	6.3 (0.52)	-1.30 (-2.69, 0.09)
*GlaxoSmithKline NAIB2007 ⁴⁶	165	159	3.5 (0.24)	3.5 (0.22)	0.0 (-0.64, 0.64)
Pooled result (Fig. 10.2)			WMD -0.37 (95% CI: -0.84, 0.09), p=0.11		
Heterogeneity			Chi ² =11.90; p=0.06; I ² =49.6%		
ALLEVIATION OF FEVER					
Puhakka (2003) ^{87, 88}	293	295	2.00 (N/A)	2.00 (N/A)	0.0

*Trials included in the Turner (2003) review

N/A: Not available

Table 5.4: The median number of days to the alleviation of symptoms and return to normal activity in the ITTI population of healthy adults treated with zanamivir (Zan.) or placebo (Pl.), with weighted median differences (WMD) and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zan.	Pl.			
ALLEVIATION OF SYMPTOMS					
Puhakka (2003) ^{87, 88}	222	213	2 (0.82)	2.33 (0.27)	-0.33 (-2.02, 1.36)
GlaxoSmithKline NAI30011 ⁸⁶	104	107	4.5 (0.32)	5.0 (0.34)	-0.50 (-1.42, 0.42)
*Hayden (1997) ⁷⁶	85	89	3.5 (0.31)	4.5 (0.46)	-1.00 (-2.09, 0.09)
*Boivin (2000) ⁹²⁻⁹⁴	276	214	5 (0.19)	6 (0.3)	-1.00 (-1.70, -0.30)
*MIST (1998) ^{79, 90, 91}	137	132	4.5 (0.36)	6 (0.48)	-1.50 (-2.65, -0.35)
*Makela (2000) ^{95, 96}	124	123	5 (0.36)	6.5 (0.71)	-1.50 (-3.06, 0.06)
Pooled result (Fig. 10.3)			WMD -0.96 (95% CI: -1.38, -0.54), p<0.0001		
Heterogeneity			Chi ² =2.82; p=0.73; I ² =0%		
TIME TO NORMAL ACTIVITY					
Puhakka (2003) ^{87, 88}	222	213	4.5 (0.55)	6.33 (0.76)	-1.83 (-3.67, 0.01)
GlaxoSmithKline NAI30011 ⁸⁶	104	107	2.4 (0.20)	2.5 (0.21)	-0.10 (-0.67, 0.47)
*Hayden (1997) ⁷⁶	85	89	3.5 (0.37)	3.5 (0.29)	0.0 (-0.92, 0.92)
*Boivin (2000) ⁹²⁻⁹⁴	276	214	6.5 (0.32)	7 (0.3)	-0.50 (-1.36, 0.36)
*MIST (1998) ^{79, 90, 91}	137	132	7 (0.33)	8 (0.90)	-1.00 (-2.88, 0.88)
*Makela (2000) ^{95, 96}	124	123	6.5 (0.46)	8.5 (0.69)	-2.00 (-3.62, -0.38)
*GlaxoSmithKline NAIB2007 ⁴⁶	96	101	3.5 (0.28)	3.5 (0.28)	0.0 (-0.57, 0.57)
Pooled result (Fig. 10.4)			WMD -0.39 (95% CI: -0.84, 0.06), p=0.09		
Heterogeneity			Chi ² =9.50; p=0.15; I ² =36.8%		
ALLEVIATION OF FEVER					
Puhakka (2003) ^{87, 88}	222	213	2.0 (NR)	2.0 (NR)	0.0

Complications

Outcomes relating to complications in healthy adults were poorly reported, with only three zanamivir trials reporting any complication rates (Table 5.5 and 5.6).^{76, 86-88} Two of these had a drop-out rate greater than 5%, but not greater than 10%.^{76, 86}

The majority of the available information is from a study in primarily healthy young men in the Finnish Defence Forces.^{87, 88} This study reported high rates of hospitalisation and GP consultations, as those suffering with influenza were isolated from their colleagues; these data are unlikely to be representative of complications rates seen in a presenting population in general practice. The information available from the other two trials is limited, with the incidence of complications low. There is therefore insufficient relevant information available from which to draw conclusions.

Table 5.5: The rate of complications in ITT population of healthy adults treated with zanamivir or placebo, with odds ratios (OR) and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
PNEUMONIA			
Puhakka (2003) ^{87, 88}	16/293	12/295	1.36 (0.63, 2.93)
BRONCHITIS			
Puhakka (2003) ^{87, 88}	9/293	11/295	0.82 (0.33, 2.00)
GlaxoSmithKline NAI30011 ⁸⁶	8/229	5/237	1.68 (0.54, 5.21)
	Pooled result (Fig. 10.5)		OR 1.08 (95% CI: 0.54, 2.17), p=0.82
	Heterogeneity		Chi ² =0.95; p=0.33; I ² =0%
ANTIBIOTIC USE			
Hayden (1997) ⁷⁶	11/132	17/144	0.68 (0.31, 1.51)
COMPLICATIONS REQUIRING HOSPITALISATION			
Puhakka (2003) ^{87, 88}	48/293	37/295	1.37 (0.86, 2.17)
GP CONSULTATIONS			
Puhakka (2003) ^{87, 88}	182/293	180/295	1.05 (0.75, 1.46)

Table 5.6: The rate of complications in ITTI population of healthy adults treated with zanamivir or placebo, with odds ratios (OR) and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS			
Puhakka (2003) ^{87, 88}	115/222	108/213	1.04 (0.72, 1.52)
COMPLICATIONS REQUIRING HOSPITALISATION			
Puhakka (2003) ^{87, 88}	34/222	20/213	1.75 (0.97, 3.14)
ANTIBIOTIC USE			
Puhakka (2003) ^{87, 88}	93/222	83/213	1.13 (0.77, 1.66)
GP CONSULTATIONS			
Puhakka (2003) ^{87, 88}	139/222	126/213	1.16 (0.79, 1.70)

Adverse events

Four trials of healthy adults reported adverse events, all of which were in the ITT population (Table 5.7).^{76, 85-88} The pooled results showed no significant differences in overall, drug-related or serious adverse events, between zanamivir and placebo. There was no statistically significant heterogeneity between studies for any of the pooled results.

Table 5.7: The rate of adverse events in the ITT population of healthy adults treated with zanamivir or placebo, with OR and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL ADVERSE EVENTS			
Puhakka (2003) ^{87, 88}	77/293	80/295	0.96 (0.66, 1.38)
GlaxoSmithKline NAI30011 ⁸⁶	80/229	77/237	1.12 (0.76, 1.64)
	Pooled result (Fig. 10.6)		OR 1.03 (95% CI: 0.79, 1.34), p=0.83
	Heterogeneity		Chi ² =0.32; p=0.57; I ² =0%
DRUG-RELATED ADVERSE EVENTS			
Puhakka (2003) ^{87, 88}	11/293	13/295	0.85 (0.37, 1.92)
GlaxoSmithKline NAI30011 ⁸⁶	15/229	13/237	1.21 (0.56, 2.60)
Matsumoto (1999) ⁸⁵	6/37	8/39	0.75 (0.23, 2.42)
Hayden (1997) ⁷⁶	30/132	26/144	1.33 (0.74, 2.40)
	Pooled result (Fig. 10.7)		OR 1.11 (95% CI: 0.76, 1.62), p=0.60
	Heterogeneity		Chi ² =1.28; p=0.73; I ² =0%
SERIOUS ADVERSE EVENTS			
Puhakka (2003) ^{87, 88}	1/293	0/295	3.03 (0.12, 74.70)
GlaxoSmithKline NAI30011 ⁸⁶	2/229	2/237	1.04 (0.14, 7.4134)
Matsumoto (1999) ⁸⁵	0/37	0/39	-
	Pooled result (Fig. 10.8)		OR 1.44 (95% CI: 0.28, 7.35), p=0.44
	Heterogeneity		Chi ² =0.32; p=0.57; I ² =0%

5.2.2.2 *Oseltamivir compared to placebo*

Symptoms

Six trials of oseltamivir in healthy adults reported the time to the alleviation of fever, all symptoms, or return to normal activity.^{46, 65, 67-69, 80, 82, 106} The follow-up period was 21 days in all six trials. Three of the trials had a drop-out rate greater than 5%, but not greater than 10%.^{65, 67, 82, 83}

Treatment with oseltamivir significantly reduced the time to the alleviation of all symptoms and to the time to return to normal activity in both the ITT and ITTI populations (Table 5.8 and 5.9, respectively). Statistically significant heterogeneity was observed only in the analysis of the alleviation of all symptoms in the ITTI population. This seems to be primarily driven by a one small trial (Roche, WV15730). When this trial was removed from the analysis, the impact of oseltamivir remained statistically significant (WMD -19.06; 95% CI: -33.02, -5.10; p=0.007), but there was no longer statistically significant heterogeneity between the studies (Chi²=7.53; p=0.11; I²=46.9%). Where there was sufficient information reported, oseltamivir also reduced the time to the alleviation of fever.

Table 5.8: The median number of hours to the alleviation of symptoms and return to normal activity in the ITT population of healthy adults treated with oseltamivir (Os.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF SYMPTOMS					
Li (2003) ⁶⁹	216	235	83.5 (5.47 [†])	87.7 (5.14 [†])	-4.20 (-18.91, 10.51)
*Nicholson (2000) ¹⁰⁶	243	239	97.6 (9.38)	116.1 (7.60)	-18.50 (-43.02, 6.02)
*Treanor (2000) ⁶⁵	210	209	76.3 (6.43)	97 (5.29)	-20.70 (-37.02, -4.38)
*Roche WV15730 ^{46, 82, 83}	31	27	74.5 (8.2)	109.8 (31.2)	-35.30 (-98.53, 27.93)
Pooled result (Fig. 10.9)			WMD -13.29 (95% CI: -25.15, -3.43), p=0.008		
Heterogeneity			Chi ² =2.90; p=0.41; I ² =0%		
TIME TO NORMAL ACTIVITY					
*Treanor (2000) ⁶⁵	210	209	108.73 (6.97 [†])	132.98 (7.82 [†])	-24.25 (-44.78, -3.72)
*Nicholson (2000) ^{80, 106}	240	234	132.4 (8.17)	172.98 (8.25)	-40.58 (-63.33, -17.83)
*Roche WV15730 ^{46, 82, 83}	31	27	152.6 (24.8)	196.2 (36.3)	-43.60 (-129.77, 42.57)
Pooled result (Fig. 10.10)			WMD -31.94 (95% CI: -46.95, -16.93), p<0.0001		
Heterogeneity			Chi ² =1.16; p=0.56; I ² =0%		
ALLEVIATION OF FEVER					
Li (2003) ⁶⁹	216	235	28.7 (N/A)	32.5 (N/A)	-3.80
*Nicholson (2000) ¹⁰⁶	243	239	45 (3.6 [†])	59 (5.24 [†])	-14.00 (-26.46, -1.54)

Complications

Six oseltamivir studies reported outcomes relating to complications in healthy adults (Tables 5.10 and 5.11);^{46, 65, 66, 68, 69, 83, 106} three of which were conducted in China^{66, 69} or Japan,⁶⁸ with two published in their respective languages.^{66, 68} Oseltamivir showed a statistically significantly reduction in the rate of antibiotic use in the ITT population. However, this results was based on only two studies, one of which was the trial by Deng (2004),⁶⁶ which was conducted in China and had a particularly high rate of antibiotic use in both arms, and which therefore has most weight in and drives the pooled result. In addition, the study by Deng (2004) was described as open label. Nonetheless the Canadian trial by Nicholson, which used a matching placebo and appeared to be double blinded, showed a similar size of relative effect. The pooled result for the ITTI analysis has the same direction of effect, does not include the trial by Deng (2004), and is of borderline statistical significance.

Overall there was limited information on complications, their incidence was low, and there were no other statistically significant differences in complication rates between oseltamivir and placebo were observed. There was no statistically significant heterogeneity between studies in any of the analyses. Two trials had a drop-out rate greater than 5%, but not greater than 10%.^{65, 82, 83}

Table 5.9: The median number of hours to the alleviation of symptoms and return to normal activity in the ITTI population of healthy adults treated with oseltamivir (Os.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF SYMPTOMS					
Li (2003) ⁶⁹	134	139	91.6 (5.46 [†])	95 (5.33 [†])	-3.40 (-18.35, 11.55)
Tan (2002) ⁶⁷	22	25	100.25 (19.43 [†])	93.75 (21.27 [†])	6.50 (-49.96, 62.96)
Kashiwagi (2000) ⁶⁸	122	130	70 (8.36 [†])	93.3 (8.86 [†])	-23.30 (-47.18, 0.58)
*Nicholson (2000) ^{80, 106}	158	161	87.4 (7.8)	116.5 (8.5)	-29.10 (-57.71, -6.49)
*Treanor (2000) ^{65, 80}	124	129	71.5 (5.6)	103.3 (7.9)	-31.80 (-50.78, -12.82)
*Roche WV15730 ^{46, 82, 83}	19	19	78.2 (10.6)	143.9 (24.8)	-65.70 (-118.56, -12.84)
Pooled result (Fig. 10.11)			WMD -22.19 (95% CI: -37.32, -7.07), p=0.004		
Heterogeneity			Chi ² =10.60; p=0.06; I ² =52.8%		
TIME TO NORMAL ACTIVITY					
*Nicholson (2000) ^{80, 106}	158	161	197.5 (19.02 [†])	241 (23.12 [†])	-43.50 (-102.18, 15.18)
*Roche WV15730 ^{46, 82, 83}	19	19	130.7 (17.4)	218.7 (36.1)	-88.00 (-166.55, -9.45)
*Treanor (2000) ⁶⁵	124	129	156.7 (10.75 [†])	225.1 (26.27 [†])	-68.40 (-124.03, -12.77)
Pooled result (Fig. 10.12)			WMD -63.17 (95% CI: -99.08, -27.27), p=0.0006		
Heterogeneity			Chi ² =0.85; p=0.65; I ² =0%		
ALLEVIATION OF FEVER					
Li (2003) ⁶⁹	134	139	27.9 (N/A)	51.5 (N/A)	-23.60
Tan (2002) ⁶⁷	22	25	22.75 (4.83 [†])	29.83 (9.0*)	-7.08 (-27.10, 12.94)
Kashiwagi (2000) ⁶⁸	122	130	33.1 (N/A)	60.5 (N/A)	-27.4
*Nicholson (2000) ¹⁰⁶	158	161	39 (3.71 [†])	67 (4.76 [†])	-28.00 (-39.83, -16.17)
*Treanor (2000) ^{65, 80}	124	129	41.5 (3.65 [†])	64.6 (4.18 [†])	-23.10 (-33.98, -12.22)
*Roche WV15730 ^{46, 82, 83}	19	19	39.5 (6.21 [†])	80.5 (10.0 [†])	-41.00 (-64.07, -17.93)
Pooled result (Fig. 10.13)			WMD -24.54 (95% CI: -31.61, -17.46), p<0.0001		
Heterogeneity			Chi ² =5.27; p=0.15; I ² =43.1%		

*Trials included in the Turner (2003) review

[†]Calculated from CIs

N/A: Not available

Table 5.10: The rate of complications in the ITT population of healthy adults treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Osetamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS			
Treanor (2000) ⁶⁵	18/210	28/209	0.61 (0.32, 1.13)
COMPLICATIONS REQUIRING HOSPITALISATION			
Deng (2004) ^{66**}	5/599	3/577	1.61 (0.38, 6.77)
Nicholson (2000) ¹⁰⁶	1/241	1/235	0.98 (0.06, 15.68)
Treanor (2000) ^{65, 80}	0/210	2/209	0.20 (0.01, 4.13)
	Pooled result (Fig. 10.14)		OR 0.97 (95% CI: 0.33, 2.90), p=0.96
	Heterogeneity		Chi ² =1.53; p=0.47; I ² =0%
BRONCHITIS			
Nicholson (2000) ¹⁰⁶	7/241	5/235	1.38 (0.43, 4.40)
PNEUMONIA			
Kashiwagi (2000) ⁶⁸	0/154	1/154	0.33 (0.01, 8.19)
Nicholson (2000) ¹⁰⁶	0/241	1/235	0.32 (0.01, 7.99)
	Pooled result (Fig. 10.15)		OR 0.33 (95% CI: 0.03, 3.16)043.1%
	Heterogeneity		
ANTIBIOTIC USE			
Deng (2004) ^{66**}	129/599	248/577	0.36 (0.28, 0.47)
Nicholson (2000) ¹⁰⁶	6/241	10/235	0.57 (0.21, 1.61)
	Pooled result (Fig. 10.16)		OR 0.37 (95% CI: 0.29, 0.48), p<0.0001
	Heterogeneity		Chi ² =0.71; p=0.40; I ² =0%

**Used symptom relief as comparator, not placebo

Table 5.11: The rate of complications in the ITTI population of healthy adults treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS			
Li (2003) ⁶⁹	7/134	7/139	1.04 (0.35, 3.05)
Treanor (2000) ⁶⁵	11/124	19/129	0.56 (0.26, 1.24)
Roche WV15730 ^{46, 82, 83}	2/19	1/19	2.12 (0.18, 25.55)
	Pooled result (Fig. 10.17)		OR 0.75 (95% CI: 0.41, 1.37), p=0.35
	Heterogeneity		Chi ² =1.53; p=0.47; I ² =0%
PNEUMONIA			
Nicholson (2000) ¹⁰⁶	0/158	1/161	0.34 (0.01, 8.35)
Treanor (2000) ⁶⁵	0/124	1/129	0.34 (0.01, 8.53)
Roche WV15730 ^{46, 82, 83}	0/19	1/19	0.32 (0.01, 8.26)
	Pooled result (Fig. 10.18)		OR 0.33 (95% CI: 0.05, 2.14), p=0.25
	Heterogeneity		Chi ² =0.0; p=1.00; I ² =0%
BRONCHITIS			
Nicholson (2000) ¹⁰⁶	5/158	3/161	1.72 (0.40, 7.33)
Treanor (2000) ⁶⁵	5/124	8/129	0.64 (0.20, 2.00)
	Pooled result (Fig. 10.19)		OR 0.94 (95% CI: 0.39, 2.24), p=0.88
	Heterogeneity		Chi ² =1.12; p=0.29; I ² =10.6%
ANTIBIOTIC USE			
Li (2003) ⁶⁹	5/134	5/139	1.04 (0.29, 3.67)
Nicholson (2000) ¹⁰⁶	1/158	8/161	0.12 (0.02, 0.99)
Treanor (2000) ⁶⁵	8/124	14/129	0.57 (0.23, 1.40)
	Pooled result (Fig. 10.20)		OR 0.52 (95% CI: 0.27, 1.00), p=0.05
	Heterogeneity		Chi ² =3.05; p=0.22; I ² =34.4%

Adverse events

Adverse events were reported in six oseltamivir studies of healthy adults, all of which were in the ITT population (Table 5.12).^{46, 66-69, 80, 82, 83, 106} Four of the studies were conducted in China^{66, 67, 69} or Japan,⁶⁸ with three published in their respective languages.⁶⁶⁻⁶⁸ Adverse event data were only reported for ITT populations. There were few events and no clear evidence of differences in drug-related or serious adverse events were observed between oseltamivir and placebo. There was no statistically significant heterogeneity between studies in any of the pooled analyses. Two trials had drop-out rates greater than 5%, but not greater than 10%.^{67, 82, 83}

Table 5.12: The rate of adverse events in the ITT population of healthy adults treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
OVERALL ADVERSE EVENTS			
Deng (2004) ⁶⁶	31/599	26/577	1.16 (0.68, 1.97)
Tan (2002) ⁶⁷	4/36	5/40	0.88 (0.22, 3.55)
Kashiwagi (2000) ⁶⁸	71/154	89/159	0.67 (0.43, 1.05)
Roche WV15730 ^{46, 82, 83}	19/31	20/27	0.55 (0.18, 1.71)
	Pooled result (Fig. 10.21)		OR 0.81 (95% CI: 0.59, 1.12), p=0.20
	Heterogeneity		Chi ² =2.82; p=0.42; I ² =0%
DRUG-RELATED ADVERSE EVENTS			
Roche WV15730 ^{46, 82, 83}	14/31	7/27	2.35 (0.77, 7.17)
Li (2003) ⁶⁹	21/216	19/235	1.22 (0.64, 2.35)
	Pooled result (Fig. 10.22)		OR 1.45 (95% CI: 0.83, 2.53), p=0.19
	Heterogeneity		Chi ² =0.99; p=0.32; I ² =0%
SERIOUS ADVERSE EVENTS			
Li (2003) ⁶⁹	0/216	0/235	-
Nicholson (2000) ^{80, 106}	1/241	3/235	0.32 (0.03, 1.17)
Roche WV15730 ^{46, 82, 83}	0/31	0/27	-

5.2.3 Effectiveness in the overall ‘at risk’ population

This section includes studies that specifically recruited children with co morbid conditions and who were therefore classified as ‘at risk’, the elderly or a population described as ‘at risk’, together with the subgroups of patients from studies recruiting a mixed population where results for those ‘at risk’ were available separately. Two trials of zanamivir^{98, 104, 105} and two of oseltamivir^{71, 72, 77, 78} were not included in Turner (2003) review.⁴⁶

5.2.3.1 Zanamivir compared to placebo

Symptoms

Nine trials of zanamivir in an ‘at risk’ population reported the time to alleviation of fever, symptoms, or return to normal activity. Of these, six were in a general ‘at risk’ population,^{46, 75, 90-96, 98} one in children with results for those ‘at risk’ provided separately by GlaxoSmithKline,^{46, 99, 100} one in the elderly,^{104, 105} and one in adults with COAD or asthma.^{97, 114, 115} The follow-up period was 5 days in two trials,^{46, 98} six days in one trial,¹⁰² 14 days in one trial,⁹²⁻⁹⁴ 21 days in one trial,⁷⁵ 28 days in four trials,^{90, 91, 95-97, 99, 100, 114, 115} and 29 days (with a follow-up telephone call at 56 days) in one trial.^{104, 105} Three of the trials had a drop-out rate greater than 5%, but not greater than 10%.^{75, 90, 91, 97, 114, 115}

Treatment with zanamivir significantly reduced the time to the alleviation of all symptoms in the overall ‘at risk’ group in both the ITT and ITTI populations. There was no clear evidence of an effect of zanamivir on the time to the return to normal activity in either population (Tables 5.13 and 5.14). There was statistically significant heterogeneity between studies for the time to return to normal activity when results for the overall ‘at risk’ groups were pooled.

Table 5.13: The median number of days (unless otherwise specified) to the alleviation of symptoms and return to normal activity in the ITT ‘at risk’ population treated with zanamivir or placebo, with WMD and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zanamivir	Placebo			
ALLEVIATION OF SYMPTOMS					
*Makela (2000) ^{79, 95, 96}	13 of 136	19 of 141	9 (2.97)	11.5 (1.43)	-2.5 (-8.96, 3.96)
*Monto (1999) ⁷⁵	48 of 419	68 of 422	6.3 (N/A)	7.8 (N/A)	-1.5
*Murphy (2000) ^{97, 114, 115}	262	263	5.5 (0.34)	6.5 (0.46)	-1.00 (-2.12, 0.12)
*Boivin (2000) ^{79, 92-94}	49 of 312	60 of 257	7.5 (1.45)	6 (0.93)	1.50 (-1.88, 4.88)
*MIST (1998) ^{79, 90, 91}	37 of 227	39 of 228	5 (0.48)	7 (1.43)	-2.00 (-4.96, 0.96)
*Hedrick (2000) ^{99, 100}	22 of 224	14 of 247	3.75 (1.01)	5.75 (2.31)	-2.00 (-6.94, 2.94)
GlaxoSmithKline NAI30012 ^{104, 105}	191	167	6.5 (0.73)	7.5 (0.66)	-1.0 (-2.92, 0.92)
			Pooled result (Fig. 10.23)		WMD -0.98 (95% CI: -1.84, -0.11), p=0.03
			Heterogeneity		Chi ² =2.91; p=0.71; I ² =0%
			Pooled result for ‘at risk’ adults; trial by Hedrick (2000) removed		WMD -0.95 (95% CI: -1.83, -0.07), p=0.03
			Heterogeneity		Chi ² =2.74; p=0.60; I ² =0%
			Result for ‘at risk’ children; trial by Hedrick (2000) only		WMD -2.00 (95% CI: -6.94, 2.94), p=0.43
TIME TO NORMAL ACTIVITY					
*Murphy (2000) ^{97, 114, 115}	160	153	8.5 (0.52)	9 (0.57)	-0.50 (-2.01, 1.01)
*GlaxoSmithKline NAIB2007 ⁴⁶	23	24	3.5 (0.23)	3.5 (0.52)	0.0 (-1.11, 1.11)
*Makela (2000) ^{79, 95, 96}	13 of 136	19 of 141	9 (0.85)	14.5 (5.85)	-5.50 (-17.09, 6.09)
*MIST (1998) ^{79, 90, 91}	37 of 227	39 of 228	8 (1.38)	13 (1.01)	-5.00 (-8.36, -1.64)
*Hedrick (2000) ^{99, 100}	22 of 224	14 of 247	6 (1.17)	7 (0.46)	-1.00 (-3.46, 1.46)
*Boivin (2000) ^{79, 92-94}	49 of 312	60 of 257	11 (3.28)	9.5 (1.05)	1.50 (-5.25, 8.25)
			Pooled result (Fig. 10.24)		WMD -0.96 (95% CI: -2.32, 0.41), p=0.17
			Heterogeneity		Chi ² =8.88; p=0.11; I ² =43.7%
			Pooled result for ‘at risk’ adults; trial by Hedrick (2000) removed		WMD -1.07 (95% CI: -2.81, 0.68), p=0.23
			Heterogeneity		Chi ² =8.73; p=0.07; I ² =54.2%
			Result for ‘at risk’ children; trial by Hedrick (2000) only		WMD -1.00 (95% CI: -3.46, 1.46), p=0.43
ALLEVIATION OF FEVER					
GlaxoSmithKline NAI30020 ⁹⁸	224	107	47.5 (0.325 [†]) hours	57 (0.465 [†]) hours	-9.50 (-10.61, -8.39)

Table 5.14: The median number of days to the alleviation of symptoms and return to normal activity in the ITTI ‘at risk’ population treated with zanamivir (Zan.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zan.	Pl.			
ALLEVIATION OF SYMPTOMS					
*Murphy (2000) ^{97, 114, 115}	160	153	5 (0.31)	7 (0.52)	-2.00 (-3.19, -0.81)
*Boivin (2000) ^{79, 92-94}	36 of 312	43 of 257	5.5 (1.8)	6 (1.14)	-0.50 (-4.68, 3.68)
*MIST (1998) ^{79, 90, 91}	24 of 161	28 of 160	5 (0.61)	8 (2.75)	-3.00 (-8.52, 2.52)
*Makela (2000) ^{79, 95, 96}	12 of 136	18 of 141	9 (2.19)	11.5 (1.58)	-2.50 (-7.79, 2.79)
*Hedrick (2000) ^{99, 100}	12 of 164	10 of 182	2 (0.28)	5.75 (1.94)	-3.75 (-7.59, 0.09)
GlaxoSmithKline NAI30012 ^{104, 105}	120	114	7.25 (0.86)	7.5 (1.01)	-0.25 (-2.85, 2.35)
Pooled result (Fig. 10.25)			WMD -1.83 (95% CI: -2.81, -0.86), p=0.0002		
Heterogeneity			Chi ² =3.09; p=0.69; I ² =0%		
Pooled result for ‘at risk’ adults; trial by Hedrick (2000) removed			WMD -1.70 (95% CI: -2.71, -0.69), p=0.0004		
Heterogeneity			Chi ² =2.0609; p=0.72; I ² =0%		
Result for ‘at risk’ children; trial by Hedrick (2000) only			WMD -3.75 (95% CI: -7.59, 0.09), p=0.06		
TIME TO NORMAL ACTIVITY					
*Murphy (2000) ^{97, 114, 115}	160	153	8.5 (0.61)	9 (0.79)	-0.50 (-2.46, 1.46)
*GlaxoSmithKline NAIB2007 ⁴⁶	17	17	3.5 (0.19)	3.5 (0.47)	0.0 (-0.99, 0.99)
*Makela (2000) ^{79, 95, 96}	12 of 136	18 of 141	8.5 (1.09)	14.5 (6.06)	-6.00 (-18.07, 6.07)
*MIST (1998) ^{79, 90, 91}	24 of 161	28 of 160	6.5 (1.36)	13 (0.85)	-6.50 (-9.64, -3.36)
*Boivin (2000) ^{79, 92-94}	36 of 312	43 of 257	11 (3.3)	9.5 (1.56)	1.50 (-5.65, 8.65)
*Hedrick (2000) ^{99, 100}	12 of 164	10 of 182	4.5 (0.87)	7 (0.39)	-2.50 (-4.37, -0.63)
GlaxoSmithKline NAI30012 ^{104, 105}	120	114	11 (N/A)	13.75 (N/A)	-2.75
Pooled result (Fig. 10.26)			WMD -1.89 (95% CI: -3.95, 0.17), p=0.07		
Heterogeneity			Chi ² =19.48; p=0.002; I ² =74.3%		
Pooled result for ‘at risk’ adults; trial by Hedrick (2000) removed			WMD -1.77 (95% CI: -4.40, 0.86), p=0.19		
Heterogeneity			Chi ² =16.08; p=0.003; I ² =75.1%		
Result for ‘at risk’ children; trial by Hedrick (2000) only			WMD -2.50 (95% CI: -4.37, -0.63), p=0.009		
ALLEVIATION OF FEVER					
GlaxoSmithKline NAI30012 ^{104, 105}	120	114	4.0 (N/A)	4.5 (N/A)	-0.5

*Trials included in the Turner (2003) review

†Calculated from published SD

N/A: Not available

For comparability with the Turner (2003) review’s separate analyses of ‘at risk’ adults and children, a sensitivity analysis was undertaken in which the study in children was excluded from the overall pooled results (Tables 5.12 and 5.13).^{99, 100} ‘At risk’ adults showed the same pattern of response as the whole ‘at risk’ population, with treatment with zanamivir resulting in a statistically significant reduction in the time to the alleviation of all symptoms in both the ITT and ITTI populations. There was no clear evidence of an effect of treatment on the time to return to normal activity in either population. Statistically significant heterogeneity across studies was

observed in the analyses of the time to return to normal activity in both the ITT and ITTI populations. One study showed a significant reduction with zanamivir in the time to alleviation of fever in the ITT population.⁹⁸

Complications

Six zanamivir trials reported complications in an ‘at risk’ population. Of these one was in patients with COAD or asthma,^{97, 114, 115} one in the elderly,^{104, 105} and four in general ‘at risk’ populations.^{90-96, 98} Two had drop-out rates of greater than 5%, but not greater than 10%.^{90, 91, 97, 114, 115} Two trials had follow-up periods of only 5 days,^{98, 102} and one of 14 days.⁹²⁻⁹⁴

Table 5.15: The rate of complications in an ‘at risk’ ITT population treated with zanamivir or placebo, with OR and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS			
Boivin (2000) ^{79, 92-94}	17/49	17/60	1.34 (0.60, 3.03)
Makela (2000) ^{79, 95, 96}	4/13	11/19	0.32 (0.07, 1.43)
MIST (1998) ^{79, 90, 91}	5/37	18/39	0.18 (0.06, 0.57)
GlaxoSmithKline NAI30012 ^{104, 105}	57/191	56/167	0.84 (0.54, 1.32)
	Pooled result (Fig. 10.27)		OR 0.73 (95% CI: 0.51, 1.04), p=0.08
	Heterogeneity		Chi ² =9.47; p=0.02; I ² =68.3%
COMPLICATIONS REQUIRING HOSPITALISATION			
Murphy (2000) ^{97, 114, 115}	3/261	6/263	0.50 (0.12, 2.01)
PNEUMONIA			
Murphy (2000) ^{97, 114, 115}	0/261	2/263	0.20 (0.01, 4.19)
GlaxoSmithKline NAI30012 ^{104, 105}	3/191	3/166	0.87 (0.17, 4.35)
	Pooled result (Fig. 10.28)		OR 0.57 (95% CI: 0.15, 2.23), p=0.42
	Heterogeneity		Chi ² =0.71; p=0.40; I ² =0%
BRONCHITIS			
Murphy (2000) ^{97, 114, 115}	9/261	26/263	0.33 (0.15, 0.71)
GlaxoSmithKline NAI30020 ⁹⁸	4/223	2/106	0.95 (0.17, 5.27)
GlaxoSmithKline NAI30012 ^{104, 105}	10/191	18/166	0.45 (0.20, 1.01)
	Pooled result (Fig. 10.29)		OR 0.41 (95% CI: 0.24, 0.70), p=0.0009
	Heterogeneity		Chi ² =1.32; p=0.52; I ² =0%
ANTIBIOTIC USE			
Boivin (2000) ^{79, 92-94}	13/49	9/60	2.05 (0.79, 5.30)
Makela (2000) ^{79, 95, 96}	0/13	5/19	0.10 (0.00, 1.94)
MIST (1998) ^{79, 90, 91}	5/37	15/39	0.25 (0.08, 0.78)
GlaxoSmithKline NAI30012 ^{104, 105}	32/191	36/167	0.73 (0.43, 1.24)
	Pooled result (Fig. 10.30)		OR 0.71(95% CI: 0.47, 1.07), p=0.10
	Heterogeneity		Chi ² =9.67; p=0.02; I ² =69.0%

The incidence of complications was low, and there was no clear evidence of a difference in rates of overall complications between zanamivir and placebo in either the ITT or ITTI populations (Tables 5.15 and 5.16). With a total of 8 events, there was no evidence of a difference in the rates of pneumonia between groups in the either population. Analysis of antibiotic use was also based on limited data and there was no clear evidence of a difference in either population. The incidence of bronchitis was significantly lower with zanamivir in the ITT populations, which included one study restricted to an elderly population¹⁰⁴ and another restricted to patients with COAD or asthma.^{97, 114, 115} Statistically significant heterogeneity was observed in three analyses, overall complications in the ITT population, and antibiotic use in both the ITT and ITTI populations.

Table 5.16: The rate of complications in an ‘at risk’ ITTI population treated with zanamivir or placebo, with OR and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS			
Makela (2000) ^{79, 95, 96}	4/12	11/18	0.32 (0.07, 1.47)
Murphy (2000) ^{97, 114, 115}	52/160	56/153	0.83 (0.52, 1.33)
Boivin (2000) ⁹²⁻⁹⁴	12/36	9/43	1.89 (0.69, 5.19)
GlaxoSmithKline NAI30012 ^{104, 105}	39/120	46/114	0.71 (0.42, 1.21)
	Pooled result (Fig. 10.31)		OR 0.82 (95% CI: 0.59, 1.13), p=0.23
	Heterogeneity		Chi ² =4.37; p=0.22; I ² =31.3%
COMPLICATIONS REQUIRING HOSPITALISATION			
GlaxoSmithKline NAI30012 ^{104, 105}	5/120	4/114	1.20 (0.31, 4.57)
PNEUMONIA			
Murphy (2000) ^{97, 114, 115}	0/160	0/153	-
ANTIBIOTIC USE			
Makela (2000) ^{79, 95, 96}	0/12	5/18	0.10 (0.00, 1.96)
Murphy (2000) ^{97, 114, 115}	7/160	16/153	0.39 (0.16, 0.98)
Boivin (2000) ⁹²⁻⁹⁴	9/36	5/43	2.53 (0.76, 8.41)
GlaxoSmithKline NAI30012 ^{104, 105}	23/120	30/114	0.66 (0.36, 1.23)
	Pooled result (Fig. 10.32)		OR 0.66 (95% CI: 0.42, 1.03), p=0.07
	Heterogeneity		Chi ² =7.63; p=0.05; I ² =60.7%

Adverse events

Four zanamivir trials reported overall adverse events in an ITT, ‘at risk’, population (Table 5.17). Of these one was in patients with COAD or asthma,^{97, 114, 115} one in the elderly,^{104, 105} and two in general ‘at risk’ populations.^{90, 91, 98} There was no significant difference in the number of overall, drug-related, or serious, adverse events. The analysis of overall adverse events was subject to a

high degree of statistical heterogeneity, seemingly caused by the study conducted in the elderly population.

Table 5.17: The rate of adverse events in an ‘at risk’ population treated with zanamivir or placebo, with OR and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL ADVERSE EVENTS			
Murphy (2000) ^{97, 114, 115}	99/261	111/263	0.84 (0.59, 1.19)
MIST (1998) ^{79, 90, 91}	14 [†] /37	22 [†] /39	0.47 (0.19, 1.18)
GlaxoSmithKline NAI30020 ⁹⁸	11/223	10/106	0.50 (0.20, 1.21)
GlaxoSmithKline NAI30012 ^{104, 105}	66 [†] /191	50 [†] /166	6.12 (3.47, 10.80)
	Pooled result (Fig. 10.33)		OR 1.24 (95% CI: 0.96, 1.60), p=0.10
	Heterogeneity		Chi ² =43.63; p<0.0001; I ² =93.1%
DRUG-RELATED ADVERSE EVENTS			
Murphy (2000) ^{97, 114, 115}	23/261	23/263	1.01 (0.55, 1.85)
SERIOUS ADVERSE EVENTS			
GlaxoSmithKline NAI30012 ^{104, 105}	5/191	9/166	1.01 (0.33, 3.12)
GlaxoSmithKline NAI30020 ⁹⁸	2/223	1/106	0.95 (0.09, 10.60)
Murphy (2000) ^{97, 114, 115}	3/261	7/263	0.43 (0.11, 1.66)
	Pooled result (Fig. 10.34)		OR 0.72 (95% CI: 0.32, 1.62), p=0.41
	Heterogeneity		Chi ² =0.98; p=0.61; I ² =0%

[†]Trial data clearly indicated that outcomes considered as complications were included in overall adverse events

5.2.3.2 Oseltamivir compared to placebo

Symptoms

Six trials of oseltamivir in an ‘at risk’ population reported the time to alleviation of fever, all symptoms, or return to normal activity. Of these, two were in a general ‘at risk’ population,^{46, 73} one in children with asthma,⁷⁸ and three in the elderly.^{46, 73} The follow-up period was 21 days in five trials,^{46, 73, 108} and 28 days in two trials.^{77, 109} The drop-out rates were unclear in six of the studies; only Whitley (2001) reported a drop-out rate less than 5%.¹⁰⁹

Although the direction of effect favoured oseltamivir, there was no clear evidence of a reduction in the time to the alleviation of symptoms or return to normal activity in the overall ‘at risk’ population with oseltamivir, in either the ITT or ITTI populations (Tables 5.18 and 5.19, respectively). For comparability with the Turner (2003) review’s separate analyses of ‘at risk’ adults and children, sensitivity analyses were undertaken in which the study in children was excluded from the overall pooled results, and analysed separately.^{78, 109} When this trial was removed, the time to return to normal activity was significantly less (by approximately 3 days) with oseltamivir in the ITTI ‘at risk’ adult population (Tables 5.18 and 5.19). There were no

statistically significant differences between oseltamivir and placebo in ‘at risk’ children for either outcome in either population. There was no statistically significant heterogeneity across studies in any of the analyses.

Table 5.18: The median number of hours to the alleviation of symptoms and return to normal activity in the ITT ‘at risk’ population treated with oseltamivir (Os.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF SYMPTOMS					
*Martin (2001) ^{73, 108}					
‘At risk’	199	203	143 (13.45)	163 (16.27)	-9.80 (-44.87, 25.27)
*Martin (2001) ^{73, 108}					
Elderly	360	376	139.2 (12.2)	149 (13.09)	-20.00 (-61.37, 21.37)
Johnston (2005) ⁷⁸	170	164	118.6 (9.87)	139.8 (8.28)	-21.20 (-46.45, 4.05)
	Pooled result (Fig. 10.35)		WMD -17.84 (95% CI: -36.20, 0.52), p=0.06		
	Heterogeneity		Chi ² =0.28; p=0.87; I ² =0%		
	Pooled result for ‘at risk’ adults; trial by Johnston (2005) excluded		WMD -14.06 (95% CI: -40.82, 12.96), p=0.30		
	Heterogeneity		Chi ² =0.14; p=0.71; I ² =0%		
TIME TO NORMAL ACTIVITY					
*Roche WV15812 ^{46, 73}	152	148	344.4 (56.12)	349.23 (57.68)	-4.83 (-162.55, 152.89)
*Roche WV15872 ^{46, 73}	47	53	205.57 (51.50)	191.73 (31.33)	13.84 (-104.31, 131.99)
*Roche WV15819 ^{46, 73}	75	93	298.48 (66.80)	388.4 (31.55)	-89.92 (-234.72, 54.88)
*Roche WV15876 ^{46, 73}	55	44	395.23 (110.09)	394.9 (76.22)	0.33 (-262.10, 262.76)
*Roche WV15978 ^{46, 73}	229	238	304.48 (34.54)	416.98 (29.57)	-112.50 (-201.62, -23.38)
	Pooled result for ‘at risk’ adults (Fig. 10.36)		WMD -58.84 (95% CI: -116.58, -1.11), p=0.05		
	Heterogeneity		Chi ² =3.67; p=0.45; I ² =0%		

Table 5.19 The median number of hours to the alleviation of symptoms and return to normal activity in the ITTI ‘at risk’ population treated with oseltamivir (Os.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF SYMPTOMS					
*Martin (2001) ^{73, 108}					
‘At risk’	118	133	151.5 (21.88)	161 (24.98)	-24.90 (-68.77, 18.97)
*Martin (2001) ^{73, 108}					
Elderly	223	254	150 (12.72)	174.9 (18.42)	-9.50 (-74.59, 55.59)
Johnston (2005) ⁷⁸	84	95	123.9 (11.99)	134.3 (7.98)	-10.40 (-38.63, 17.83)
Pooled result (Fig. 10.37)			WMD -14.04 (95% CI: -36.34, 8.26), p=0.22		
Heterogeneity			Chi ² =0.32; p=0.85; I ² =0%		
Pooled result for ‘at risk’ adults; trial by Johnston (2005) excluded			WMD -20.09 (95% CI: -56.47, 16.29), p=0.28		
Heterogeneity			Chi ² =0.15; p=0.70; I ² =0%		
TIME TO NORMAL ACTIVITY					
Johnston NV16871 (2005) ⁷⁸	84	95	101.4 (8.73)	114 (8.29)	-12.60 (-36.20, 11.00)
*Roche WV15812 ^{46, 73}	97	104	299.9 (83.28)	335.48 (53.40)	-35.58 (-229.48, 158.32)
*Roche WV15872 ^{46, 73}	21	29	199.73 (59.09)	282.9 (59.70)	-83.17 (-247.81, 81.47)
*Roche WV15819 ^{46, 73}	52	69	277.9 (60.00)	370.48 (51.5)	-92.58 (-247.55, 62.39)
*Roche WV15876 ^{46, 73}	26	20	464.73 (129.48)	428.53 (44.70)	36.20 (-232.28, 304.68)
*Roche WV15978 ^{46, 73}	145	165	336.65 (46.18)	416.98 (14.65)	-80.33 (-175.29, 14.63)
Pooled result (Fig. 10.38)			WMD -19.20 (95% CI: -41.42, 3.01), p=0.09		
Heterogeneity			Chi ² =3.52; p=0.62; I ² =0%		
Pooled result for ‘at risk’ adults; trial by Johnston (2005) excluded			WMD -70.79 (95% CI: -136.75, -4.84), p=0.04		
Heterogeneity			Chi ² =0.87; p=0.93; I ² =0%		
ALLEVIATION OF FEVER					
*Martin (2001) ^{73, 108}					
‘At risk’	118	133	42.8 (N/A)	67.9 (N/A)	-25.1
*Martin (2001) ^{73, 108}					
Elderly	222	254	66.9 (N/A)	89.5 (N/A)	-22.6

*Trials included in the Turner (2003) review

†Calculated from CIs

N/A: Not available

Complications

Seven trials reported the rate of complications in ‘at risk’ populations in trials of oseltamivir, one in children with asthma,⁷⁸ two in the elderly (combined)⁷³, and four in a general ‘at risk’ population, three of which were combined.⁷¹⁻⁷³ (Tables 5.20 and 5.21). Treatment with oseltamivir significantly reduced antibiotic use in the ITTI population. However, the incidence of other outcomes was low, and there was no clear evidence of other differences between oseltamivir and the comparator. No statistically significant heterogeneity was observed in the pooled analyses.

Table 5.20: The rate of complications in the ITT ‘at risk’ population treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
COMPLICATIONS REQUIRING HOSPITALISATION			
Roche NV16871 ⁷⁷	0/165	1/164	0.33 (0.01, 8.14)
PNEUMONIA			
Johnston NV16871 (2005) ⁷⁸	1/170	2/164	0.48 (0.04, 5.34)
BRONCHITIS			
Johnston NV16871 (2005) ⁷⁸	5/170	1/164	4.94 (0.57, 42.74)
ANTIBIOTIC USE			
Johnston NV16871 (2005) ⁷⁸	16/170	16/164	0.96 (0.46, 1.99)

Table 5.21: The rate of complications in the ITTI ‘at risk’ population treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS			
Roche NV16871 ⁷⁷	1/43	8/51	0.13 (0.02, 1.07)
COMPLICATIONS REQUIRING HOSPITALISATION			
Johnston NV16871 (2005) ⁷⁸	2/84	1/95	2.29 (0.20, 25.75)
Lin (2006) ^{71, 72}	2/27	5/29	0.38 (0.07, 2.17)
Martin (2001) ^{73, 108} Elderly	3/223	8/254	0.42 (0.11, 1.60)
	Pooled result (Fig. 10.39) Heterogeneity		OR 0.54 (95% CI: 0.21, 1.37), p=0.20 Chi ² =1.66; p=0.44; I ² =0%
PNEUMONIA			
Martin (2001) ^{73, 108} Elderly	5/223	6/254	0.95 (0.29, 3.15)
Martin (2001) ^{73, 108} ‘At risk’	2/118	2/133	1.13 (0.16, 8.15)
	Pooled result (Fig. 10.40) Heterogeneity		OR 0.99 (95% CI: 0.36, 2.77), p=0.99 Chi ² =0.02; p=0.88; I ² =03%
GP CONSULTATIONS			
Johnston NV16871 (2005) ⁷⁸	21/84	21/95	1.17 (0.59, 2.35)
ANTIBIOTIC USE			
Lin (2006) ^{71, 72**}	10/27	20/29	0.26 (0.09, 0.80)
Martin (2001) ^{73, 108} Elderly	31/223	49/254	0.68 (0.41, 1.10)
Martin (2001) ^{73, 108} ‘At risk’	21/118	27/133	0.85 (0.45, 1.60)
Roche NV16871 ⁷⁷	1/43	7/51	0.15 (0.02, 1.27)
	Pooled result (Fig. 10.41) Heterogeneity		OR 0.57 (95% CI: 0.33, 0.98), p=0.04 Chi ² =5.04; p=0.17; I ² =40.5%

**Used symptomatic relief as comparator, not placebo

Adverse events

Two trials reported the incidence of adverse events in ‘at risk’ populations in trials of oseltamivir, one in children with asthma⁷⁸ and one in a general ‘at risk’^{71, 72} population (Table 5.22). There was no evidence of a difference in the rate of overall, drug-related or serious adverse events in the ITT or ITTI populations between oseltamivir and placebo. No statistically significant heterogeneity was observed in the pooled analysis.

Table 5.22: The rate of adverse events in an ‘at risk’ population treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
OVERALL ADVERSE EVENTS (ITT)			
Lin (2006) ^{71, 72**}	2/58	0/60	5.35 (0.25, 113.95)
Johnston NV16871 (2005) ⁷⁸	83/170	84/164	0.91 (0.59, 1.40)
	Pooled result (Fig. 10.42)		OR 0.96 (95% CI: 0.63, 1.46), p=0.83
	Heterogeneity		Chi ² =1.27; p=0.26; I ² =21.53%
OVERALL ADVERSE EVENTS (ITTI)			
Roche NV16871 ⁷⁷	10/43	11/51	1.10 (0.42, 2.91)
SERIOUS ADVERSE EVENTS (ITTI)			
Roche NV16871 ⁷⁷	1/43	1/51	1.19 (0.07, 19.62)

**Used symptomatic relief as comparator, not placebo

5.2.4 Effectiveness in children

Four studies reported the effectiveness of zanamivir⁹⁹⁻¹⁰³ or oseltamivir^{78, 109} specifically in children. One trial of zanamivir^{102, 103} and one of oseltamivir⁷⁸ were not included in Turner (2003) review.⁴⁶ One direct head-to-head comparison between zanamivir and oseltamivir that met the inclusion criteria,¹¹⁰ and was not included in the Turner (2003) review,⁴⁶ did not provide data in a format that could be used in the current review. Therefore four studies are included in the analyses. These are analysed separately from the general ‘at risk’ population. The age of the children recruited varied across studies; two recruited 5 to 12 year olds,^{78, 99, 100} one 5 to 14 year olds,^{102, 103} one 6 to 17 year olds,⁷⁷ and one 1 to 12 year olds.¹⁰⁹

5.2.4.1 Zanamivir compared to placebo

Symptoms

Two studies reported the effectiveness of zanamivir on the time to the alleviation of symptoms and return to normal activity in children (Table 5.23 and 5.24).^{99, 100, 102} The follow-up period was 6 days in one trial,¹⁰² and 28 days on the other.^{99, 100} Both trials had a drop-out rate less than 5%.^{99,}

^{100, 102} Data were available for healthy and ‘at risk’ children separately for the trial by Hedrick (2000)^{99, 100} but not for the NAI30028 trial.¹⁰²

Zanamivir resulted in a significant reduction in the time to alleviation of symptoms, with no statistically significant heterogeneity observed in the pooled analysis of the ITT population. When the population recruited in Hedrick^{99, 100} was split into healthy and ‘at risk’ children. This study showed a statistically significant reduction in the time to normal activity in the ITTI ‘at risk’ population, however, this analysis included only 22 children. The effect of zanamivir was more pronounced in healthy children, and the analysis was based upon 324 children. There were no significant differences between zanamivir and placebo for the time to return to normal activity.

Table 5.23: The median number of days to the alleviation of symptoms and return to normal activity in the ITT population of children treated with zanamivir or placebo, with WMD and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zanamivir	Placebo			
ALLEVIATION OF SYMPTOMS					
GlaxoSmithKline NAI30028 ^{102, 103}	176	90	5 (0.371)	5.5 (0.633)	-0.50 (-1.94, 0.94)
*Hedrick (2000) ^{99, 100}	224	247	4 (0.21)	5.0 (0.16)	-1.00 (-1.52, -0.48)
All children	Pooled result for all children (Fig. 10.43)		WMD -0.94 (95% CI: -1.43, -0.46), p<0.0001		
	Heterogeneity		Chi ² =0.41; p=0.52; I ² =0.3%		
*Hedrick (2000) ^{99, 100}	202 of 224	233 of 247	4 (0.2)	5.0 (0.16)	-1.00 (-1.50, -0.50)
Healthy children					
*Hedrick (2000) ^{99, 100}	22 of 224	14 of 247	3.75 (1.01)	5.75 (2.31)	-2.00 (-6.94, 2.94)
‘At risk’ children					
TIME TO NORMAL ACTIVITY					
*Hedrick (2000) ^{99, 100}	224	247	5.5 (0.26)	6 (0.28)	-0.50 (-1.25, 0.25)
All children					
*Hedrick (2000) ^{99, 100}	202 of 224	233 of 247	5.5 (0.26)	6 (0.29)	-0.50 (-1.26, 0.26)
Healthy children					
*Hedrick (2000) ^{99, 100}	22 of 224	14 of 247	6 (1.17)	7 (0.46)	-1.00 (-3.46, 1.46)
‘At risk’ children					
ALLEVIATION OF FEVER					
GlaxoSmithKline NAI30028 ^{102, 103}	176	90	2.5 (N/A)	3.0 (N/A)	-0.5

*Trial included in the Turner (2003) review

Table 5.24: The median number of days to the alleviation of symptoms and return to normal activity in the ITTI population of children treated with zanamivir or placebo, with WMD and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zanamivir	Placebo			
ALLEVIATION OF SYMPTOMS					
*Hedrick (2000) ^{99, 100}	164	182	4 (0.24)	5 (0.19)	-1.00 (-1.60, -0.40)
All children					
*Hedrick (2000) ^{99, 100}	152 of 164	172 of 182	4 (0.23)	5 (0.19)	-1.00 (-1.59, -0.41)
Healthy children					
*Hedrick (2000) ^{99, 100}	12 of 164	10 of 182	2 (0.28)	5.75 (1.94)	-3.75 (-7.59, 0.09)
'At risk' children					
TIME TO NORMAL ACTIVITY					
*Hedrick (2000) ^{99, 100}	164	182	5.5 (0.30)	6 (0.31)	-0.50 (-1.35, 0.35)
All children					
*Hedrick (2000) ^{99, 100}	152 of 164	172 of 182	5.5 (0.30)	6 (0.32)	-0.50 (-1.36, 0.36)
Healthy children					
*Hedrick (2000) ^{99, 100}	12 of 164	10 of 182	4.5 (0.87)	7 (0.39)	-2.50 (-4.37, -0.63)
'At risk' children					

*Trial included in the Turner (2003) review

N/A: Not available

Complications

Two studies of zanamivir in children reported data on complications (Table 5.25 and 5.26),⁹⁹⁻¹⁰³ one of these had a follow-up period of only 5 days.¹⁰² There was no clear evidence of differences between zanamivir and placebo for any complication in the ITT or ITTI populations.

Adverse events

The same two studies reported adverse event data,^{99, 100, 102, 103} the study with a follow-up period of 5 days for previous outcomes, had a follow-up period of 14 days for adverse events.¹⁰² Adverse event data were only reported for the ITT population (Table 5.27). The pooled odds ratios revealed no significant differences between the zanamivir and placebo groups for overall, drug-related, or serious, adverse events. No statistically significant heterogeneity was observed in any analysis.

Table 5.25: The rates of complications in the ITT population of children treated with zanamivir or placebo, with OR and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS			
Hedrick (2000) ^{99, 100}	37/224	53/247	0.72 (0.45, 1.15)
GlaxoSmithKline NAI30028 ¹⁰²	59/172	28/89	1.14 (0.66, 1.97)
	Pooled result (Fig. 10.44)		OR 0.88 (95% CI: 0.62, 1.24), p=0.46
	Heterogeneity		Chi ² =1.52; p=0.22; I ² =34.1%
COMPLICATIONS REQUIRING HOSPITALISATION			
GlaxoSmithKline NAI30028 ^{102, 103}	1/176	0/90	1.55 (0.06, 38.36)
PNEUMONIA			
GlaxoSmithKline NAI30028 ^{102, 103}	2/176	2/90	0.51 (0.07, 3.65)
BRONCHITIS			
Hedrick (2000) ⁹⁹⁻¹⁰¹	2/224	0/247	5.56 (0.27, 116.48)
GlaxoSmithKline NAI30028 ^{102, 103}	3/176	3/90	0.50 (0.10, 2.54)
	Pooled result (Fig. 10.45)		OR 1.05 (95% CI: 0.28, 3.89), p=0.95
	Heterogeneity		Chi ² =1.94; p=0.16; I ² =48.6%
ANTIBIOTIC USE			
Hedrick (2000) ⁹⁹⁻¹⁰¹	2/224	35/247	0.05 (0.01, 0.23)
GP CONSULTATIONS			
GlaxoSmithKline NAI30028 ^{102, 103}	29/176	17/90	0.85 (0.44, 1.64)
OTITIS MEDIA			
GlaxoSmithKline NAI30028 ^{102, 103}	5/176	4/90	0.63 (0.16, 2.40)

Table 5.26: The rates of complications in the ITTI population of children treated with zanamivir or placebo, with OR and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS			
Hedrick (2000) ⁹⁹⁻¹⁰¹	26/164	41/182	0.65 (0.38, 1.12)
PNEUMONIA			
Hedrick (2000) ⁹⁹⁻¹⁰¹	1/164	2/182	0.55 (0.05, 6.15)
BRONCHITIS			
Hedrick (2000) ⁹⁹⁻¹⁰¹	3/164	2/182	1.68 (0.28, 10.16)
ANTIBIOTIC USE			
Hedrick (2000) ⁹⁹⁻¹⁰¹	19/164	27/182	0.75 (0.40, 1.41)
OTITIS MEDIA			
Hedrick (2000) ⁹⁹⁻¹⁰¹	15/164	17/182	0.98 (0.47, 2.03)

Table 5.27: The rate of adverse events in the ITT population of children treated with zanamivir or placebo, with OR and 95% confidence intervals

Study	Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL ADVERSE EVENTS			
Hedrick (2000) ^{99, 100}	48/224	65/247	OR 0.76 (0.50, 1.17)
GlaxoSmithKline NAI30028 ^{102, 103}	40 [‡] /176	18 [‡] /90	OR 1.18 (0.63, 2.20)
	Pooled result (Fig. 10.46)		OR 0.88 (95% CI: 0.62, 1.24), p=0.46
	Heterogeneity		Chi ² =1.25; p=0.26; I ² =20.1%
DRUG-RELATED ADVERSE EVENTS			
Hedrick (2000) ^{99, 100}	7/224	5/247	OR 1.56 (0.49, 4.99)
GlaxoSmithKline NAI30028 ^{102, 103}	11/176	5/90	OR 1.13 (0.38, 3.37)
	Pooled result (Fig. 10.47)		OR 1.32 (95% CI: 0.59, 2.92), p=0.50
	Heterogeneity		Chi ² =0.16; p=0.69; I ² =0%
SERIOUS ADVERSE EVENTS			
Hedrick (2000) ^{99, 100}	1/224	0/247	OR 3.32 (0.13, 81.97)
GlaxoSmithKline NAI30028 ^{102, 103}	1/176	0/90	OR 1.55 (0.06, 38.36)
	Pooled result (Fig. 10.48)		OR 2.29 (95% CI: 0.24, 22.09), p=0.47
	Heterogeneity		Chi ² =0.11; p=0.74; I ² =0%

[‡] Trial data clearly indicated that outcomes considered as complications were included in overall adverse events

5.2.4.2 Oseltamivir compared to placebo

Symptoms

Two studies reported the effectiveness of oseltamivir on the time to the alleviation of symptoms and return to normal activity in children;^{78, 109} one was restricted to children with asthma.⁷⁸ The follow-up period was 21 days in one trial,⁷⁸ and 28 days in the other.¹⁰⁹ The drop-out rate was less than 10% in both trials. The time to the alleviation of fever, all symptoms, and return to normal activity were significantly lower with oseltamivir compared to placebo (Tables 5.28 and 5.29). The analysis of time to normal activity in the ITTI population was subject to statistically significant heterogeneity. One of the studies was restricted to children aged 6 to 12 years who had asthma,⁷⁸ whereas the other included a larger number of children from a more representative population, aged between 1 and 12 years,¹⁰⁹ which could explain the observed heterogeneity.⁷⁸

Table 5.28: The median number of hours to the alleviation of symptoms and return to normal activity in the ITT population of children treated with oseltamivir (Os.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF SYMPTOMS					
Johnston (2005) ⁷⁸ 'At risk' children	170	164	118.6 (9.87 [†])	139.8 (8.28 [†])	-21.20 (-46.45, 4.05)
*Whitley (2001) ¹⁰⁹	344	351	105 (5.58)	126 (5.08)	-21.00 (-35.79, -6.21)
Pooled result (Fig. 10.49)			WMD -21.05 (95% CI: -33.81, -8.29), p=0.001		
Heterogeneity			Chi ² =0.0; p=0.99; I ² =0%		
TIME TO NORMAL ACTIVITY					
*Whitley (2001) ¹⁰⁹	331	338	70 (4.26)	100.08 (5.26)	-30.08 (-43.35, -16.81)
ALLEVIATION OF FEVER					
*Whitley (2001) ¹⁰⁹	344	351	44 (2.05 [†])	68 (6.38 [†])	-24.00 (-37.13, -10.87)

Table 5.29: The median number of hours to the alleviation of symptoms and return to normal activity in the ITTI population of children treated with oseltamivir (Os.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF SYMPTOMS					
*Whitley (2001) ¹⁰⁹	217	235	101 (7.15)	137 (5.36)	-36.00 (-53.51, -18.49)
Johnston NV16871 (2005) ⁷⁸ 'At risk' children	84	95	123.9 (11.99 [†])	134.3 (7.98 [†])	-10.40 (-38.63, 17.83)
Pooled result (Fig. 10.50)			WMD -28.88 (95% CI: -43.77, -14.0), p=0.0001		
Heterogeneity			Chi ² =2.28; p=0.13; I ² =56.2%		
TIME TO NORMAL ACTIVITY					
Johnston NV16871 (2005) ⁷⁸ 'At risk' children	84	95	101.4 (8.73)	114 (8.29)	-12.60 (-36.20, 11.00)
*Whitley (2001) ¹⁰⁹	209	225	67.1 (6.28)	111.667 (7.50)	-44.57 (-63.75, -25.39)
Pooled result (Fig. 10.51)			WMD -31.85 (95% CI: -46.73, -16.96), p<0.0001		
Heterogeneity			Chi ² =4.25; p=0.04; I ² =76.4%		

*Trial included in the Turner (2003) review

[†]Calculated from CIs

N/A: Not available

Complications

The same two studies reported on complications (Tables 5.30 and 5.31),^{78, 109} one reported a significant reduction in antibiotic use and the incidence of otitis media in the ITTI population.¹⁰⁹ The other study, restricted to children with asthma, reported no statistically significant difference

between oseltamivir and placebo for any complication, GP consultations or hospitalisation rates.⁷⁸
 The trials had drop-out rates of 3%¹⁰⁹ and 9%.⁷⁸

Table 5.30: The rate of complications in the ITT population of children treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
COMPLICATIONS REQUIRING HOSPITALISATION			
Whitley (2001) ¹⁰⁹	0/344	2/351	0.20 (0.01, 4.24)
PNEUMONIA			
Johnston NV16871 (2005) ⁷⁸			
'At risk' children	3/170	6/164	0.47 (0.12, 1.92)
Whitley (2001) ¹⁰⁹	7/344	11/351	0.64 (0.25, 1.68)
	Pooled result (Fig. 10.52)		OR 0.58 (95% CI: 0.26, 1.28), p=0.18
	Heterogeneity		Chi ² =0.12; p=0.72; I ² =0%
BRONCHITIS			
Johnston NV16871 (2005) ⁷⁸			
'At risk' children	5/170	1/164	4.94 (0.57, 42.74)
OTITIS MEDIA			
Johnston NV16871 (2005) ⁷⁸			
'At risk' children	6/170	7/164	0.82 (0.27, 2.50)
ANTIBIOTIC USE			
Johnston NV16871 (2005) ⁷⁸			
'At risk' children	16/170	16/164	0.96 (0.46, 1.99)

Table 5.31: The rate of complications in the ITTI population of children treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
COMPLICATIONS REQUIRING HOSPITALISATION			
Johnston NV16871 (2005) ⁷⁸			
'At risk' children	2/84	1/95	2.29 (0.20, 25.75)
Whitley (2001) ¹⁰⁹	0/217	2/235	0.21 (0.01, 4.50)
	Pooled result (Fig. 10.53)		OR 0.79 (95% CI: 0.16, 4.02), p=0.78
	Heterogeneity		Chi ² =1.45; p=0.23; I ² =31.0%
PNEUMONIA			
Whitley (2001) ¹⁰⁹	3/217	4/235	0.81 (0.18, 3.66)
GP CONSULTATIONS			
Johnston NV16871 (2005) ⁷⁸			
'At risk' children	21/84	21/95	1.17 (0.59, 2.35)
OTITIS MEDIA			
Whitley (2001) ¹⁰⁹	36/217	65/235	0.52 (0.33, 0.82)
ANTIBIOTIC USE			
Whitley (2001) ¹⁰⁹	26/217	50/235	0.50 (0.30, 0.84)

Adverse events

The same two trials reported the numbers of overall or serious adverse events in the ITT population, with no evidence of differences between oseltamivir and placebo (Table 5.32).^{78, 109} The trial by Johnston had a particularly high rate of adverse events, which may have been due to the fact that the trial was restricted to children with asthma, and classed complications such as bronchitis and pneumonia as adverse events.⁷⁸

Table 5.32: The rate of adverse events in children treated with oseltamivir or placebo, with OR and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
OVERALL ADVERSE EVENTS			
Johnston NV16871 (2005) ⁷⁸			
‘At risk’ children	83 [‡] /170	84 [‡] /164	0.91 (0.59, 1.40)
SERIOUS ADVERSE EVENTS			
Whitely (2001) ¹⁰⁹	3/344	2/351	1.54 (0.25, 9.24)

[‡]Trial data clearly indicated that outcomes considered as complications were included in overall adverse events

5.2.5 Effectiveness in the elderly

Eight studies reported effectiveness in the elderly (aged 65 years and over), five of zanamivir^{92-97, 104, 105, 114, 115} and three of oseltamivir.⁷³ All of the trials of oseltamivir were conducted in a population restricted to the elderly, whereas only one study of zanamivir recruited solely an elderly population;^{104, 105} the results for the other studies were small subgroups from mixed populations. These data are analysed separately from the general ‘at risk’ population.

5.2.5.1 Zanamivir compared to placebo

Symptoms

Five studies reported the effectiveness of zanamivir on the time to the alleviation of symptoms and return to normal activity in the elderly, although the numbers of patients in four of these were very small as the data were obtained from studies with mixed populations.^{90, 91, 95-97, 104, 105, 115, 116} One trial of zanamivir was not included in the Turner (2003) review,^{104, 105} and although the trials of mixed populations evaluating zanamivir were included in the Turner (2003) review,⁴⁶ the separate data for the elderly are new to this review. There were no new trials for oseltamivir. The follow-up period was 14 days in one trial,⁹²⁻⁹⁴ 28 days in three trials,^{90, 91, 95-97, 115, 116} and 29 days with a further telephone call at 59 days in one trial.^{104, 105} The drop-out rate less than 5% in all

trials. There was no clear evidence of differences between zanamivir and placebo for either outcome in any population assessed (Tables 5.33 and 5.34).

Table 5.33: The median number of days to the alleviation of symptoms in an elderly ITT population treated with zanamivir (Zan.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zan.	Pl.			
ALLEVIATION OF SYMPTOMS					
Boivin (2000) ⁹²⁻⁹⁴	23	21	7 (2.01)	7.5 (1.83)	-0.50 (-5.83, 4.83)
GlaxoSmithKline NAI30012 ^{104, 105}	191	167	6.5 (0.73)	7.5 (0.66)	-1.00 (-2.92, 0.92)
Makela (2000) ^{95, 96}	4	9	11 (6.10)	14.5 (8.35)	-3.50 (-23.77, 16.77)
MIST (1998) ^{79, 90, 91}	7	7	5.5 (3.74)	13 (3.42)	-7.50 (-17.43, 2.43)
Murphy (2000) ^{97, 114, 115}	24	22	12.5 (6.22)	10 (6.25)	2.50 (-14.78, 19.78)
Pooled result (Fig. 10.54)			WMD -1.13 (95% CI: -2.90, 0.63), p=0.21		
Heterogeneity			Chi ² =1.87; p=0.76; I ² =0%		

Table 5.34: The median number of days to the alleviation of symptoms and return to normal activity in an elderly ITTI population treated with zanamivir (Zan.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zan.	Pl.			
ALLEVIATION OF SYMPTOMS					
Boivin (2000) ⁹²⁻⁹⁴	21	16	4.5 (2.23)	7.25 (1.68)	-2.75 (-8.22, 2.72)
MIST (1998) ^{79, 90, 91}	4	5	2.75 (3.23)	13 (4.34)	-10.25 (-20.85, 0.35)
Makela (2000) ^{95, 96}	4	8	11 (6.19)	21.25 (7.21)	-10.25 (-28.88, 8.38)
Murphy (2000) ^{97, 114, 115}	16	15	10 (4.27)	12 (6.94)	-2.00 (-17.97, 13.97)
GlaxoSmithKline NAI30012 ^{104, 105}	120	114	7.25 (0.86)	7.5 (1.01)	-0.25 (-2.85, 2.35)
Pooled result (Fig. 10.55)			WMD -1.85 (95% CI: -4.77, 1.07), p=0.21		
Heterogeneity			Chi ² =4.53; p=0.34; I ² =11.7%		
TIME TO NORMAL ACTIVITY					
GlaxoSmithKline NAI30012 ^{104, 105}	120	114	11 (N/A)	13.75 (N/A)	-2.75
ALLEVIATION OF FEVER					
GlaxoSmithKline NAI30012 ^{104, 105}	120	114	4 (N/A)	4.5 (N/A)	-0.5

N/A: Not available

Complications

One study reported no significant differences between the treatment groups for any complication measured in the elderly (Tables 5.35 and 5.36).¹⁰⁴

Table 5.35: The rate of complications in an elderly ITT population treated with zanamivir or placebo, with OR and 95% confidence intervals¹⁰⁴

Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS		
57/191	56/167	0.84 (0.54, 1.32)
PNEUMONIA		
3/191	3/167	0.87 (0.17, 4.38)
BRONCHITIS		
10/191	18/167	0.46 (0.20, 1.02)
ANTIBIOTIC USE		
32/191	36/167	0.73 (0.43, 1.24)

Table 5.36: The rate of complications in an elderly ITTI population treated with zanamivir or placebo, with OR and 95% confidence intervals¹⁰⁴

Zanamivir n/N	Placebo n/N	OR (95% CI)
OVERALL COMPLICATIONS		
39/120	46/114	0.71 (0.42, 1.21)
COMPLICATIONS REQUIRING HOSPITALISATION		
5/120	4/114	1.20 (0.31, 4.57)
ANTIBIOTIC USE		
23/120	30/114	0.66 (0.36, 1.23)

Adverse events

One study reported no significant differences between zanamivir and placebo in the incidence of overall (zanamivir: 66/191; placebo: 50/166; OR 1.22, 95% CI: 0.78, 1.91) or serious (zanamivir: 5/191; placebo: 9/166; OR 0.47, 95% CI: 0.15, 1.43) adverse events.¹⁰⁴

5.2.5.2 Osetamivir compared to placebo

Symptoms

Three trials evaluated the effectiveness of oseltamivir in the elderly with regards to the time to the alleviation of symptoms and return to normal activity. Results for these were reported either

combined in the publication by Martin,⁷⁷ or separately in the previous review by Turner (2003).⁴⁶ The follow-up periods were 21 days, and the drop-out rates unclear. There was no evidence that oseltamivir reduced the time to the alleviation of symptoms in either the ITT or ITTI population. Oseltamivir significantly reduced the time to normal activities in the ITT population, but not the ITTI population (Tables 5.37 and 5.38). There was no statistically significant heterogeneity across studies in either of the analyses.

Table 5.37: The median number of hours to the alleviation of symptoms and return to normal activity in an ITT elderly population treated with oseltamivir (Os.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF SYMPTOMS					
Martin (2001) ^{73, 108}	360	376	139.2 (12.2 [†])	149 (13.09 [†])	-10.00 (-45.05, 25.05)
TIME TO NORMAL ACTIVITY					
*Roche WV15819 ^{46, 73}	75	93	298.48 (66.80)	388.4 (31.55)	-89.92 (-234.72, 54.88)
*Roche WV15876 ^{46, 73}	55	44	395.23 (110.09)	394.9 (76.22)	0.33 (-262.10, 262.76)
*Roche WV15978 ^{46, 73}	229	238	304.48 (34.54)	416.98 (29.57)	-112.50 (-201.62, -23.38)
Pooled result (Fig. 10.56)			WMD -98.07 (95% CI: -170.98, -25.16), p=0.008		
Heterogeneity			Chi ² =0.65; p=0.72; I ² =0%		

Table 5.38: The median number of hours to the alleviation of symptoms and return to normal activity in an ITTI elderly population treated with oseltamivir (Os.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF SYMPTOMS					
Martin (2001) ^{73, 108}	223	254	150 (12.72 [†])	174.9 (18.42 [†])	-24.9 (-68.77, 18.97)
TIME TO NORMAL ACTIVITY					
*Roche WV15819 ^{46, 73}	52	69	277.9 (60.00)	370.48 (51.5)	-92.58 (-247.55, 62.39)
*Roche WV15876 ^{46, 73}	26	20	464.73 (129.48)	428.525 (44.70)	36.20 (-232.28, 304.68)
*Roche WV15978 ^{46, 73}	145	165	336.65 (46.18)	416.983 (14.65)	-80.33 (-175.30, 14.63)
Pooled result (Fig. 10.57)			WMD -73.68 (95% CI: -151.20, 3.84), p=0.06		
Heterogeneity			Chi ² =0.72; p=0.70; I ² =0%		
ALLEVIATION OF FEVER					
Martin (2001) ^{73, 108}	222	254	66.9 (N/A)	89.5 (N/A)	-22.6

*Trials included in the Turner (2003) review

N/A: Not available

Complications

Three trials with results combined reported complications in an elderly ITTI population (Table 5.39).⁷³ The numbers of patients and events were small and there were no significant differences between oseltamivir and placebo.

Table 5.39: The rate of complications in an elderly ITTI population treated with oseltamivir or placebo, with WMD and 95% confidence intervals

Study	Oseltamivir n/N	Placebo n/N	OR (95% CI)
PNEUMONIA			
Martin (2001) ^{73, 108}	5/223	6/254	0.95 (0.29, 3.15)
ANTIBIOTIC USE			
Martin (2001) ^{73, 108}	31/223	49/254	0.68 (0.41, 1.10)
COMPLICATIONS HOSPITALISATION			
Martin (2001) ^{73, 108}	3/223	8/254	0.42 (0.11, 1.60)

*Trial included in the Turner (2003) review

Adverse events

No data were available for adverse events associated with oseltamivir in the elderly.

5.2.6 Effectiveness in all patients

This section combines the results from all the studies described above, together with those recruiting mixed populations where results for individual subgroups of patients were not available. For the trials of zanamivir recruiting mixed populations, data for the alleviation of symptoms and the time to the return to normal activity for healthy and ‘at risk’ adults were available separately, and those data are used in these analyses. For oseltamivir, the largest trial (1459 participants) recruited a mixed population, with no separate symptom data available for healthy and ‘at risk’ adults.⁸¹

Six trials of zanamivir were not included in the Turner (2003) review;⁴⁶ three in healthy adults,⁸⁵⁻⁸⁹ one in an ‘at risk’ population,⁹⁸ one in children,^{102, 103} and one in the elderly.^{104, 105} Eight trials of oseltamivir were not included in the Turner (2003) review;⁴⁶ four in healthy adults,⁶⁶⁻⁷⁰ two in mixed populations,^{57, 81} one in an ‘at risk’ population,^{71, 72, 107} and one in children/adolescents.^{77, 78} One direct head-to-head comparison between zanamivir and oseltamivir that met the inclusion criteria,¹¹⁰ and was not included in the Turner (2003) review,⁴⁶ did not provide data in a format that could be used in the current review.

5.2.6.1 *Zanamivir compared to placebo*

Symptoms

Thirteen trials evaluated the impact of zanamivir on the duration of symptoms and the time to return to normal activity. Of these, five recruited a mixed population (for which symptoms data for healthy and ‘at risk’ adults were available separately),^{46, 75, 79, 90-96} three healthy adults,^{76, 86-88} two those ‘at risk’,^{97, 98, 114, 115} two children,^{99, 100, 102} and one the elderly.^{87, 88} The follow-up period was 5 days in two trials,^{46, 98} six days in one trial,¹⁰² 14 days in one trial,⁹²⁻⁹⁴ 21 days in two trials,^{75, 86} 28 days in five trials,^{87, 88, 90, 91, 95-97, 99, 100, 114, 115} between 21 and 28 days in one trial,⁷⁶ and 29 days with a follow-up telephone call at 56 days in one trial.^{104, 105} Four of the trials had a drop-out rate greater than 5%, but not greater than 10%.^{75, 76, 90, 91, 97, 114} Figures 5.2 to 5.5 illustrate the results for all trials of zanamivir versus placebo grouped according to the participant subgroups described in previous sections.

For time to alleviation of symptoms, results in all patient subgroups favour the use of zanamivir and are statistically significant in both the ITT and ITTI analyses. As might be expected, the size of treatment effects were larger in the ITTI analyses, reducing the median time to alleviation of symptoms by about 1 day in healthy adults (WMD -0.96, 95% CI -1.38, -0.54) and healthy children (WMD -1.00, 95%CI -1.59, -0.41) and by about 2 days in the ‘at risk’ population (WMD -1.83, 95%CI -2.81, -0.86).

There is no overall statistically significant heterogeneity among the results of all trials in either the ITT or ITTI population. Therefore, although the focus of this review is around the individual subgroups that populate the decision model, on this basis it is not unreasonable to pool results across all trials to obtain overall ‘average’ estimates, with the use of zanamivir reducing the median time to alleviation of symptoms by 1 day (WMD -1.07 95%CI -1.39, -0.74) in the ITTI population.

A similar pattern of results is observed for time to return to normal activity where all subgroups in both the ITT and ITTI populations favour the use of zanamivir, reducing the median time to return to normal activity by about 0.5 days in healthy adults and by about 2 days in ‘at risk’ adults with confirmed influenza. However, none of these differences were statistically significant. Statistically significant heterogeneity was observed within the healthy adult ITT and ‘at risk’ ITTI groups, and also for the overall population in both the ITT and ITTI analyses.

Figure 5.2: Time to the alleviation of all symptoms in the overall ITT population

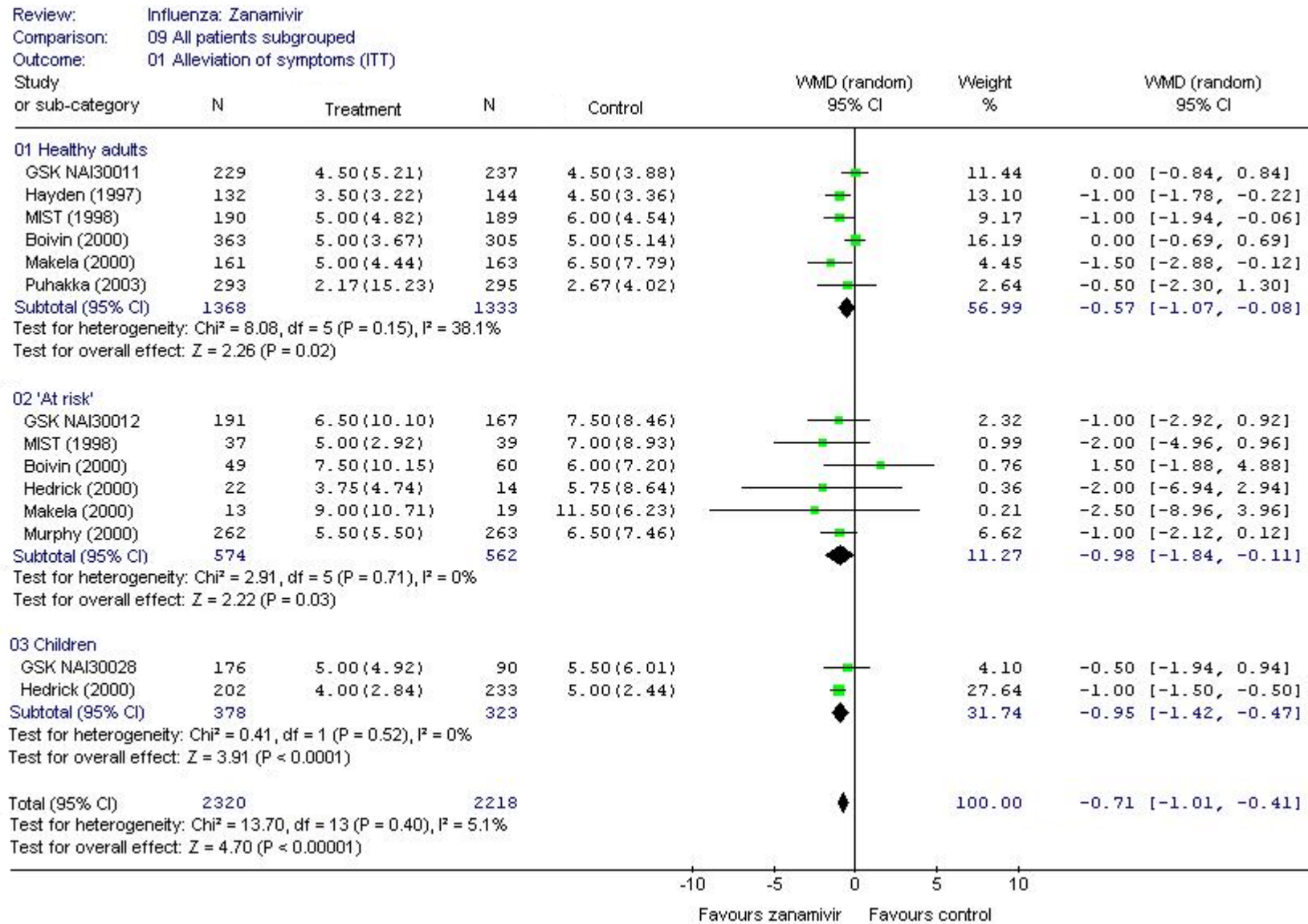


Figure 5.3: Time to the alleviation of all symptoms in the overall ITTI population

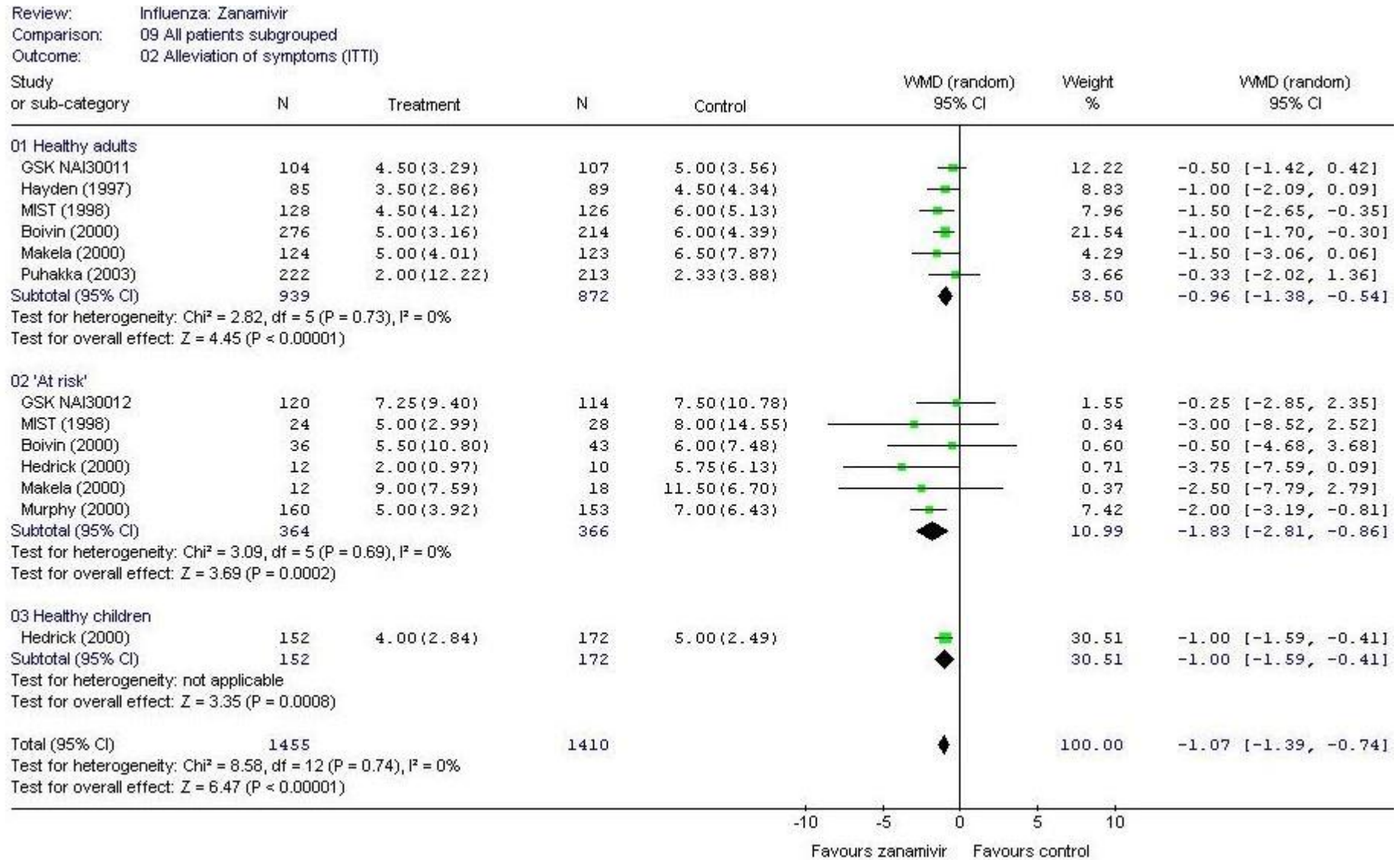


Figure 5.4: Time to return to normal activity in the overall ITT population

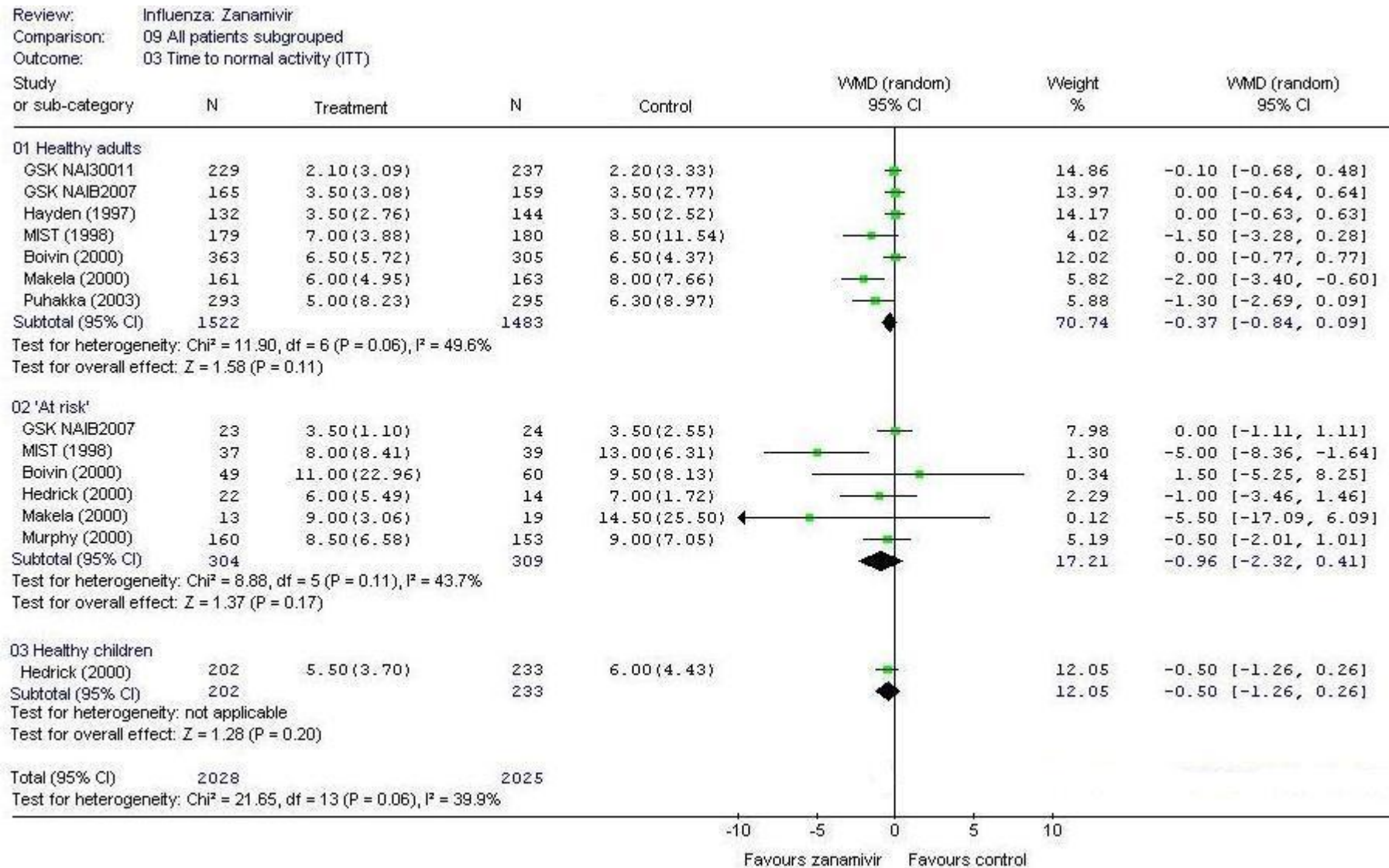
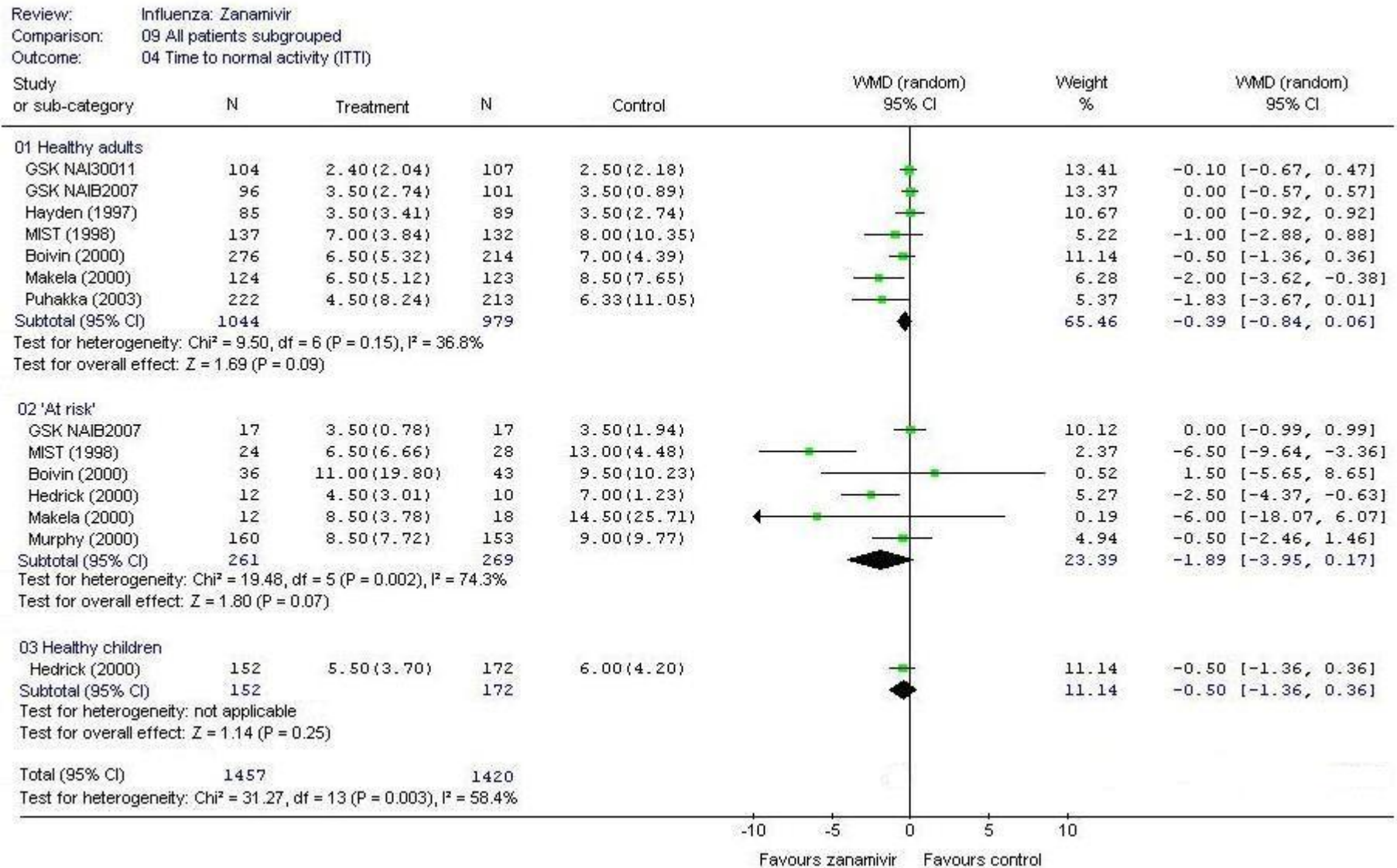


Figure 5.5: Time to return to normal activity in the overall ITTI population



There was no measure of variance available for two studies,^{75, 104, 105} therefore these could not be included in the pooled analyses. One trial reported a reduction in the median time to alleviation of symptoms of one day in the ITT population, and 1.5 days in the ITTI population. The other reported a reduction of 2.75 days in the median time to return to normal activity in the ITTI population. These are therefore broadly consistent with the results of the trials included in the analyses.

Very little data were available on time to resolution of fever which was reported in only four trials. Only one of these trials, which reported a statistically significant reduction with zanamivir in the ITT population, provided a measure of variance. Therefore pooled analyses could not be done. (Table 5.40).⁹⁸

Table 5.40: The median number of days (unless otherwise stated) to the alleviation of fever all participants recruited in the included studies treated with zanamivir (Zan.) or placebo (Pl.), with WMD and 95% confidence intervals

Study	Number randomised		Zanamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Zan.	Pl.			
ITT					
Puhakka (2003) ^{87, 88}	293	295	2.0 (N/A)	2.0 (N/A)	0.0
GlaxoSmithKline NAI30020 ⁹⁸	224	107	47.5 (0.33*)	57 (0.47*)	-9.50 (-10.61, -8.39)
GlaxoSmithKline NAI30028 ¹⁰²	176	90	hours	hours	
			2.5 (N/A)	3 (N/A)	-0.5
ITTI					
Puhakka (2003) ^{87, 88}	222	213	2.0 (N/A)	2.0 (N/A)	0.0
GlaxoSmithKline NAI30012 ^{104, 105}	120	114	4 (N/A)	4.5 (N/A)	-0.5

N/A: Not available

Complications

Of the 13 trials of zanamivir reporting complications, three recruited healthy adults,^{76, 86-88} two children,⁹⁹⁻¹⁰³ one patients with COAD or asthma,^{97, 114, 115} one elderly,^{104, 105} and one a general ‘at risk’ population,⁹⁸ and five recruited a mixed population of people aged 12 or 13 years and older including those with co-morbid conditions.^{74, 75, 79, 90-96}

The data for the incidence of complications were sparse, and are presented in Figures 5.6 and 5.7. The incidence of overall complications and the use of antibiotics showed a statistically significant reduction in both the ITT and ITTI analyses for those treated with zanamivir. In the ITTI population the odds ratio for overall complications was 0.77 (95%CI 0.65 to 0.92). However, trials differed in which events were included in the composite of overall complications and it is

unclear whether this is a meaningful clinical outcome. Antibiotic use was significantly reduced in both the ITT (OR 0.76, 95% CI 0.62, 0.94) and ITTI (OR 0.88, 95% CI 0.66, 0.99) populations.

There was little information on bronchitis in the ITTI populations, but in the ITT population where there were more data, zanamivir appeared to be associated with a statistically significant reduction in the incidence of bronchitis (OR 0.62, 95% CI 0.4, 0.90).

Numbers of events were low and there was no clear evidence of differences in the incidence of pneumonia, GP consultations or hospitalisations. Statistically significant heterogeneity was observed only in the analysis of GP consultations in the ITTI population. This was based on only two studies, one of which, as discussed previously, was a study of young Finnish soldiers reporting a particularly high rate of consultations, unlikely to be representative of a civilian population.⁸⁷⁻⁸⁹

There were no deaths in the seven trials that reported on mortality.^{79, 86-88, 90-94, 97, 98, 102, 114, 115}

Adverse events

Of the 13 trials of zanamivir reporting adverse events in ITT populations, four recruited healthy adults,^{76, 85-88} two children,⁹⁹⁻¹⁰³ one patients with COAD or asthma,^{97, 114, 115} one the elderly,^{104, 117in 2} one a general 'at risk' population,⁹⁸ and four a mixed population of people aged 12 or 13 years and older that included people with co-morbid conditions.^{75, 79, 90-96}

Across all trials, treatment with zanamivir significantly reduced the incidence of overall adverse events (OR 0.85, 95%CI 0.75 to 0.96). There was no evidence of a difference in the incidence of drug-related adverse events between zanamivir and placebo. Even when pooled across all studies there were very few serious adverse events and there was no evidence of a difference between zanamivir and placebo (Figure 5.8). There was no statistically significant heterogeneity in any of the analyses

Figure 5.6: Complication rates associated with zanamivir and placebo in the overall ITT population

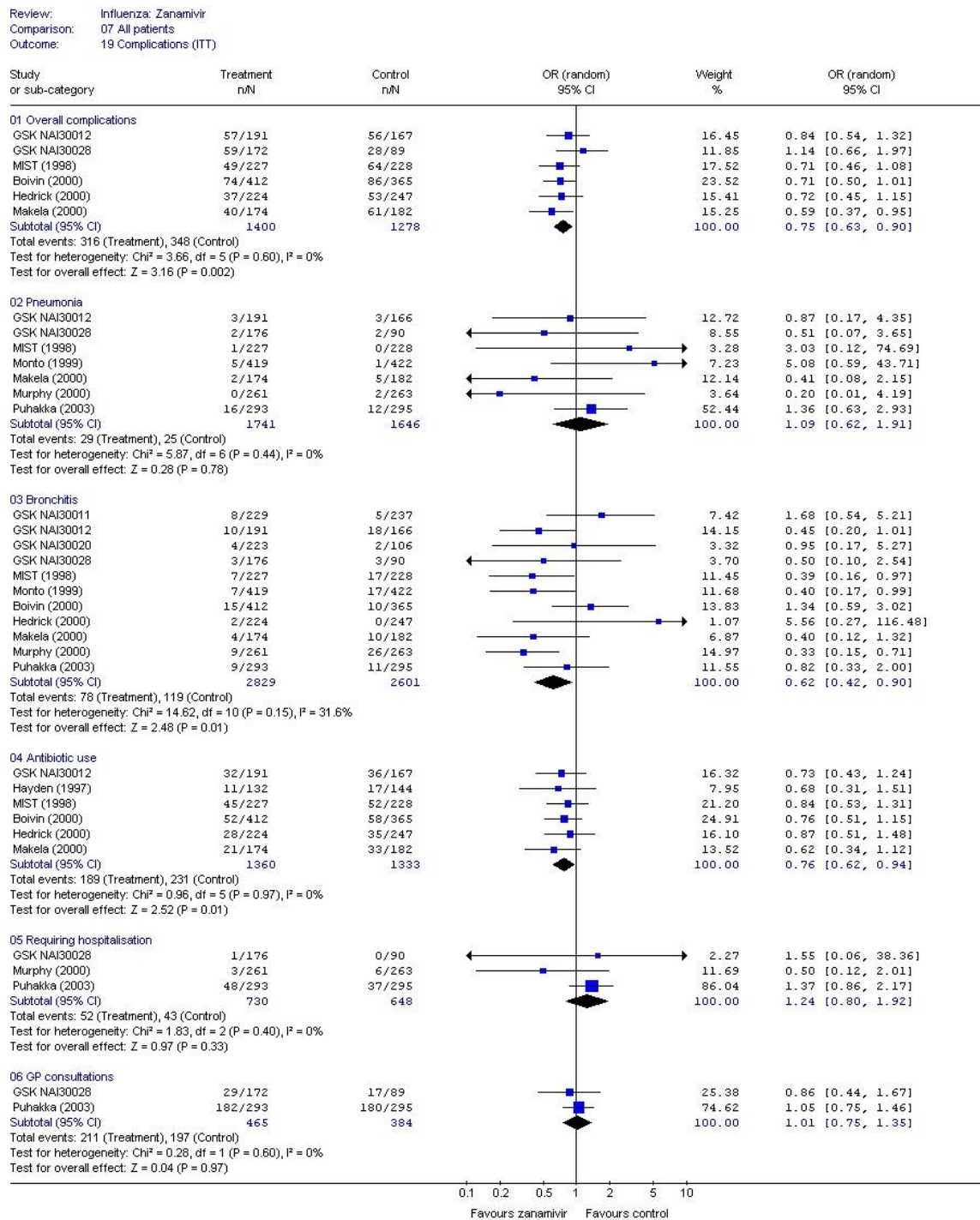


Figure 5.7: Complication rates associated with zanamivir and placebo in the overall ITTI population

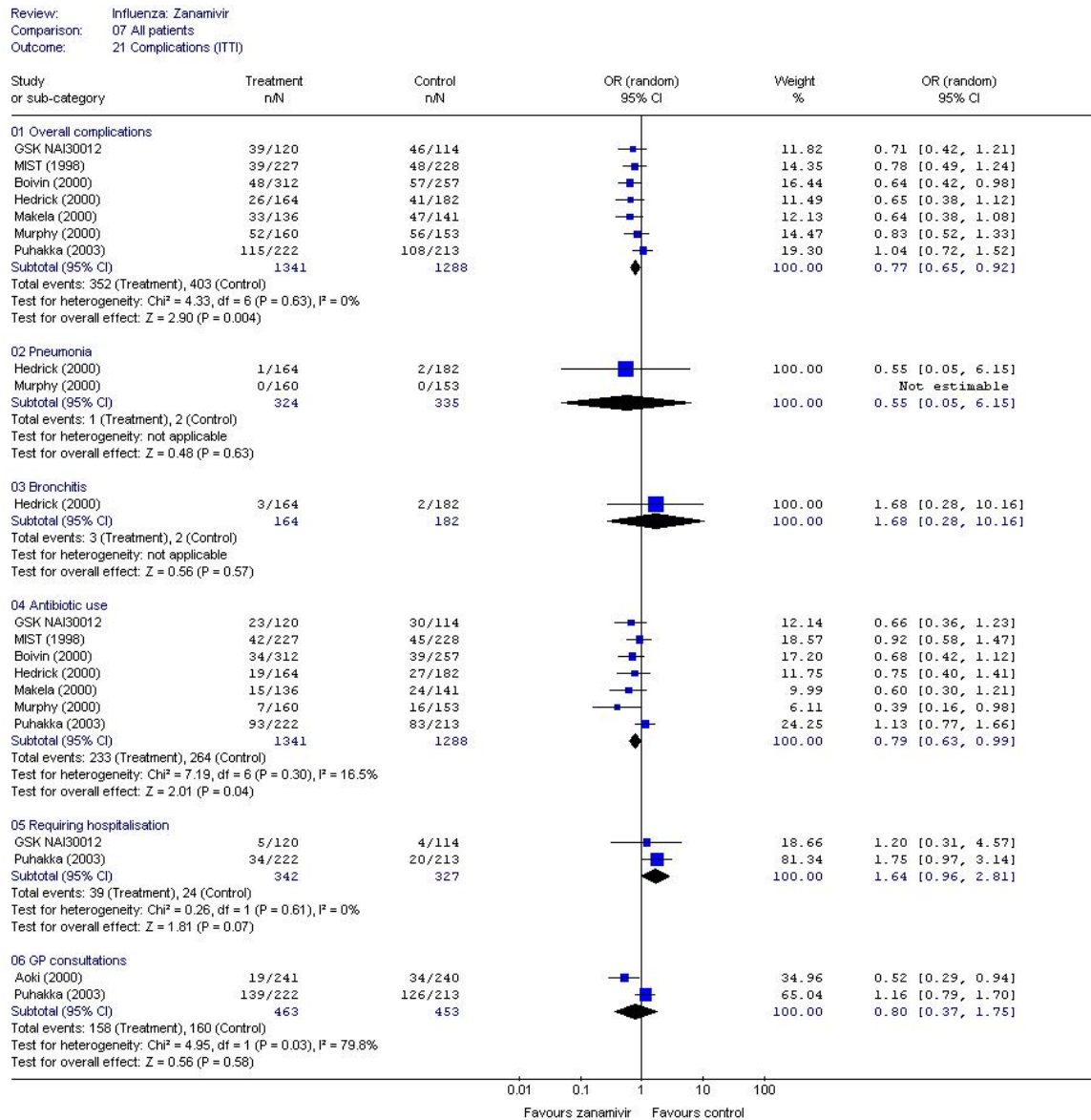
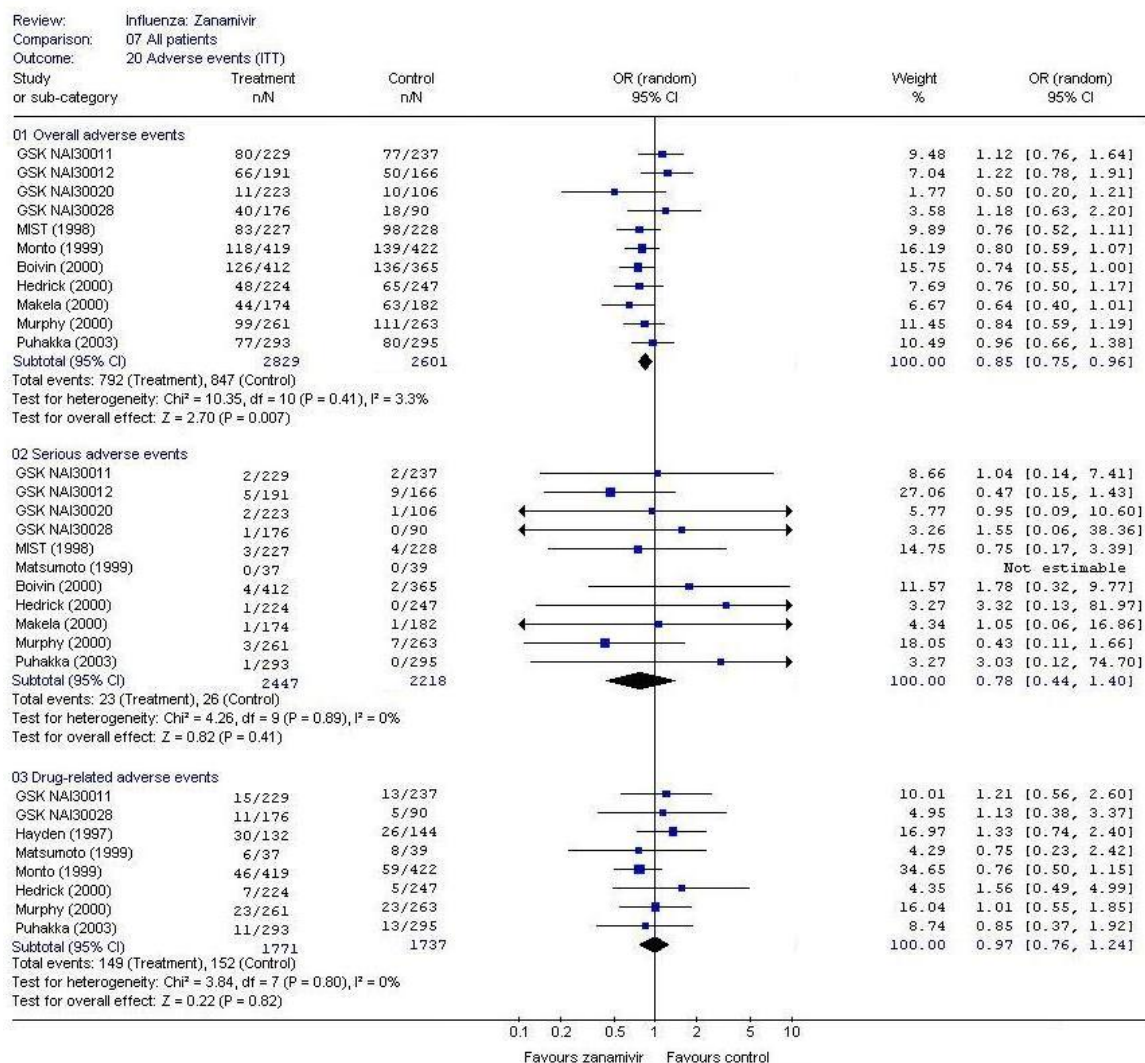


Figure 5.8: Adverse event rates associated with zanamivir and placebo in the overall ITT population



Summary for the effectiveness of zanamivir

The strength of evidence for effectiveness of zanamivir in alleviating symptoms was greatest in the healthy adult population with analyses based on between 1811 and 3005 individuals. In those with confirmed influenza, reductions of approximately 1 day were seen in median time to alleviation of symptoms and approximately 0.5 days in the median time taken to return to normal activity. The evidence base was more limited for the healthy children and ‘at risk’ populations. Children were studied in only two trials (for one of these, data for healthy children and ‘at risk’ children were available separately⁹⁹) and analyses were based on between 324 and 701 individuals. Results for healthy children showed similar reductions in time to alleviation of

symptoms and time to return to normal activity as for healthy adults. Analyses for the ‘at risk’ group, which comprised adults and children with co-morbid conditions and the elderly, were based on between 530 and 1136 individuals, and there is more uncertainty around the results for this group. In ‘at risk’ individuals with confirmed influenza, the results suggest that zanamivir reduces the median time to the alleviation of symptoms and the time to return to normal activity by approximately 2 days. Data for most individual complications were sparse and results largely inconclusive. The evidence is strongest for overall complications and use of antibiotics, which both show reduced incidence associated with zanamivir.

5.2.6.2 Oseltamivir compared to placebo

Symptoms

Fourteen trials evaluated the impact of oseltamivir on the duration of symptoms and the time to normal activity. Of these, six recruited healthy adults,^{46, 65, 67-69, 80, 82, 83, 106} one a mixed adult population,⁵⁷ two those ‘at risk’,^{46, 73} two children,^{77, 109} and three the elderly.^{46, 73} The follow-up period was 10 days in one trial,⁵⁷ 21 days in eleven,^{46, 65, 67-69, 73, 80, 82, 83, 106} and 28 days in two trials.^{77, 109} The drop-out rate was unclear in eight trials,^{46, 57, 65, 73, 77} and greater than 5%, but not 10%, in two trials.^{67, 81, 83} Figures 5.9 to 5.12 illustrate the results for all trials of oseltamivir versus placebo grouped according to the participant subgroups described in previous sections together with a further ‘mixed’ subgroup which includes a large trial that could not be separated into subgroups.⁸¹

For time to the alleviation of symptoms, results in each patient subgroup favoured the use of oseltamivir in both the ITT and ITTI analyses. These were statistically significant for healthy adults, healthy children and for the trial with a mix of participant types (data only for ITT). For the ‘at risk’ group, results were in the same direction and comparable to the other subgroups, but there was more uncertainty around these findings. Treatment effects were generally greater in the analyses of individuals with confirmed influenza, where oseltamivir reduced the median time to alleviation of symptoms by about 1 day in healthy adults (WMD -22.19 hours, 95% CI -37.32, -7.07), by about 1.5 days in healthy children (WMD -36.00 hours, 95%CI -53.51, -18.49) and by approximately 0.5 days in the ‘at risk’ group (WMD -14.04 hours, 95%CI -36.34, 8.26). With the exception of the ITT analyses of healthy adults, there was no overall statistically significant heterogeneity within any of the subgroups. There was no overall statistically significant heterogeneity among the results of all trials in either the ITT or ITTI population. Therefore, although the focus of this review is around the individual subgroups that populate the decision model, on this basis it is not unreasonable to pool results across all trials to obtain the overall

‘average’ estimate that the use of oseltamivir reduces the time to alleviation of symptoms by about 1 day (WMD -22.75 hours 95%CI -33.39, 12.11) in individuals with confirmed influenza.

A similar pattern of results is observed for time to return to normal activity where all subgroups in both the ITT and ITTI populations favour the use of oseltamivir. Results are statistically significant in all groups except the ‘at risk’ subgroup in the ITTI analyses. In individuals with confirmed influenza oseltamivir reduced the median time to return to normal activity by approximately 2.5 days (WMD -63.17 hours, 95%CI -99.08, -27.22) in healthy adults, approximately 1 day in the ‘at risk’ subgroup (WMD -19.20 hours, 95%CI -41.42, 3.01) and approximately 2 days (WMD -44.57 hours, 95% CI: -63.75, -25.39) in the trial of healthy children. There was no consistency across subgroups as to whether the size of reduction was greater in the ITT or ITTI analysis. Again, there is no overall statistically significant heterogeneity in the results within any of the subgroups or over all trials in either the ITT or ITTI analyses. Pooling results across all trials gives an overall estimate that ‘on average’ the use of oseltamivir reduces the median time to return to normal activity by about 1.5 days (WMD -36.31 hours 95%CI -48.44, -24.17) in individuals with confirmed influenza.

Some studies did not provide a measure of variance, and could therefore not be included in the meta-analyses (Table 5.41), but results are broadly consistent with the trials that could be analysed.

Figures 5.13 and 5.14 illustrate the data that were available on time to alleviation of fever. As information was reported for only a small number of trials, and primarily in healthy or mixed populations, they are not shown by subgroup. All trials show a reduction in the time to alleviation of fever associated with oseltamivir, and with the exception of one small trial, individually show statistically significant results. There is no statistically significant heterogeneity. Overall, oseltamivir reduced the median time to alleviation of fever by about one day in the ITTI population (WMD: -24.41 hours, 95%CI -31.64, -17.17).

Figure 5.9: Time to the alleviation of all symptoms in the overall ITT population

Review: Influenza: Oseltamivir
 Comparison: 08 All patients subgrouped
 Outcome: 01 Alleviation of symptoms (ITT)

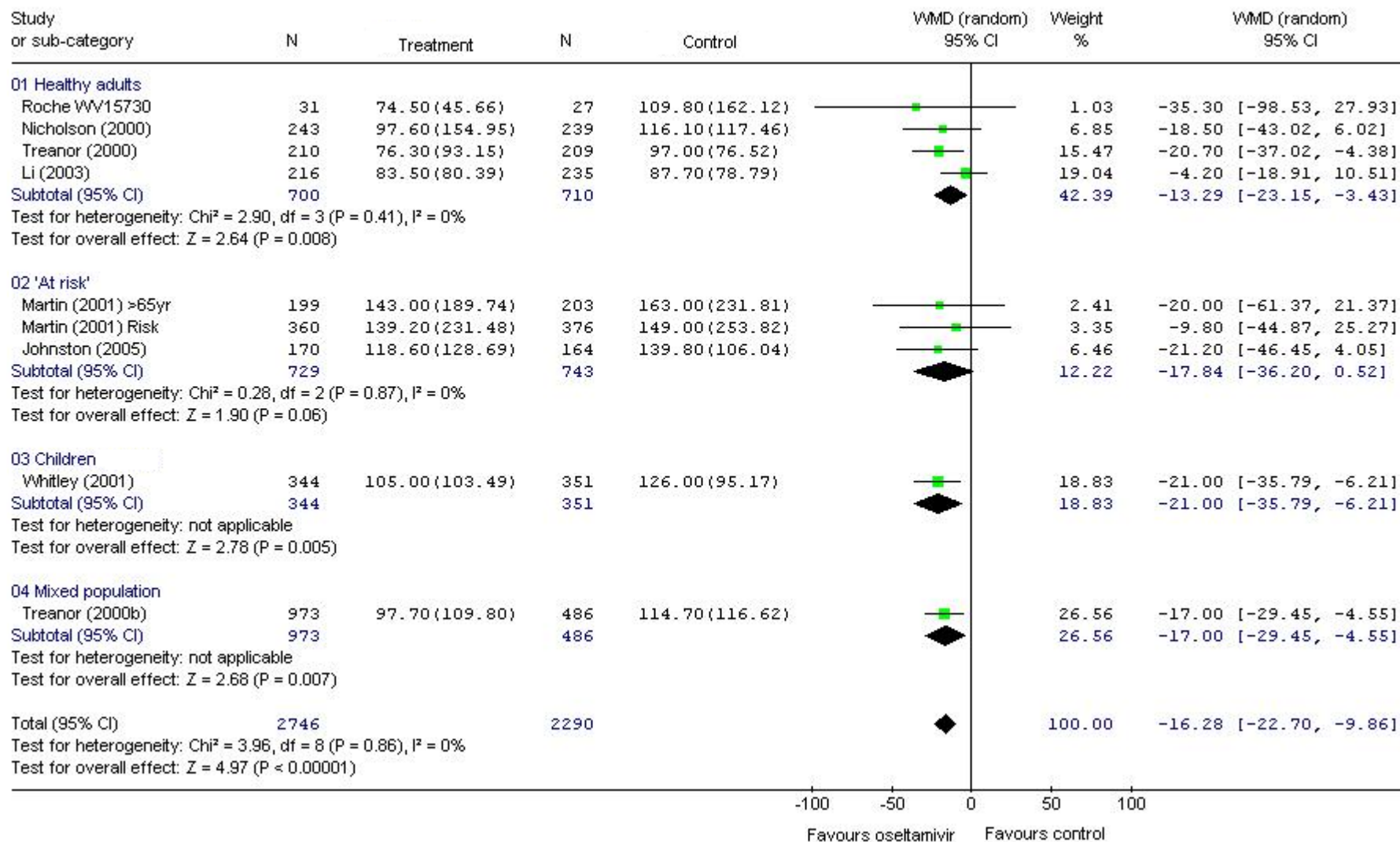


Figure 5.10: Time to the alleviation of all symptoms in the overall ITTI population

Review: Influenza: Oseltamivir
 Comparison: 08 All patients subgrouped
 Outcome: 02 Alleviation of symptoms (ITTI)

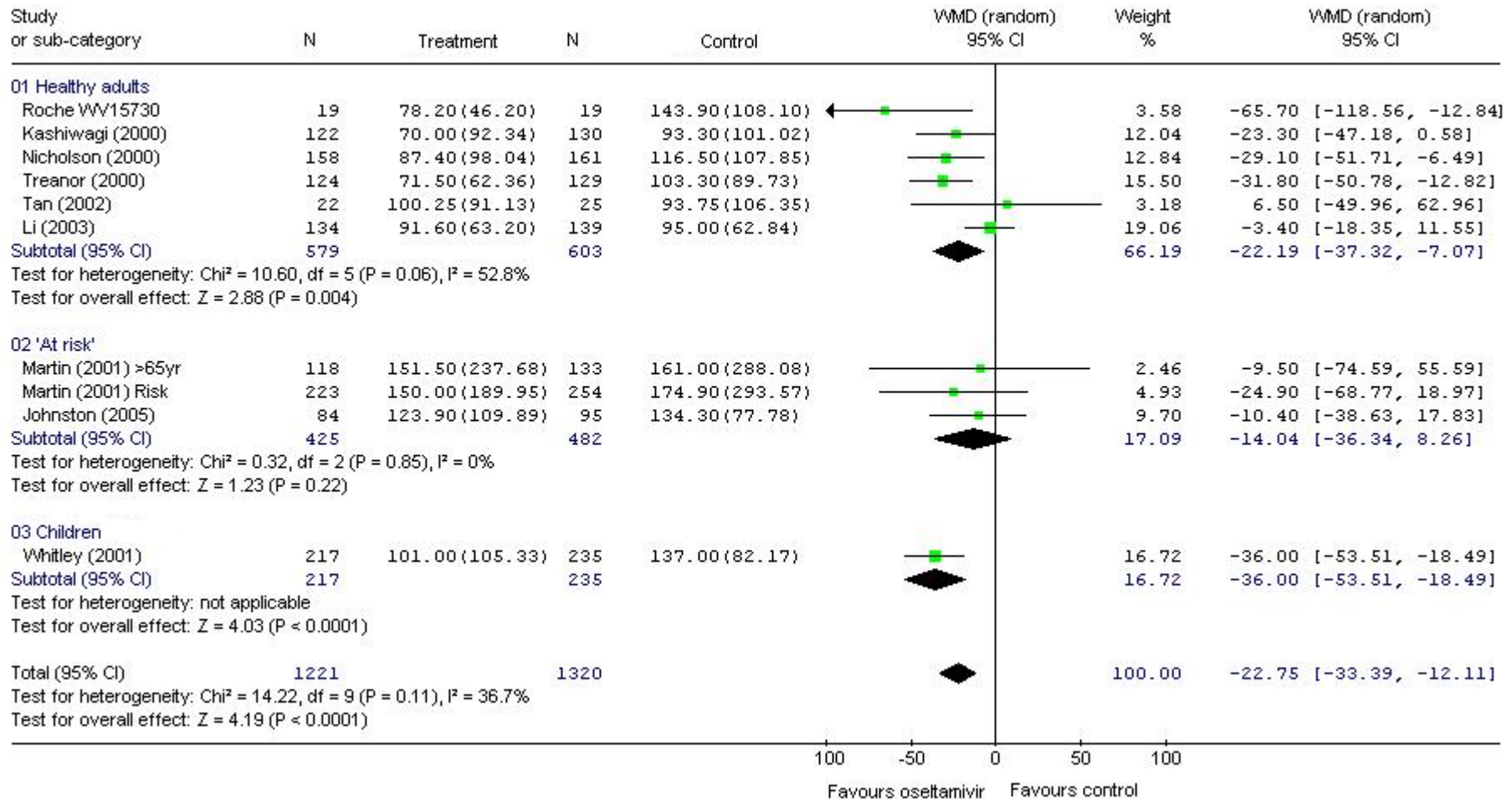


Figure 5.11: Time to the return to normal activity in the overall ITT population

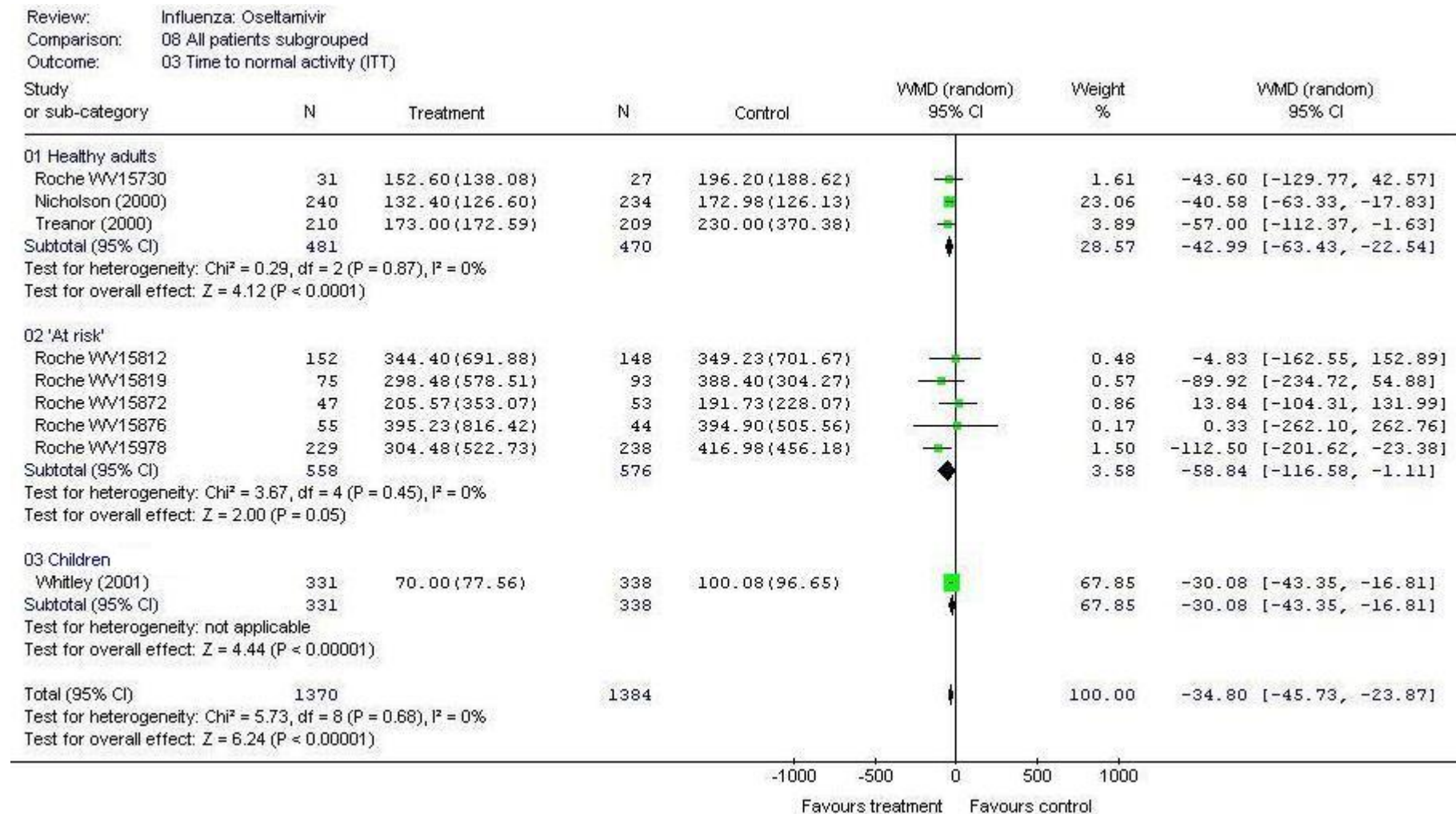


Figure 5.12: Time to the return to normal activity in the overall ITTI population

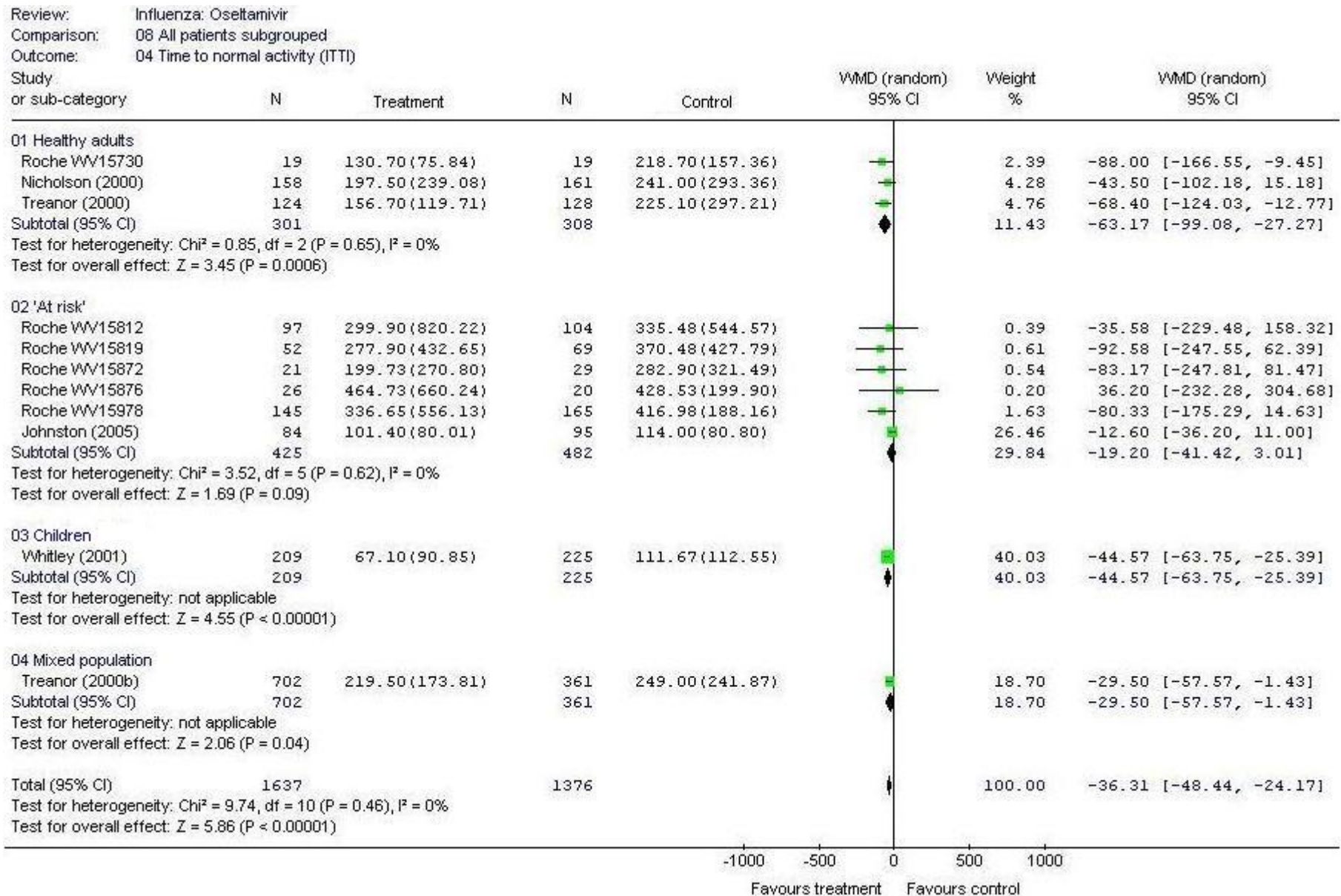


Table 5.41: The median number of hours (unless otherwise stated) to the alleviation of fever and all symptoms for the studies not providing a measure of variance, and therefore not included in the forest plots

Study	Number randomised		Oseltamivir Median (SE)	Placebo Median (SE)	Median difference (95% CI)
	Os.	Pl.			
ALLEVIATION OF FEVER (ITT)					
Li (2003) ⁶⁹	216	235	28.7	32.5	-3.80
ALLEVIATION OF SYMPTOMS (ITTI)					
Markovski (2002) ⁵⁷	17	24	4 days	6 days	-2.0
ALLEVIATION OF FEVER (ITTI)					
*Martin (2001) ^{73, 108} 'At risk'	118	133	42.8	67.9	-25.10
*Martin (2001) ^{73, 108} Elderly	222	254	66.9	89.5	-22.60
Kashiwagi (2000) ⁶⁸	122	130	33.1	60.5	-27.40
Li (2003) ⁶⁹	134	139	27.9	51.5	-23.60

Figure 5.13: Time to the alleviation of fever in the overall ITT population

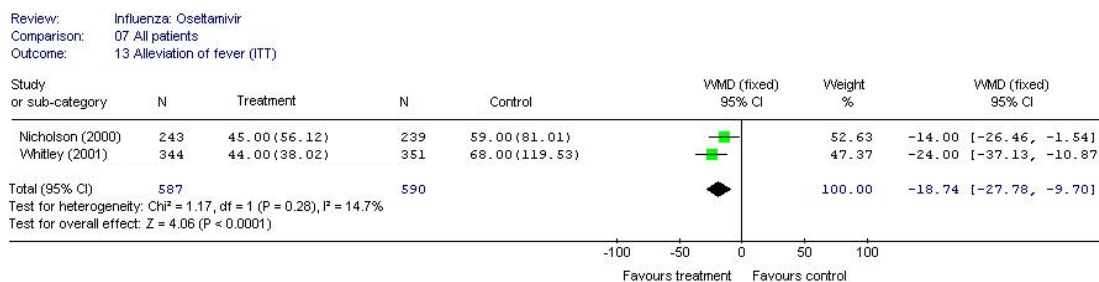
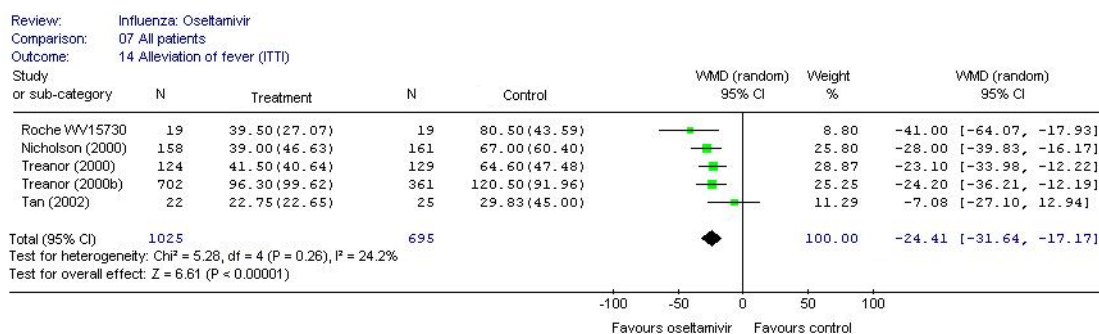


Figure 5.14: Time to the alleviation of fever in the overall ITTI population



Complications

Of the 16 trials of oseltamivir reporting complications, two were in mixed populations,^{57, 81} two in children,^{77, 78, 109} three in a general ‘at risk’ population,^{71-73, 107} three in the elderly,⁷³ and six in healthy adults.^{46, 65, 66, 68, 69, 83, 106} Three trials were conducted in China^{66, 69} or Japan,⁶⁸ with two published in their respective languages.^{66, 68} One trial had a drop-out rate greater than 5%, but not greater than 10%.^{82, 83}

As for zanamivir, data on complications were sparse and results are presented for all trials rather than split into different patient subgroups. These are given in figures 5.15 and 5.16. Very little data were available for the ITT analysis, for example, across all trials a total of only 46 overall complications were reported. There is therefore considerable uncertainty in these results and there was no clear evidence of differences in the incidence of bronchitis, pneumonia, GP consultation, hospitalisation, or overall complications.

More data were available for the ITTI analyses where the incidence of the use of antibiotics showed a statistically significant reduction for those treated with oseltamivir with an odds ratio of 0.62 (95%CI 0.46 to 0.83).

With the exception of the ITT analysis of antibiotic use and ITTI analysis of overall complications, there was no statistically significant heterogeneity observed in the results when analysed in this way.

Of the nine trials that reported on mortality,^{65, 69, 73, 78, 80, 83, 106, 108-110} a single death was reported in the placebo arm of a trial in an ‘at risk’ population; it was unclear whether this was related to influenza.⁷³

Adverse events

Of the nine oseltamivir trials that reported adverse events, six were in healthy adults,^{46, 66-69, 80, 83, 106} (of which four were conducted in China^{66, 67, 69} or Japan⁶⁸), two in children^{77, 78, 109} and one in a general ‘at risk’ population.^{71, 72} Two trials had a drop-out rate of greater than 5%, but not greater than 10%.^{67, 82, 83}

Analyses of adverse event data are shown in figures 5.17 and 5.18. Data were limited and there was no evidence of a difference in the incidence of overall, serious or drug-related adverse effects in either the ITT or ITTI analyses. There was no statistically significant heterogeneity in any of the pooled analyses.

Figure 5.15: Complication rates associated with oseltamivir and placebo in the overall ITT population

Review: Influenza: Oseltamivir
 Comparison: 07 All patients
 Outcome: 19 Complications (ITT)

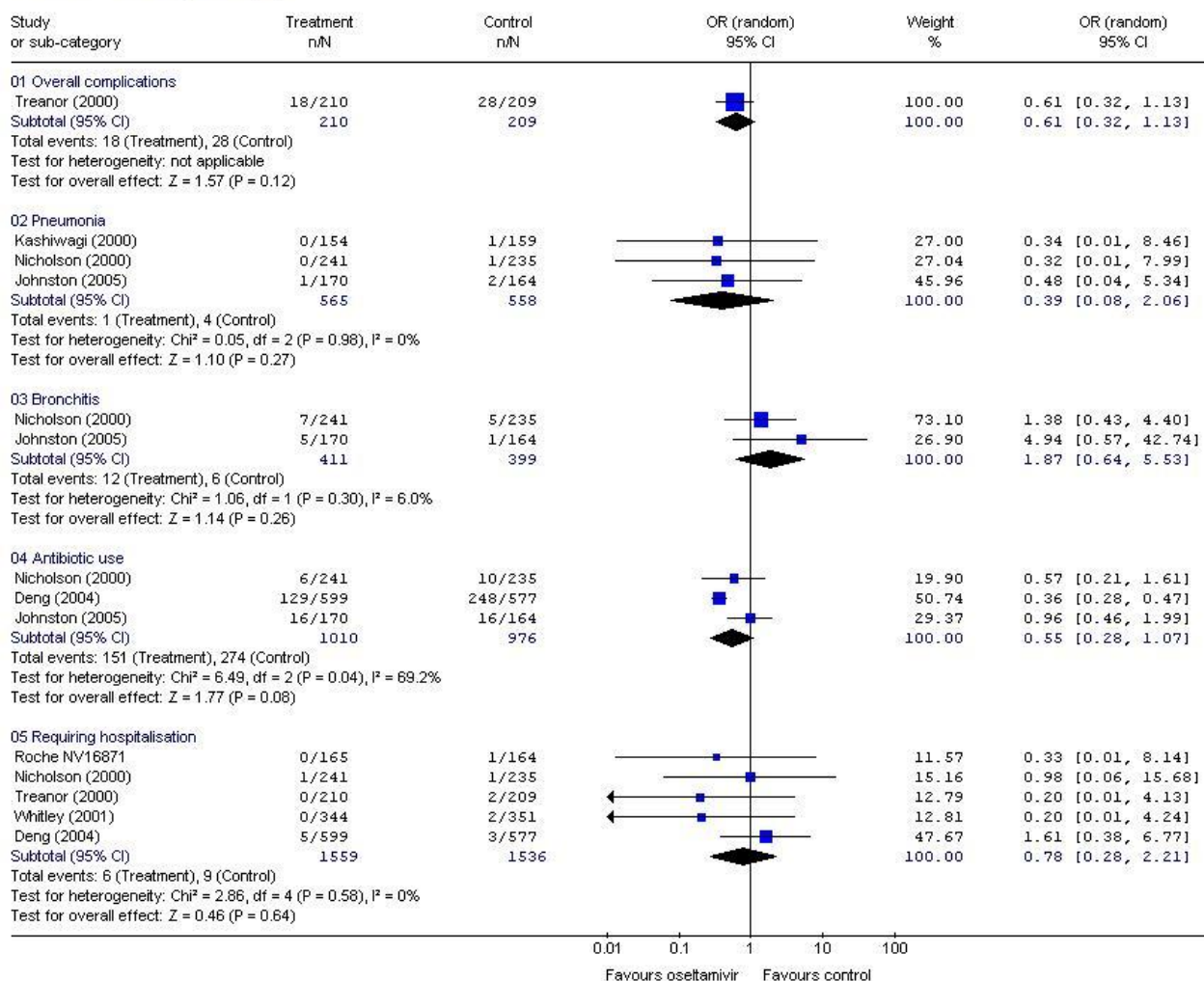


Figure 5.16: Complication rates associated with oseltamivir and placebo in the overall ITTI population

Review: Influenza: Oseltamivir
 Comparison: 07 All patients
 Outcome: 21 Complications (ITTI)

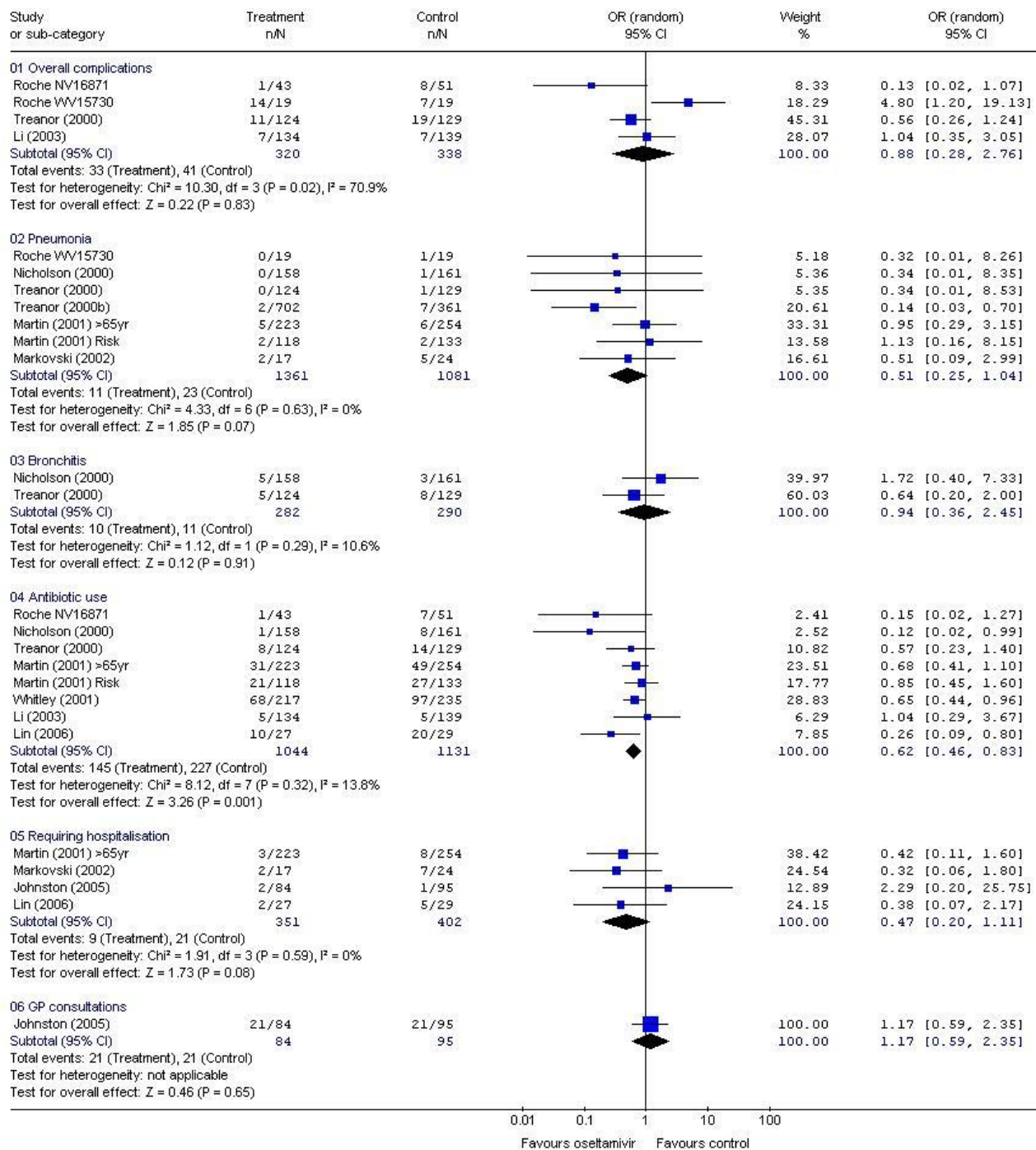


Figure 5.17: Adverse event rates associated with oseltamivir and placebo in the overall ITT population

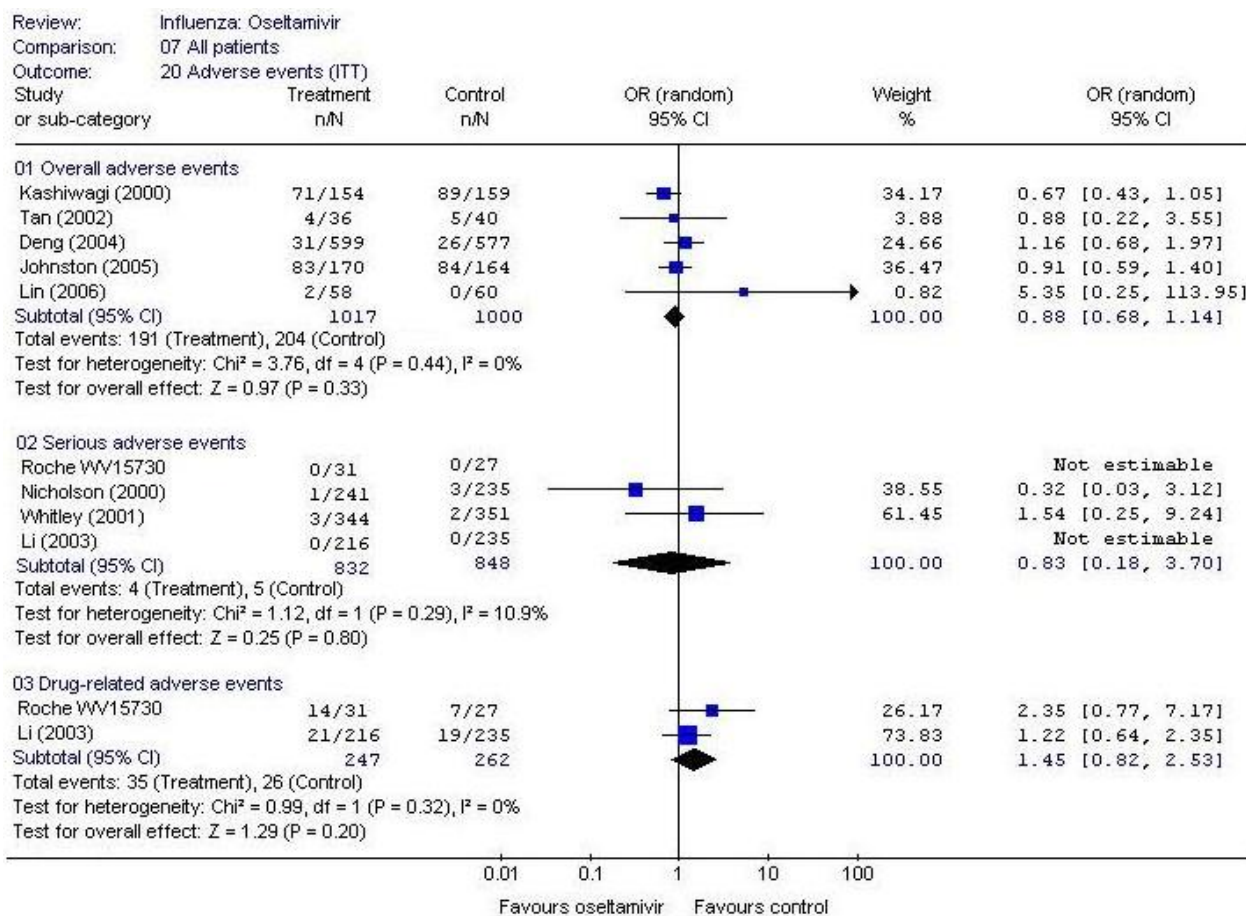
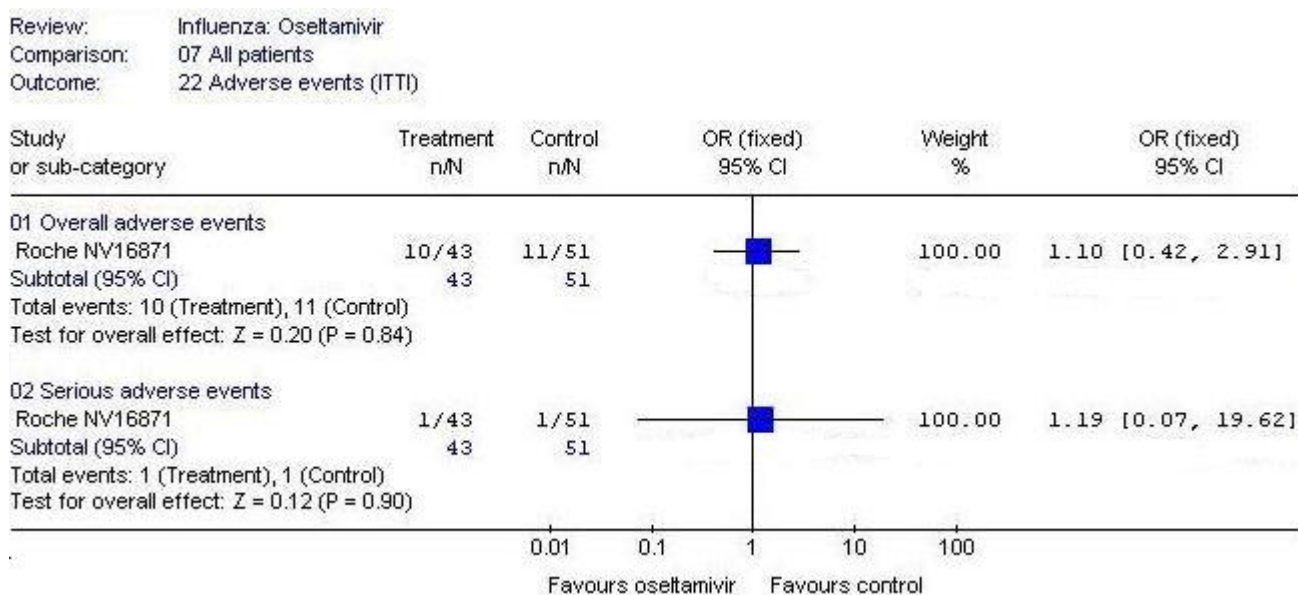


Figure 5.18: Adverse event rates associated with oseltamivir and placebo in the overall ITTI population



Summary for the effectiveness of oseltamivir

Although analyses are based on similar numbers of individuals (between 609 and 1410 in the healthy adult subgroup and between 907 and 1472 individuals in the ‘at risk’ subgroup), the evidence for the effectiveness of oseltamivir in alleviating symptoms was stronger in healthy adults and children. Results in healthy adults and children showed statistically significant reductions in the median time to the alleviation of symptoms and the time to return to normal activity, in both the ITT and ITTI analyses. For healthy adults with confirmed influenza, reductions of approximately one day were seen in median duration of symptoms and approximately 2.5 days in the median time taken to return to normal activity. Healthy children were studied in only one trial, which showed a reduction in median time to alleviation of symptoms of 1.5 days, and median time to return to normal activity of around 2 days. Results for ‘at risk’ individuals were broadly similar, but there was more uncertainty around these results, and there was no clear evidence that oseltamivir reduced median time to alleviation of symptoms or return to normal activity. In ‘at risk’ individuals with confirmed influenza, the median time to alleviation of symptoms was reduced by about half a day and the median time to return to normal activity reduced by about one day (reduction in the median time to return to normal activity in the ITT analysis was approximately 2.5 days and of borderline statistical significance). There was little statistical heterogeneity observed in any of these analyses. Data for most individual complications were sparse and results largely inconclusive. The evidence is strongest for the use of antibiotics in the ITTI population, which showed reduced incidence associated with oseltamivir use.

5.2.7 Discussion of the clinical evaluation

5.2.7.1 Effectiveness

The decision problem emphasised the need to give specific consideration to healthy and vulnerable patient groups. Data were therefore described and analysed within patient subgroups, primarily healthy adults, healthy children and individuals considered to be ‘at risk’. This required that data from trials that recruited a mixed patient population were, where possible, sub-divided and analysed within these subgroups. Trials that could not be split in this way therefore contributed only to final summary meta-analyses that present results for each subgroup alongside each other. All comparisons made in this section are of the individual drugs versus placebo or symptomatic relief; they do not consider the relative effectiveness of zanamivir and oseltamivir.

Key findings

This review showed that treatment with zanamivir or oseltamivir, when compared to placebo, generally reduced the median duration of symptoms and median time to return to normal activity.

In healthy adults, zanamivir reduced the median duration of symptoms by between approximately 0.5 and 1 day, and oseltamivir by between 0.5 and 1 day. The median reduction in the time taken to return to normal activity was about 0.5 days with zanamivir and approximately 1 to 2.5 days with oseltamivir. Although these results were statistically significant, the absolute effects were small and their clinical significance questionable, particularly in an otherwise healthy population. As might be expected, estimates derived from the analyses of those with confirmed flu generally produced greater effect sizes than those derived from all randomised patients.

For the ‘at risk’ subgroups, estimates of difference in symptom duration often failed to reach statistical significance, though the direction of effect remained in favour of the NI treatments. Treatment reduced the median duration of symptoms in ‘at risk’ populations by approximately 1 to 3.75 days (ITTI high risk children) with zanamivir, and by 0.5 to 1 day (elderly ITTI population) with oseltamivir. These effect sizes were generally larger, and potentially more clinically significant, than those seen in healthy adults. However, there was greater uncertainty around these results. A similar pattern was seen in the time taken to return to normal activity, with the median time being reduced by between 1 and 2.5 days (ITTI high risk children) with zanamivir and by 0.5 to 4 days (elderly ITT population) with oseltamivir in ‘at risk’ populations. Very limited data were available for the ‘at risk’ subgroups of children and the elderly. The ranges for the overall ‘at risk’ population may therefore be more representative of the response in these subgroups. In the overall ‘at risk’ population, treatment reduced the median duration of symptoms by

approximately 1 to 2 days with zanamivir, and by 0.5 to 0.75 days with oseltamivir, and the median time to return to normal activity by between 1 to 2 days with zanamivir and by 0.75 to 2.5 (data for ‘at risk’ adults only) days with oseltamivir.

Where data were available for adverse events and complication rates, there was little overall difference associated with the use of either zanamivir or oseltamivir when compared individually to placebo. However, data were reported for few trials, studies were not designed to detect changes in these outcomes, and the numbers of events were generally very small. There is therefore considerable remaining uncertainty in all subgroups with respect to these outcomes. The majority of available data were for ‘overall complications’ and antibiotic use. However, the definition of overall complications varied considerably between studies and the clinical value of this composite outcome is unclear. The most consistent data and strongest evidence related to antibiotic use. Both zanamivir and oseltamivir appeared to reduce antibiotic use which could be regarded as a surrogate measure for reduced incidence of bacterial infections.

Comparison with the review by Turner (2003)⁴⁶

The results reported here expand on those reported by Turner (2003), which helped inform the current NICE guidelines (TA58). This review adds 14 trials to those used by Turner, six in zanamivir (three in healthy adults, one in the elderly, one in ‘at risk’ adults and one in children which included a minority of ‘at risk’ participants) and eight in oseltamivir (four in healthy adults, one in an ‘at risk’ population of undefined age, one in ‘at risk’ children and two in adult populations which included both healthy and ‘at risk’ individuals). It additionally analyses incidence of complications and adverse events. This review also excluded one trial (NA130010)⁸⁴ that was primarily of prophylaxis and found to be ineligible here, but which had been included in the Turner (2003) review. Despite the inclusion of additional studies, the results for median time to resolution of symptoms and median time to return to normal activity remain similar to those reported by Turner.⁴⁶ The results of both reviews are summarised in Tables 5.42 and 5.43. For ease of comparison, the results for oseltamivir have been converted from hours to days.

Zanamivir

When comparing the results of the two reviews, the new data for zanamivir resulted in a slightly smaller pooled effect estimate for the time to alleviation of symptoms in healthy adults, nevertheless, this remained statistically significant in favour of zanamivir for both the ITT and ITTI populations, and the conclusion drawn remain the same. Likewise, there was a slightly reduced pooled effect estimate for the impact of zanamivir on the time to return to normal activities in the healthy adult ITTI population such that the confidence interval now includes zero effect and there is no longer a statistically significant reduction with

zanamivir. However, the overall direction of effect was the same, and the difference in the actual pooled estimates between the two reviews was very small.

Table 5.42: The weighted median difference (WMD) between treatment and placebo groups for the continuous outcomes as reported in the current and previous review for the ITT populations

Population	Zanamivir WMD (95% CI)		Oseltamivir WMD (95% CI)	
	Previous HTA report ⁴⁶	Current review	Previous HTA report ⁴⁶	Current review
Time to alleviation of symptoms				
Healthy adults	-0.78 [†] (-1.31, -0.26)	-0.57* (-1.07, -0.07)	-0.86 (-1.42, -0.31)	-0.55* (-1.05, -0.14)
High risk adults	-0.93 [†] (-1.90, 0.05)	-0.95 (-1.83, -0.07)	-0.35 (-1.40, 0.71)	-0.59* (-1.70, 0.54)
Healthy children	-1.00 (-1.50, -0.50)	-1.00 (-1.50, -0.50)	-0.87 (-1.49, -0.25)	-0.88 (-1.41, -0.26)
High risk children	-2.00 (-6.90, 2.90)	-2.00 (-6.94, 2.94)	No results available	-0.88 (-1.94, 0.17)
All children	No results available	-0.94* (-1.43, -0.46)	No results available	-0.88* (-1.41, -0.35)
Elderly	No results available	-1.13* (-2.90, 0.63)	No results available	-0.41* (-1.87, 1.05)
All 'at risk'	No results available	-0.98* (-1.84, -0.11)	No results available	-0.74* (-36.20, 0.52)
Whole population	-0.94 [†] (-1.23, -0.65)	-0.71* (-1.01, -0.41)	-0.80 (-1.18, -0.41)	-0.68* (-0.95, -0.41)
Time to return to normal activities				
Healthy adults	-0.51 [†] (-1.04, 0.02)	-0.37* (-0.84, 0.09)	-1.33 (-1.96, -0.71)	-1.33 (-1.96, -0.71)
High risk adults	-0.09 [†] (-0.95, 0.78)	-1.07* (-2.81, 0.68)	-2.45 (-4.86, -0.05)	-2.45 (-4.86, -0.05)
Healthy children	-0.50 (-1.30, 0.30)	-0.50 (-1.26, 0.26)	-1.25 (-1.80, -0.70)	-1.25 (-1.81, -0.70)
High risk children	-1.00 (-3.50, 1.50)	-1.00 (-3.46, 1.46)	No results available	No results available
All children	No results available	No results available	No results available	No results available
Elderly	No results available	No results available	No results available	-4.09* (-7.12, -1.05)
All 'at risk'	No results available	-0.96* (-2.32, 0.41)	No results available	No results available
Whole population	-0.37 [†] (-0.74, -0.01)	-0.44* (-0.84, -0.05)	-1.32 (-1.73, -0.91)	-1.32 (-1.73, -0.91)

[†]Includes NAI30010

*Includes results from studies not included in the last review

Table 5.43: The weighted median difference (WMD) between treatment and placebo groups for the continuous outcomes as reported in the current and previous review for the ITTI populations

Population	Zanamivir WMD (95% CI)		Oseltamivir WMD (95% CI)	
	Previous HTA report ⁴⁶	Current review	Previous HTA report ⁴⁶	Current review
Time to alleviation of symptoms				
Healthy adults	-1.26 [†] (-1.93, -0.59)	-0.96* (-1.38, -0.54)	-1.38 (-1.96, -0.80)	-0.92* (-1.56, -0.29)
High risk adults	-1.99 [†] (-3.08, -0.90)	-1.96 (-3.05, -0.86)	-0.45 (-1.88, 0.97)	-0.84 (-2.35, 0.68)
Healthy children	-1.00 (-1.60, -0.4)	-1.00 (-1.59, -0.41)	-1.49 (-2.22, -0.76)	-1.50 (-2.23, -0.77)
High risk children	-3.80 (-7.60, 0.10)	-3.75 (-7.59, 0.09)	No results available	-0.43* (-1.61, 0.74)
All children	No results available	No results available	No results available	-1.20* (-1.82, -0.58)
Elderly	No results available	-1.85* (-4.77, 1.07)	No results available	-1.00* (-2.83, 0.83)
All 'at risk'	No results available	-1.83* (-2.81, -0.86)	No results available	-0.59* (-1.51, 0.34)
Whole population	-1.26 [†] (-1.616, -0.90)	-1.07* (-1.39, -0.74)	-1.33 (-1.77, -0.90)	-0.95* (-1.39, -0.50)
Time to return to normal activities				
Healthy adults	-0.46 [†] (-0.90, -0.02)	-0.39* (-0.84, 0.06)	-1.64 (-2.58, -0.69)	-2.63 (-4.13, -1.14),
High risk adults	-0.20 [†] (-1.19, 0.79)	-1.77 (-4.40, 0.86)	-3.00 (-5.88, -0.13)	-2.95 (-5.70, -0.20)
Healthy children	-0.50 (-1.40, 0.40)	-0.50 (-1.36, 0.36)	-1.86 (-2.65, -1.06)	-1.86 (-2.66, -1.06)
High risk children	-2.50 (-4.40, -0.60)	-2.50 (-4.37, -0.63)	No results available	-0.50* (-1.51, 0.46)
All children	No results available	No results available	No results available	-1.33* (-1.95, -0.71)
Elderly	No results available	No results available	No results available	-3.07* (-6.30, 0.16)
All 'at risk'	No results available	-1.89* (-3.95, 0.17)	No results available	-0.80* (-1.73, 0.13)
Whole population	-0.37 [†] (-0.72, -0.02)	-0.71* (-1.24, -0.19)	-1.64 (-2.11, -1.17)	-1.51* (-2.02, -1.01)

[†]Includes NAI30010

*Includes results from studies not included in the last review

The overall 'at risk' group in the current review included children with co-morbid conditions. Therefore, in order to be able to make a direct comparison with the previous report, we also analysed data for 'at risk' children and 'at risk' adults separately. There were no differences in effectiveness in either the ITT or ITTI

populations for time to alleviation of symptoms between the two reviews. There were no new data relating to high-risk children. The current review included approximately twice as many patients in the analyses of time to normal activity for ‘at risk’ adults, making these analyses less dominated by one study, NAIB2007,⁴⁶ that reported a zero effect with very narrow confidence intervals. As a result, the weighted median difference was increased in favour of zanamivir compared to the previous report, for both the ITT and ITTI populations, although there remained no statistically significant difference when zanamivir was compared to placebo.

Oseltamivir

The new data available for oseltamivir in this review resulted in smaller effect estimates for the time to alleviation of symptoms in otherwise healthy adults,⁶⁷⁻⁶⁹ and the results were statistically significant in both reviews. There were no new trials included in this analysis; the increase in the effect size in the ITTI population appears to result from the use of N rather than r, as the studies included in this particular analysis had high numbers of patients who had not returned to normal activity (the number censored is unclear); for the studies combined the rate was substantially higher in patients receiving placebo compared to that seen in patients receiving oseltamivir (35% and 20%, respectively).

The overall ‘at risk’ group in the current review included children with co-morbid conditions. Therefore, in order to be able to make a direct comparison with the previous report, we also analysed data for ‘at risk’ children and ‘at risk’ adults separately. There is a difference between the two reviews in the results for the time to the alleviation of symptoms in ‘at risk’ ITTI adults, despite data from the same studies being used. The reported WMDs were -10.91 hours (0.45 days) and -20.09 hours (0.84 days) from the previous and current review, respectively. We repeated the analysis using the data we extracted, and using standard deviations calculated from the standard errors reported in the previous review, and ‘r’ instead of N. All these analyses resulted in a WMD of approximately -20 hours. Despite this discrepancy, none of these analyses reported a significant difference between oseltamivir and placebo, and therefore the conclusions drawn from these data would not be altered. No differences in effectiveness were seen in either ITT or ITTI populations for time to return to normal activity.

Generally, zanamivir and oseltamivir reduced the median duration of symptoms and median time to return to normal activity when compared to placebo, in both the current and Turner (2003) review, and in terms of symptom relief the conclusions drawn from the two reviews are similar.

5.2.7.2 *Trial design and quality*

The majority of included studies were described as randomised, double blind, controlled trials, although the details of the methods of randomisation, allocation concealment, and particularly blinding, were poorly reported. Two trials specified that they were open label,^{66, 71}

The types of participants recruited to some subgroups differed across studies. Although the elderly were consistently defined (over 65 years of age), there was less consistency for other subgroups. The age of the children recruited varied from 1 to 12 years, to 6 to 17 years. Most studies that reported results specifically for healthy adults defined this group as aged between 18 and 65 years of age and not otherwise 'at risk'. However, some studies included healthy elderly patients and/or older children (over 12 years) and adolescents. Although heterogeneity was observed in some analyses of children and healthy adults, this did not seem to be attributable to these differing definitions.

Definitions of outcomes varied across studies. Time to alleviation of symptoms incorporated a composite of between three and eighteen symptoms, and time to return to normal activity was defined as time to return to work/school, 'feeling better' or 'feeling as before illness'. In a few trials time to alleviation of symptoms was greater than time to normal activity. However, given that the most common definition used was the time to return to work, it is not inconceivable that participants would consider themselves to be back to normal activity before all symptoms were alleviated.

Definitions of adverse events also varied across trials and often incorporated data on complications, notably so in the zanamivir trials (insufficient detailed data were available to examine this in any detail for the oseltamivir trials), such that some studies appeared to have very high overall adverse event rates. However, provided that definitions were applied consistently across treatment arms within trials, this is unlikely to have led to systematic bias. The definition of a serious adverse event was also unclear in most trials.

Most trial protocols specified follow-up periods of either 21 or 28 days; the minimum period over which a trial evaluated patients was the duration of treatment, 5 days. Despite such short of follow-up, there was often incomplete follow up of participants. Censoring data meant that participants who were still ill at the end of the follow-up period had either missing or inaccurate symptom data, depending on the way a given trial reported data. Given that those still ill at the end of follow up are likely to be so because of a complication or a serious adverse event, if censoring differs by treatment arms, outcomes could be biased (i.e. those with the worst outcomes are not contributing to the analysis of symptoms). Losses to follow-up of more than 5% occurred in a quarter of the trials. Considering the relatively low numbers of participants

recruited, and the short duration of follow up, it is disappointing that for many trials full follow-up was not achieved.

Many trials recruited patients in small numbers over a large number of sites which may lead to trial data quality issues.¹¹¹ For example, one trial of zanamivir in participants recruited 525 participants from 159 sites⁹⁷ and one oseltamivir trial recruited 316 participants from 79 sites.⁶⁸

Fourteen out of 29 studies (9 zanamivir,^{75, 76, 86, 87, 92, 95, 97, 99, 105} 5 oseltamivir^{65, 78, 83, 106, 109}) reported the use of a power calculation to determine sample sizes. Of these, five (3 zanamivir,^{76, 99, 105} 2 oseltamivir^{78, 83}) did not recruit their stated required size. A further five studies that did not report the use of a power calculation recruited low numbers (maximum of 60 participants per arm).^{57, 71, 77, 85, 110} In addition, data for the children, elderly, and 'at risk' subgroups were often obtained from studies of mixed populations, which were unlikely to be designed to be powered to detect treatment effects in these subgroups. As a consequence, even meta-analyses of subgroup data lack statistical power.

All except one zanamivir trial reported continuous outcomes in days, rounded to either full or half days. This rounding depended on whether participants were randomised before or after 2pm, this being the halfway point between when routine doses were taken and symptoms recorded (8am and 8pm). Most zanamivir trials recorded symptoms twice daily, but some recorded symptom scores four times daily during treatment, providing a more accurate measurement. All except one of the oseltamivir trials reported the continuous outcomes in hours, however it was largely unclear how this level of precision was achieved. The imprecision of measurements of symptom duration should be borne in mind when interpreting the relatively modest observed reductions in time to recovery.

5.2.7.3 Factors potentially impacting on the effectiveness of NIs where data is limited

A number of factors that could not be addressed directly using the trial data may also be pertinent in evaluating the likely role of these drugs, and are discussed below.

Antipyretics and other symptomatic relief were variously banned, restricted or freely available in studies. Although, this is likely to have most affect on the time to alleviation of fever, which was poorly reported across the studies, differing use of symptomatic relief could also affect the time to alleviation of symptoms or return to normal activity. Not all patients may present with fever, particularly the elderly and those who have undergone immunisation.¹¹⁸ Without further data, the impact of the impact of antipyretics and other symptomatic relief in the included trials is unclear.

Limited information was available on the number of vaccinated individuals present in the included trials. Five trials did not mention whether participants were vaccinated or not (2 zanamivir^{98, 102}; 3 oseltamivir^{66, 67, 69}). Seven studies either excluded individuals vaccinated within the previous 12 months, or reported a zero recruitment without indication whether lack of vaccination was a criteria for inclusion (2 zanamivir^{76, 85} and 5 oseltamivir^{65, 68, 71, 83, 106}). The highest rate of vaccination in a study of healthy adults was 9%.⁸⁶ Six studies had higher rates of vaccination than this, all of which were either in a mixed population that included ‘at risk’ people (14%⁹²) or were restricted to ‘at risk’ populations (general ‘at risk’, 23%⁹⁷ and 28%;⁷³ children, 19%;⁷⁸ and the elderly, 40%¹⁰⁴ and 43%⁷³). There was insufficient data to explore the impact of vaccination on the effectiveness of zanamivir or oseltamivir in these analyses. The remainder reported proportions vaccinated of between 1% and 4%, with similar rates across treatment arms.

The eligibility criteria concerning the maximum permitted time delay between onset of symptoms and treatment varied across studies. Where reported, this was either 36 or 48 hours, with most studies specifying 48 hours. The actual time between symptom onset and the initiation of treatment was reported in approximately 50% of the oseltamivir trials and 75% of the zanamivir trials. Of these, six studies recruited a few participants who had exceeded the maximum duration specified by the study protocols, two zanamivir^{85, 86} and four oseltamivir trials.^{65, 68, 106, 109} Where reported, the mean time between the onset of symptoms and initiation of treatment was similar across the studies despite the inclusion criteria. Very few trials reported analyses comparing efficacy in groups according to time to the initiation of treatment, but those that did suggested that earlier treatment might yield greater benefit.^{76, 87, 99, 106} However, there were insufficient data available for us to examine this further. In current clinical practice, time between symptom onset and GP presentation is likely to be linked to patient type, with those with more severe disease and children most likely to present within 48 hours and the elderly perhaps least likely to present within 48 hours due to absence of fever and the reluctance to ‘disturb the doctor’.¹¹⁸

As described previously, surveillance schemes monitor the number of people presenting to GPs with ILIs in the UK, and once a threshold of consultations for presentation of ILI is reached (currently 30 per 100,000 population), antiviral drugs are currently recommended for use as treatment for influenza in ‘at risk’ groups. Of the 29 studies included in this review, 18 stated that influenza was circulating in the community prior to recruitment into the study. Only six of these stated that participants were recruited in the UK, and UK citizens constituted a minority of the population in these studies. Whilst other countries have surveillance schemes, we are unclear as to the method of diagnosis used, the threshold over which influenza is deemed to be circulating, and the consistency of application of these factors across countries or continents.

The true positive rate (TPR) for influenza in those presenting with ILI is related to the threshold for influenza circulating in the community; data from the RCGP suggest that the TPR during peak weeks of

influenza activity was approximately 50%. Clearly the TPR will impact on the effectiveness of antiviral treatment in an ITT population, which is the effective clinical population given that rapid diagnosis is not currently an option. As neuraminidase inhibitors are specific for influenza, the lower the true positive rate, the less effective the treatment is likely to be in the presenting population as a whole. There are several areas of uncertainty surrounding this issue. These include the extent to which the presentation rate for ILI will be affected by availability of drugs, varying TPR will impact on effectiveness, and how representative the trials population is to the general population. The impact of these factors is explored in the economic model (Section 7). In practice, these issues could be potentially addressed by using rapid diagnostic tests prior to prescribing antiviral treatment. However, the clinical and cost effectiveness of introducing such screening was beyond the scope of the current review.

It has been suggested that during periods of increased influenza activity, general practitioners may not have the resources to meet the increased demand for consultation, particularly within the 48 hours of onset required for the prescription of antiviral drugs.¹¹⁹ It has been suggested that community pharmacists could assist with dispensing medications if activity increases and GP resources are stretched.¹¹⁹ One study, conducted over the 2003-2005 influenza seasons, investigated the accuracy of the diagnosis of 217 patients with ILI by 15 community pharmacists, using PCR as the gold standard.¹²⁰ Of 54 patients that were diagnosed with influenza by pharmacists, 27 (positive predictive value (PPV) of 51%; 95% CI: 33%, 64%) were confirmed influenza positive by PCR. This level of accuracy was stated as being comparable to trials of neuraminidase inhibitors where recruitment was limited to early presentation (58% to 79%), and that there may be a role for pharmacists in the clinical management of influenza epidemics.¹²⁰ Expectant treatment of NIs for family members, or those who have been in contact with those already diagnosed as suffering from influenza, to be taken at onset of fever, could help to address the difficulty of obtaining a prescription within 48 hours and lessen the consultation burden on general practitioners, although the evidence for this seems limited and its effectiveness may require investigation.

Limited information on resistances was reported in the trials. Where it was assessed as an outcome, (2 oseltamivir^{65, 78} and 2 zanamivir^{92, 99} studies) only one case of potential resistance to oseltamivir was encountered.⁶⁵ There was therefore insufficient evidence in the trials to estimate the rate of naturally occurring resistance to either drugs. However, naturally occurring resistance has been noted, primarily to oseltamivir,^{28, 29, 39, 40} with a single reported case of resistance to zanamivir.^{29, 39} Until recently, the rate of resistance to oseltamivir has generally been low. However, over the 2007/8 influenza season, European surveillance has shown an increase in resistance of the H1N1 subtype of type A influenza to oseltamivir, with an 11% resistance rate observed in the UK.^{21, 41-43} To date, this increase has only been observed in the H1N1 A influenza subtype, often associated with milder illness than other influenza subtypes, and the data available is from a relatively small number of isolates and it is not yet clear whether 2007/8 figure are

anomalous or indicate the start of a trend. Oseltamivir-resistant subtypes remain sensitive to zanamivir.²¹,

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The studies included in this review recruited patient groups that were narrower than the current licensed population (zanamivir 5 years of age and over; oseltamivir 1 year of age and over) limiting the ability to draw general conclusions on the effectiveness of antiviral drugs in the wider licensed population.

Although combining the results across all the included studies considers a wider patient group, as 36% of the patients were recruited into studies restricted to subgroups considered as ‘at risk’ according to the DOH Green Book,¹⁰ and between 9% and 17% of patients in the trials of mixed populations were classified as ‘at risk’ by the trialists, it is uncertain whether this is representative of those that present to GPs in practice.

The meta-analyses presented here have found reasonable evidence that both zanamivir and oseltamivir reduce the median time to alleviation of symptoms and the median time to return to normal activity when compared to placebo. The clinical significance of the modest sizes of effect observed is, however, debatable. These analyses have not compared, either directly or indirectly, the relative efficacy of zanamivir and oseltamivir. This is explored in Section 6. Data on the effect of these drugs on complications were limited, but suggest that both drugs may reduce the use of antibiotics. Data on adverse effects were limited, but there is no clear evidence of an effect of either drug on the incidence of serious or drug-related adverse effects. A number of other factors that could impact on the effectiveness of these drugs in practice could not be addressed from the trial data. These are explored further in the economic model section (Section 7).

6 Bayesian multi-parameter evidence synthesis of symptom data with indirect comparisons

6.1 Introduction

The results of the meta-analysis reported in earlier sections considered each of the two NI treatments compared to standard care separately, but they do not address how the NIs compare with each other - which treatment for influenza is ‘best’. The meta-analyses evaluated differences in *median* symptom duration, which is consistent with how individual trial results were reported, and with the methods used by Turner (2003) in the previous clinical effectiveness review.⁴⁶ However, the economic model, reported in Section 7 requires estimates of the differences in *mean* symptom duration.

Therefore, in the absence of head-to-head trials comparing zanamivir and oseltamivir directly, and given the lack of routinely reported data on mean symptom duration, we have developed a Bayesian multi-parameter evidence synthesis with indirect comparisons. The term ‘multi-parameter evidence synthesis’, adapted from Hasselblad (1995)¹²¹ is used to refer generally to complex forms of synthesis, including extension of standard meta analysis to indirect comparisons, and combinations of evidence on multiple endpoints.¹²² This approach addresses the need for suitable statistical methods for comparing multiple treatments that fully respect randomisation for decision making purposes.¹²³

The approach reported here is based on recent methodological work by Welton (2008)¹²⁴ that was originally developed using data from the earlier appraisal of antiviral treatment by Turner (2003).⁴⁶ This work has been further developed as part of this review to include the addition of more recent data that have been made available since the earlier appraisal and alterations to the model to more explicitly account for the separate subgroups presented here.

A Bayesian ‘hierarchical’ model is used to characterise the joint distribution of the efficacy of the treatments simultaneously, using information on time to resolution of symptoms, time to return to normal activity and numbers still ill at the end of the reported follow up. By considering outcomes together, the model takes account of differences in which trials are available for analysis in each outcome, as some report only resolution of symptoms and others report time to return to normal activities, although many report both. The model is fitted separately to the ITT and ITTI populations. Given the relatively short follow-up and censoring present in the symptom data reported, the model also uses the number of trial participants who are still ill with one or more influenza symptoms at the end of the trial follow-up period to inform symptom outcomes. This is potentially relevant information in relation to the shape of the distribution and helps to inform the extrapolation required to estimate mean durations for the economic model.

These issues present a number of potential challenges to conventional synthesis approaches: (i) to be able to combine information on two different (but potentially related) outcomes related to recovery from influenza; (ii) to combine data on medians and the survivor function at specific points in time (e.g. 21 and 28 days); and (iii) to allow for implied correlations between median time to end of symptoms and the survivor function, where studies report both of these measures calculated from the same data. The approach outlined here is based on a flexible statistical model which can accommodate the full ‘network’ of evidence represented by the different (and sometimes incomplete) sources of information available for each treatment option and according to different patient subgroups.

The approach further develops the pairwise results presented previously in the following respects:

- It allows a single coherent analysis of several inter-related outcomes, time to resolution of symptoms and time to normal activity, both of which are considered within the economic model.
- It simultaneously considers evidence on symptom duration reported in different forms (time to resolution of symptoms/return to normal activities), corroborating this with information on asymptomatic patient numbers at different time points where available.
- Estimates are presented based on a common ‘metric’ (i.e. days) to improve comparability between data from zanamivir (reported in days) and oseltamivir (reported in hours).
- The model is fitted to the entirety of the symptom data considered in the previous meta-analyses and, while respecting potential differences between subgroups, "borrows strength" across different studies for each treatment/subgroup combination; thereby improving the precision of the subgroup-specific estimates.
- Additional data reported on the survivor function can inform the distributional assumptions necessary to obtain estimates of mean symptom duration for the economic analysis.
- It facilitates a direct comparison between the separate antiviral treatments simultaneously with comparison to no antiviral treatment.
- Separate pairwise evaluations can be made for all possible comparisons of interest (i.e. even those without direct evidence) to help identify issues of data consistency with the direct evidence.

In addition to providing a single and coherent approach to comparing the relative efficacy of all relevant alternative treatment options, this approach also provides estimates suitable for the requirements of both the clinical and cost-effectiveness analyses. It does not, however, examine data on complications and the economic model draws on the pairwise comparison of this data.

6.2 Methods

The model considers the two main outcome measures reported in previous sections: the time to alleviation of symptoms and the time to return to normal activity. Based on the prior methodological work by Welton and colleagues, a Weibull model was assumed for both outcomes determined by shape and scale

parameters. A random effects model was assumed for the shape parameters across studies and outcome with common mean and between study and outcome standard deviation. The scale parameters were modelled on the log-scale and the baseline scale parameter was defined to be the time to alleviation of symptoms on the placebo arm. A separate random effects model for these baselines was applied to each subgroup, i.e. it was assumed that the time to alleviation of symptoms on placebo depended on the subgroup with a between trial and subgroup standard deviation. It was assumed that the time to return to normal activity on the placebo arm differs from the time to alleviation of symptoms on the placebo arm, and there is a random effects model for these differences across study and subgroup.

An additive treatment effect on a log-scale is assumed, with a random effects model for treatment effect across study and subgroup. Two cases for the mean treatment effect were considered: (a) the treatment effect is assumed the same for all subgroups; and (b) the treatment effect also depends on patient subgroup (i.e. there is a treatment by subgroup interaction).

The separate models (a) and (b) were compared using the Deviance Information Criteria (DIC) to aid model selection. The DIC is the sum of the residual deviance and the effective number of model parameters, and provides a measure of model fit that penalises model complexity. For the ITTI data, model (b) gave the best fit, suggesting that treatment effect differs according to patient subgroup for those with confirmed influenza. However, for the ITT data there was little to choose between the models, suggesting that treatment effect does not depend on subgroup when considering all those treated (and not just those with confirmed influenza). The results of model (b) are reported here. Results for the ITTI population were subsequently applied in the economic model.

The data were split into 4 types: median time to alleviation of symptoms; median time to return to normal activity; number still ill at end of follow-up conditional on median time to alleviation of symptoms; number still ill at end of follow-up with no median time to alleviation of symptoms reported. The modelling was carried out using Markov Chain Monte Carlo (MCMC) methods, as implemented in the Bayesian analysis software WinBUGS.¹²⁵ The WinBUGS model and code applied is reported in Appendix 10.7. Convergence was assessed using the Brooks-Gelman-Rubin diagnostic tool, and considered adequate after 50,000 iterations. For each model, a further sample of 100,000 simulations (using 2 separate chains) was then run. These were subsequently thinned to a sample of 20,000 to eliminate any auto-correlation, and provide the basis for the results presented here.

6.3 Results

Results from the multi-parameter evidence synthesis of the two symptom outcomes, for both the ITT and ITTI populations, are reported in Tables 6.1 to 6.8. Separate results are presented for otherwise healthy

adults, otherwise healthy children and an ‘at risk’ group. The ‘at risk’ group combines the separate ‘at risk’ populations into a single group (‘at risk’ children, ‘at risk’ adults and the elderly). The ‘at risk’ groups were combined in this way owing to the small number of trials in each of the separate populations. Prior to combination of the ‘at risk’ groups, the model was run for each subgroup separately (‘at risk’ adults, elderly, ‘at risk’ children). It was also run for the ‘at risk’ adults and elderly combined, keeping the ‘at risk’ children separate. Although the results of each of the separate analyses were broadly consistent in their findings in relation to the separate treatments, the differences across the separate individual populations appeared to lack internal consistency suggesting that particular trials in some of the ‘at risk’ populations may not be entirely consistent with the broader set of studies considered. Given these discrepancies and the relatively sparse data for the individual ‘at risk’ groups, the final results are presented for a single, combined ‘at risk’ group.

Each table presents estimates of median and mean days (together with the 95% credibility intervals (CrI)) separately for each treatment for each of the three main subgroups, along with the estimated probability that each treatment is best. The multi-parameter synthesis model with indirect comparisons also provides a full set of comparisons of the three potential pairwise comparisons of interest (e.g. zanamivir vs. placebo, oseltamivir vs. placebo and zanamivir vs. oseltamivir). Comparisons of the individual pairwise results for active treatment versus placebo derived from the multi-parameter synthesis model with those from the standard meta-analysis indicated broad consistency. In particular subgroups (e.g. the comparison of zanamivir vs. placebo for return to normal activities in both the ITT and ITTI analyses), the “borrowing of strength” and consideration of wider evidence (i.e. the proportion of patients still ill at the end of follow-up), provided by the multi-parameter synthesis model, increased the precision of the subsequent estimates of effect size such that the 95% CrI of the difference in median duration between active treatment and placebo did not overlap zero as they did previously.

Table 6.1: The median and mean (95% CrI) number of days to the alleviation of symptoms in the ITT population

Subgroup	Treatment	Probability ‘best’	Median (95% CrI)	Mean (95% CrI)
Healthy adults	Placebo	0.00	5.48 (2.04, 12.08)	9.88 (3.69, 21.82)
	Zanamivir	0.05	4.99 (1.86, 11.04)	8.99 (3.35, 19.91)
	Oseltamivir	0.95	4.43 (1.63, 9.88)	7.98 (2.93, 17.72)
‘At risk’	Placebo	0.00	8.29 (3.15, 18.15)	14.92 (5.65, 32.78)
	Zanamivir	0.89	6.67 (2.51, 14.66)	12.01 (4.54, 26.43)
	Oseltamivir	0.11	7.65 (2.9, 16.76)	13.78 (5.21, 30.31)
Healthy Children	Placebo	0.00	3.79 (1.25, 8.77)	6.82 (2.26, 15.89)
	Zanamivir	0.74	2.96 (0.98, 6.91)	5.33 (1.76, 12.48)
	Oseltamivir	0.26	3.19 (1.03, 7.52)	5.74 (1.87, 13.52)

Table 6.2: The median and mean difference in days (95% CrI) for the time to alleviation of symptoms in the ITT population

Subgroup	Treatment	Difference in symptom duration	
		Median (95% CrI)	Mean (95% CrI)
Healthy adults	Zanamivir vs. placebo	-0.49 (-1.35, -0.05)	-0.89 (-2.43, -0.09)
	Oseltamivir vs. placebo	-1.05 (-2.57, -0.28)	-1.90 (-4.60, -0.51)
	Zanamivir vs. oseltamivir	0.56 (-0.16, 1.72)	1.01 (-0.28, 3.09)
'At risk'	Zanamivir vs. placebo	-1.62 (-3.95, -0.47)	-2.91 (-7.15, -0.85)
	Oseltamivir vs. placebo	-0.63 (-2.24, 0.50)	-1.14 (-4.04, 0.90)
	Zanamivir vs. oseltamivir	-0.98 (-3.27, 0.30)	-1.77 (-5.89, 0.54)
Healthy Children	Zanamivir vs. placebo	-0.83 (-2.17, -0.17)	-1.49 (-3.93, -0.30)
	Oseltamivir vs. placebo	-0.60 (-1.74, 0.01)	-1.08 (-3.14, 0.03)
	Zanamivir vs. oseltamivir	-0.23 (-1.28, 0.59)	-0.41 (-2.29, 1.05)

Table 6.3: The median and mean (95% CrI) number of days to the alleviation of symptoms in the ITTI population

Subgroup	Treatment	Probability 'best'	Median (95% CrI)	Mean (95% CrI)
Healthy adults	Placebo	0.00	5.36 (2.47, 10.12)	8.96 (4.11, 16.89)
	Zanamivir	0.12	4.58 (2.09, 8.64)	7.66 (3.49, 14.46)
	Oseltamivir	0.88	4.12 (1.86, 7.86)	6.88 (3.12, 13.15)
'At risk'	Placebo	0.00	8.28 (3.84, 15.84)	13.83 (6.41, 26.45)
	Zanamivir	0.99	5.47 (2.48, 10.53)	9.13 (4.14, 17.59)
	Oseltamivir	0.01	7.34 (3.33, 14.24)	12.27 (5.53, 23.70)
Healthy Children	Placebo	0.00	5.80 (2.32, 12.03)	9.69 (3.88, 20.22)
	Zanamivir	0.26	4.74 (1.83, 10.13)	7.92 (3.07, 16.86)
	Oseltamivir	0.74	4.22 (1.61, 9.04)	7.06 (2.69, 15.18)

Table 6.4: The median and mean difference in days (95% CrI) for the time to alleviation of symptoms in the ITTI population

Subgroup	Treatment	Difference in symptom duration	
		Median (95% CrI)	Mean (95% CrI)
Healthy adults	Zanamivir vs. placebo	-0.78 (-1.77, -0.18)	-1.3 (-2.96, -0.30)
	Oseltamivir vs. placebo	-1.25 (-2.61, -0.43)	-2.08 (-4.34, -0.73)
	Zanamivir vs. oseltamivir	0.47 (-0.3, 1.50)	0.78 (-0.52, 2.51)
'At risk'	Zanamivir vs. placebo	-2.81 (-5.64, -1.18)	-4.70 (-9.44, -1.98)
	Oseltamivir vs. placebo	-0.93 (-2.79, 0.47)	-1.56 (-4.66, 0.78)
	Zanamivir vs. oseltamivir	-1.88 (-4.57, -0.27)	-3.14 (-7.73, -0.44)
Healthy Children	Zanamivir vs. placebo	-1.06 (-3.07, 0.25)	-1.77 (-5.10, 0.41)
	Oseltamivir vs. placebo	-1.58 (-3.93, -0.23)	-2.63 (-6.53, -0.38)
	Zanamivir vs. oseltamivir	0.52 (-1.20, 2.68)	0.86 (-2.01, 4.47)

Table 6.5: The median and mean (95% CrI) number of days to the return to normal activities in the ITT population

Subgroup	Treatment	Probability 'best'	Median (95% CrI)	Mean (95% CrI)
Healthy adults	Placebo	0.00	6.50 (2.25, 14.79)	11.71 (4.03, 26.69)
	Zanamivir	0.05	5.91 (2.04, 13.38)	10.66 (3.67, 24.28)
	Oseltamivir	0.95	5.25 (1.80, 12.01)	9.46 (3.24, 21.66)
'At risk'	Placebo	0.00	9.81 (3.49, 22.21)	17.68 (6.23, 40.3)
	Zanamivir	0.89	7.89 (2.77, 17.89)	14.23 (4.97, 32.42)
	Oseltamivir	0.11	9.06 (3.16, 20.65)	16.33 (5.7, 37.67)
Healthy Children	Placebo	0.00	4.49 (1.39, 10.97)	8.09 (2.51, 19.66)
	Zanamivir	0.74	3.51 (1.08, 8.62)	6.32 (1.94, 15.46)
	Oseltamivir	0.26	3.78 (1.16, 9.27)	6.81 (2.08, 16.82)

Table 6.6: The median and mean difference in days (95% CrI) for the time to the return to normal activities in the ITT population

Subgroup	Treatment	Difference in the time to normal activity	
		Median (95% CrI)	Mean (95% CrI)
Healthy adults	Zanamivir vs. placebo	-0.58 (-1.64, -0.06)	-1.05 (-2.95, -0.11)
	Oseltamivir vs. placebo	-1.25 (-3.16, -0.32)	-2.25 (-5.69, -0.57)
	Zanamivir vs. oseltamivir	0.67 (-0.18, 2.09)	1.20 (-0.32, 3.80)
'At risk'	Zanamivir vs. placebo	-1.91 (-4.84, -0.52)	-3.45 (-8.78, -0.94)
	Oseltamivir vs. placebo	-0.75 (-2.72, 0.60)	-1.35 (-4.96, 1.08)
	Zanamivir vs. oseltamivir	-1.16 (-3.94, 0.35)	-2.10 (-7.13, 0.63)
Healthy Children	Zanamivir vs. placebo	-0.98 (-2.64, -0.19)	-1.77 (-4.78, -0.34)
	Oseltamivir vs. placebo	-0.71 (-2.15, 0.02)	-1.28 (-3.88, 0.03)
	Zanamivir vs. oseltamivir	-0.27 (-1.53, 0.71)	-0.49 (-2.78, 1.28)

Table 6.7: The median and mean (95% CrI) number of days to the return to normal activities in the ITTI population

Subgroup	Treatment	Probability 'best'	Median (95% CrI)	Mean (95% CrI)
Healthy adults	Placebo	0.00	6.80 (2.91, 13.42)	11.37 (4.83, 22.66)
	Zanamivir	0.12	5.81 (2.47, 11.44)	9.72 (4.12, 19.28)
	Oseltamivir	0.88	5.22 (2.22, 10.38)	8.73 (3.68, 17.54)
'At risk'	Placebo	0.00	10.50 (4.51, 21.03)	17.56 (7.49, 35.39)
	Zanamivir	0.99	6.93 (2.91, 14.01)	11.59 (4.85, 23.46)
	Oseltamivir	0.01	9.32 (3.92, 18.92)	15.58 (6.54, 31.64)
Healthy Children	Placebo	0.00	7.36 (2.73, 15.90)	12.31 (4.57, 26.78)
	Zanamivir	0.26	6.02 (2.15, 13.43)	10.06 (3.57, 22.34)
	Oseltamivir	0.74	5.36 (1.92, 11.86)	8.97 (3.20, 19.95)

Table 6.8: The median and mean difference in days (95% CrI) for the time to the return to normal activities in the ITTI population

Subgroup	Treatment	Difference in the time to normal activity	
		Median (95% CrI)	Mean (95% CrI)
Healthy adults	Zanamivir vs. placebo	-0.99 (-2.34, -0.21)	-1.65 (-3.94, -0.35)
	Oseltamivir vs. placebo	-1.58 (-3.44, -0.52)	-2.64 (-5.83, -0.86)
	Zanamivir vs. oseltamivir	0.59 (-0.39, 1.97)	0.99 (-0.66, 3.29)
'At risk'	Zanamivir vs. placebo	-3.57 (-7.48, -1.39)	-5.97 (-12.65, -2.32)
	Oseltamivir vs. placebo	-1.18 (-3.64, 0.59)	-1.98 (-6.09, 0.99)
	Zanamivir vs. oseltamivir	-2.39 (-6.04, -0.33)	-3.99 (-10.15, -0.55)
Healthy Children	Zanamivir vs. placebo	-1.35 (-3.96, 0.31)	-2.25 (-6.66, 0.52)
	Oseltamivir vs. placebo	-2.00 (-5.16, -0.28)	-3.34 (-8.60, -0.47)
	Zanamivir vs. oseltamivir	0.65 (-1.53, 3.48)	1.09 (-2.56, 5.78)

Across all analyses and subgroups, the probability that an NI treatment was more effective than placebo was 100%. However, there was clearly variation across both the subgroups and the different sets of results (e.g. ITT vs. ITTI) in terms of which NI treatment had the greater probability of being 'best'. In general the overall results for the otherwise healthy adult and 'at risk' populations appeared consistent across the different analyses. For healthy adults, oseltamivir consistently had a higher probability of being the better treatment, whilst for 'at risk' populations, zanamivir consistently had a higher probability of being better. Despite the large differences observed in the probability that each intervention was optimal, the pairwise results for the comparison of the separate NIs revealed that in each of the subgroups and for each of the different symptom measures, the 95% CrI consistently overlapped each other and in all instances (with the exception the ITTI results for 'at risk' populations) the credibility interval around the indirect comparison of the separate NIs included zero.

The results for the otherwise healthy children were more varied across the separate analyses. In the analyses based on the ITT population zanamivir had the highest associated probability of being best, whereas in the ITTI population this switched to oseltamivir. This suggests that the different set of trials available for the analysis of otherwise healthy children in the ITT and ITTI analyses influence which treatment appears optimal. However, it should also be recognised that the pairwise comparison of median duration between the separate NIs revealed that the overall difference was relatively small across the separate analyses (between 0.23 and 0.65 days) and the associated credibility intervals were wide and overlapped a finding of no difference.

As expected, the differences in median and mean symptom duration between active treatments and placebo were consistently greater in the ITTI populations. Similarly, time to return to normal activities was generally longer than to resolution of symptoms. Finally, it is worth noting that the differences between treatments based on the mean difference in symptom measures between the NI treatments and placebo were larger than those based on the median differences, as expected from a skewed distribution. However,

the associated credibility intervals indicated higher uncertainty in these estimates. This is important since the estimates of mean duration are those subsequently employed in the base-case analysis of the cost-effectiveness model, although separate scenarios are also undertaken using differences based on median symptom duration.

Given the potential inconsistency noted when considering individual 'at risk' populations, further checks were undertaken on the studies informing these estimates and also for RCTs reporting both 'at risk' and otherwise healthy subgroup data. An inconsistency was identified within the ITTI subgroup data reported in Hedrick (2000),⁹⁹ in which the median symptom duration in 'at risk' children receiving zanamivir was shorter than the comparable estimate for otherwise healthy children (the placebo median time was longer in the 'at risk' group as would be expected). The importance of this inconsistency in the subgroup also needs to be considered against the much smaller number of 'at risk' children reported in this study compared to the healthy children population which is likely to be the cause (36 in the 'at risk' group compared to 435 in the otherwise healthy population). In order to ensure that this inconsistency was not adversely influencing the model, a separate analysis was undertaken which excluded 'at risk' children subgroup data. This is reported in Appendix 10.7.

This re-analysis provided consistent results in the ITT population, although there was minor variation within the ITTI results in children (with the difference in median time to resolution of symptom between oseltamivir and zanamivir reducing to 0.15 days (95% CrI: -1.01 to 1.53) and the associated probability that oseltamivir is best was lower (0.60). This difference was relatively small and simply reinforced the existing uncertainty surrounding which of oseltamivir and zanamivir is 'best' in a healthy children population. While these differences were not considered significant, a separate scenario was considered in the cost-effectiveness analysis employing the results from the analysis excluding 'at risk' children subgroup data.

6.4 Discussion

This multi-parameter evidence synthesis approach provides a number of potential advantages for decision making purposes. It addresses some of the problems caused by variation in reporting summary statistics and in combining evidence on multiple parameters related to the summary outcome of interest. This approach also ensures that the appropriate summary outputs (mean durations) are available for the economic model.

Despite the potential advantages, it is also worth considering the additional assumptions required in this analysis. The key assumption used in the model is that the relative effects for each of the subgroups in each trial are derived from a common distribution which is the same across each set of trials in the separate

groups. This assumption is similar to that employed in standard pairwise meta-analysis, except that there is an additional assumption that the similarity of the relative effect of treatment holds across the entire set of trials, regardless of which treatments were actually evaluated.¹²³ If this assumption does not hold, then the subsequent results are subject to potential bias (although the bias would not be expected generally to work in any particular direction). Given that the assumptions employed here are not likely to be statistically verifiable (this is compounded by the inclusion of additional parameters for the proportion of patients remaining ill at the end of the trial), the subsequent results need to be considered in the light of both clinical and epidemiological judgement in terms of whether these additional assumptions are reasonable. However, the comparison of a subset of results from the multi-parameter synthesis and their subsequent interpretation appears consistent with the results presented in earlier sections.

The results suggest that oseltamivir is consistently the ‘best’ treatment in terms of reduction in symptom duration for healthy adults, and equally zanamivir appears the ‘best’ for ‘at risk’ populations. For healthy children, the results were less consistent between the different set of analyses due in part to the limited data available in this population. Indeed, the ‘best’ treatment for healthy children actually switched between the alternative NIs in the ITT and ITTI populations. Consequently, the conclusions that can be drawn in a healthy children population in terms of which the ‘best’ NI treatment remain highly uncertain. Furthermore, in addition to the assumptions of the model employed here, these results also need to be set in a wider context. The amount of weight that can be subsequently placed on the relative differences between the NIs needs to be considered against the clinical plausibility that a particular NI treatment could work more effectively in one particular population (and that this relationship could be different in another population), the lack of confirmatory direct ‘head-to-head’ evidence and also the finding that the 95% CrI on the difference between the NIs consistently overlapped a finding of no difference.

Finally, it should also be recognised that the analysis presented here is primarily used as the basis for providing the required estimates for the economic model in terms of mean symptom durations. Clearly the probability ‘best’ statements reported in this section refer only to the symptom duration themselves and not to the wider clinical (e.g. their relative impact on complications) and economic considerations (e.g. their impact on quality of life and costs). However, a framework for combining the relevant evidence on each of these different elements is considered more formally in the cost-effectiveness model reported in Section 7.

7 Assessment of cost-effectiveness evidence

7.1 Systematic review of existing cost-effectiveness evidence

7.1.1 Methods

A broad range of studies were considered for inclusion in the assessment of cost effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) were included.

Two reviewers independently assessed all obtained titles and abstracts for inclusion based on the search strategies reported in Section 5.1.1.1 and Appendix 10.1. Any discrepancies were resolved by discussion and consultation with a third reviewer. All studies meeting the inclusion criteria were summarised and used as the basis for identifying major structural issues, assumptions and key drivers of cost-effectiveness. Due to the large number of individual studies identified, only the most relevant studies from the perspective of the NHS were then considered in more detail. The quality of these particular studies was assessed according to a general checklist based on that developed by Drummond (1996)¹²⁶ together with a more specific checklist for decision-models from Philips (2004).¹²⁷ This information is summarised within the text of the report, alongside a detailed critique of each study and the relevance to the UK NHS. The differences in approaches and assumptions are then explored in detail in order to explain any discrepancies in findings and to identify key areas of remaining uncertainty. The findings from the review provide the basis for the development of a new model reported in Section 6.

The following sections provide a detailed overview of the cost-effectiveness evidence and an assessment of the quality and relevance of the data from the perspective of the UK NHS. Summary data extraction tables (all studies) and the quality checklists applied to the most relevant studies are reported in Appendices 9.2 and 9.5, respectively. An overall summary of the cost-effectiveness evidence and the key issues is provided at the end of the section.

7.1.2 Results

The systematic literature search identified 358 references, of which 21 studies subsequently met the inclusion criteria. In addition, a separate cost-effectiveness analysis and electronic model was also submitted by Roche. No separate cost-effectiveness submission was made by GlaxoSmithKline as part of their overall submission.

A brief summary of the 22 studies is reported in Table 7.1. More detailed summary tables are reported in Appendix 10.2. The majority of studies evaluated the cost-effectiveness of neuraminidase inhibitors (NIs) for the treatment of influenza. However, there was significant variation in the choice of comparators assumed in the different studies. Importantly, 50% of studies considered the cost-effectiveness of only a single NI (either oseltamivir [7 studies] or zanamivir [4 studies]) compared to usual care and hence no comparisons were made with other NIs or alternative treatments. Of the remaining studies, 5 included both oseltamivir and zanamivir (although these were often presented as separate pairwise comparisons against usual care and no attempt was made to consider the relative cost-effectiveness of the alternative NIs); in the remaining 6 studies, at least one NI was assessed in combination with either rapid diagnostic testing, other antiviral treatment (amantadine and/or rimantadine) and/or vaccination.

The majority of studies (17/22) were conducted primarily from a health-care or payer perspective, although approximately half of all studies also considered productivity losses attributed to work-days lost due to influenza illness (and/or premature mortality). The studies covered a broad scope in terms of population settings, including otherwise healthy or 'at risk' (i.e. with chronic respiratory, cardiac or gastrointestinal co-morbidities) adults, elderly and children. 11 of the 22 studies were solely restricted to otherwise healthy populations (children, adults or elderly). 9 of the remaining studies considered a mixture of populations including both otherwise healthy and 'at risk' populations and 2 considered only 'at risk' populations. Most studies considered a relatively short time span (typically a single influenza season), although 9 of them explicitly allowed for appropriately discounted (either in base-case or sensitivity analysis) quality-adjusted life-years lost due to mortality resulting from secondary complications. With the exception of one-study (Griffin (2001)¹³¹), which was based on individual patient data, all studies were based on decision-analytic models typically employing a decision tree to represent the potential pathways during the course of an influenza illness over a single season. In those studies that considered the potential loss in QALYs due to premature mortality, this was modelled as a separate extrapolation exercise based on an assessment of the remaining life years and associated quality of life.

There was marked variation across the studies in the data sources and assumptions employed in relation to a number of important aspects, including: (i) the clinical epidemiology of influenza (i.e. the relevant pathways, associated probabilities and variation across the different patient groups - including the likelihood of experiencing secondary complications and mortality); (ii) behavioural aspects such as the probability that an individual consults a healthcare provider; (iii) the probability that a patient who presents to a healthcare provider has influenza as opposed to an alternative ILI; (iv) the quality of life associated with influenza, associated complications and premature mortality; (v) the relative effectiveness of the different treatment strategies in terms of symptoms as well as potentially in relation to the subsequent course of secondary complications.

Table 7.1: Summary of cost-effectiveness studies

Study	Country (Perspective)	Population	Comparators	Outcome	ICER
Armstrong (2000) ¹²⁸	USA (Managed care)	Otherwise healthy adults	Oseltamivir, zanamivir, usual care	Incremental cost per symptom free day	\$16 (zanamivir vs usual care) \$39 (oseltamivir vs usual care)
Brady (2001) ¹²⁹	Canada (Govt payer, societal)	(i) Otherwise healthy adults, (ii) 'at risk' adults	Zanamivir, usual care	Incremental cost per QALY	(i) \$94,600 - \$235,000 (ii) \$77,500 - \$195,000
Burls (2002) ¹³⁰	UK (NHS)	(i) Otherwise healthy adults, (ii) 'at risk'	Zanamivir, usual care	Incremental cost per QALY	(i) £65,000 (ii) £54,000
Griffin (2001) ¹³¹	UK (NHS)	'At risk' adults	Zanamivir, usual care	Incremental cost per QALY	£7,490
Husereau (2001) ¹³²	Canada (Govt payer, societal)	(i) Otherwise healthy adults, (ii) 'at risk' elderly	Oseltamivir, usual care	Incremental cost per QALY	(i) \$61,300 - \$299,500 (ii) \$78,800 - \$454,800
Inoue (2005) ¹³³	Japan (Health care payer)	(i) Otherwise healthy adults, (ii) 'at risk' adults	Oseltamivir, zanamivir, usual care	Incremental cost per QALY	(i) Dominant; (ii) \$2139 (oseltamivir vs. usual care) (i) \$107; (ii) dominant (zanamivir vs. usual care)
Jarvinen (2007) ¹³⁴	Finland (Payer, societal)	(i) Otherwise healthy adults, (ii) 'at risk' elderly, (iii) children	Oseltamivir, usual care	Incremental cost per QALY	(i) Euro 13,405 (payer), dominant (societal) (ii) Euro 754 (payer), dominant (societal) (iii) Euro 15,404 (payer), Euro 5,745 (societal)
Lee (2002) ¹³⁵	USA (Societal)	Otherwise healthy adults	Vaccination (Yes/No) + rimantadine, zanamivir, oseltamivir, usual care	Incremental net benefit	NA
Masukopf (2000) ¹³⁶	Australia (Payer)	'At risk' elderly	Zanamivir, usual care	Incremental cost per QALY	\$11,715
O'Brien (2003) ¹³⁷	Canada (Payer)	Otherwise healthy adults	Oseltamivir, usual care	Incremental cost per QALY	\$57,863
Postma (2007) ¹³⁸	Netherlands (Payer, societal)	(i) Otherwise healthy adults; (ii) 'at risk' elderly; (iii) 'at risk' adults	Oseltamivir, usual care	Incremental cost per QALY	(i) Euro 1,759, (ii) dominant; (iii) Euro 429 (payer)/dominant (societal)
Reisinger (2004) ¹³⁹	UK (NHS)	(i) Otherwise healthy children (1-12); (ii) otherwise healthy children (1-5)	Oseltamivir, usual care	Incremental cost per QALY	(i) £11,173 (ii) Dominant
Roche submission (2008)	UK (NHS)	(i) Otherwise healthy adults; (ii) 'at risk' adults; (iii) Otherwise healthy children (1-12), (iv) Otherwise healthy children (1-5)	Oseltamivir, zanamivir, usual care	Incremental cost per QALY	Oseltamivir vs. usual care (zanamivir not reported in table due to error in costs) (i) £5,452 (ii) £652 (iii) £5,992 (iv) £4,687
Rothberg (2003a) ¹⁴⁰	USA (Societal)	Otherwise healthy elderly	Alternative antivirals (amantadine, rimantadine, oseltamivir, zanamivir), Diagnostic test + antiviral, usual care	Incremental cost per QALY	\$1,129 (amantadine vs usual care) \$5,025 (flu test + oseltamivir vs amantadine) \$19,296 (oseltamivir vs flu test + oseltamivir)
Rothberg (2003b) ¹⁴¹	USA (Societal)	Otherwise health adults	Alternative antivirals (amantadine, rimantadine, oseltamivir, zanamivir), Diagnostic	Incremental cost per QALY	\$77,000 (amantadine vs usual care) \$133,000 (zanamivir vs oseltamivir)

Study	Country (Perspective)	Population	Comparators	Outcome	ICER
			test + antiviral, usual care		
Rothberg (2005) ¹⁴²	USA (Societal)	Otherwise healthy children aged: (i) 2, (ii) 7, (iii) 15	Alternative antivirals, alternative diagnostic tests, usual care	Incremental cost per QALY	Numerous
Sander (2004) ¹⁴³	UK (NHS)	Otherwise healthy elderly and 'at risk' adults	Oseltamivir, standard care	Incremental cost per QALY	£225
Sander (2005) ¹⁴⁴	UK (NHS and societal)	Otherwise healthy adults	Oseltamivir, zanamivir, usual care	Incremental cost per QALY	£5,600 (oseltamivir vs usual care), zanamivir dominated (vs oseltamivir)
Schwarzinger (2003) ¹⁴⁵	USA (Societal)	Otherwise healthy adults	Flu test + zanamivir, zanamivir, usual care	Incremental cost per flu day averted	\$37 (zanamivir vs usual care), \$22 (flu test + zanamivir)
Smith (2002) ¹⁴⁶	USA (Payer, societal)	Otherwise healthy adults	NI treatment, amantadine, flu test + NI, flu test + amantadine, usual care	Incremental cost per flu day averted	\$12 (amantadine vs. usual care), \$185 (zanamivir vs. amantadine)
Turner (2003) ⁴⁶	UK (NHS, Societal)	(i) Otherwise health adults, (ii) 'at risk' adults, (iii) children, (iv) residential care elderly	Amantadine, oseltamivir, zanamivir, usual care	Incremental cost per QALY	(i) £6,190 (amantadine vs usual care), £19,015 (oseltamivir vs usual care), £31,529 (zanamivir vs usual care) (ii) £4,535 (amantadine vs usual care), £22,502 (oseltamivir vs usual care), £17,289 (zanamivir vs usual care) (iii) £6,117 (amantadine vs usual care), £19,461 (oseltamivir vs usual care), £30,825 (zanamivir vs usual care) (iv) £6,117 (amantadine vs usual care), £19,461 (oseltamivir vs usual care), £30,825 (zanamivir vs usual care)
Vindt Holm (2004) ¹⁴⁷	Denmark (Payer, societal)	Otherwise healthy adults	Oseltamivir, usual care	Incremental cost per QALY	Euro 5,063 (Payer), dominant (societal)

Despite the differences noted above, all models typically assumed that the benefits of antivirals, compared to standard care, were only conferred to patients with influenza (as opposed to other ILIs). Symptomatic benefits were typically evaluated with respect to the duration of illness, with the majority employing ITTI analyses to estimate the duration of illness and relative impact of antivirals. However, the duration of illness was evaluated in a variety of ways – notably time to symptom resolution or time to return to normal activity. There were also differences in whether the mean or median duration of illness was used in the model.

The probability of ILI being influenza in a subject presenting to a healthcare provider was largely obtained with reference to a typical influenza season (only 3 studies also presented alternative rates to reflect epidemic or peri-epidemic periods) from trial data or surveillance reports, and was commonly subjected to detailed sensitivity analysis. The majority of evaluations derived estimates of the probability from trial-based estimates, as opposed to employing data from routine surveillance programs. This is of particular importance since the estimates emerging from the RCTs (65% to 80%) appear markedly higher than those informed by national surveillance data (15% to 47%).

Information on the subtype split (type A/B) only featured within studies including amantadine among the comparators. However, all studies assumed that the alternative NIs were equally effective against either circulating influenza type, and no distinction was made between the course of the illness due to the different types.

Resource utilisation and costs were commonly evaluated with respect to GP/physician contacts and associated drug prescribing (e.g. the antiviral themselves, antibiotics and over the counter (OTC) medications). Moreover, a minority of studies also addressed (through sensitivity analysis only) the potential impact that the availability of NIs themselves might have on consultation rates with a GP/physician and on the associated estimates of the probability that ILI is influenza. There was more variation between studies in whether secondary complications (including associated hospitalisation and mortality) were considered relevant or not. Typically there were 3 approaches employed: (i) secondary complications were excluded altogether; (ii) they were presented as sensitivity analyses only or (iii) they formed part of the base-case (which could differ according to the group considered i.e. in ‘at risk’ only).

The variation in approaches to secondary complications appears due to the limited information on both the complication rates themselves and the impact of antivirals reported in

the RCTs (primarily due to the low power of the RCTs and the associated uncertainty). Paucity of reliable data informing the relationship between influenza, hospitalisations and mortality rates was normally tackled at a subgroup (e.g. for ‘at risk’ patients only) or sensitivity analysis level, by combining information gathered from population-based studies with alternative assumptions regarding the potential treatment effect of the NIs. The relative effect of treatments on major complications and hospitalisations was typically modelled via a proxy measure (e.g. applying the relative risk reported for a reduction in antibiotic usage) or with reference to published meta-analyses focusing more specifically on these events. Any impact on mortality, where this was considered, was always modelled via a similar proxy approach (e.g. employing the relative risk of hospitalisation or pneumonia) due to the lack of direct evidence in relation to mortality benefits.

Adverse events due to influenza treatment were inconsistently reported across clinical trials and were often not clearly distinguishable from certain complications; moreover, those related to the NIs were usually reported to be infrequent, mild and transient. Due to scarce trial-based and observational evidence, the 8 evaluations allowing for adverse events in the base-case scenario formalised them via assumptions (subsequently tested in sensitivity analysis in only 5 cases) on extended length of illness or of hospital stay (either directly or indirectly through treatment discontinuance) or reduced quality of life. Antiviral resistance was rarely considered.

The impact of health-related QoL associated with the incidence of influenza and ensuing health states was modelled in all but 3 evaluations. Symptomatic benefits were commonly informed by patient level visual analogue scale (VAS) data collected as part of oseltamivir trials (often transformed into an equivalent utility score using an algorithm) or via the use of generic preference based instruments (e.g. EQ-5D, HUI-3). In general, the available QoL data was recognised as a major limitation in most studies. Although several studies were reported to be based on generic instruments such as EQ-5D, these were subject to a number of limitations including the size of the sample, the timing of administration (often undertaken retrospectively) or their completion by a limited number of clinical experts. Health-related QoL was generally recognised as an important driver in most evaluations, and the uncertainty surrounding it was frequently addressed through sensitivity analysis.

The variation in approaches, settings, populations and assumptions employed inevitably lead to important differences in the subsequent cost-effectiveness estimates. Although no clear consensus appears, the use of NI appeared consistently more cost-effective in particular populations such as ‘at risk’, elderly and paediatric populations. The variation between

studies was most evident in terms of whether the NIs appeared cost-effective in otherwise healthy populations. More favourable estimates were largely reported in studies adopting a high probability that ILI is influenza (i.e. employing estimates from RCTs as opposed to national surveillance systems) and when complications and productivity costs were also considered. However, the more consistent findings in particular populations (e.g. ‘at risk’, elderly) also need to be balanced against the more limited data (and uncertainty therein) related to these groups.

Across the full range of studies considered a number of common issues and limitations were identified which preclude reliable conclusions to be drawn from the existing evidence base.

These include:

- A lack of robust data for the different subgroups considered (both in terms of the absolute event rates and the relative effectiveness of NIs)
- Variability in the populations used to estimate the various model parameters (while the assessment of clinical efficacy was usually conducted on a ITTI basis, other inputs to the economic models, such as hospitalisation and mortality estimates, appeared to be informed by the wider ITT population including other ILI which may be less generalisable);
- The lack of head-to-head RCTs on the efficacy of alternative NIs, resulting in the presentation of separate pairwise comparisons or the exclusion of relevant alternatives;
- Marked variability in the estimates that ILI is influenza and differences in sources (e.g. RCTs vs. routine surveillance data);
- A lack of reliable estimates employing preference-based valuations, related to the impact on QoL of influenza and the respective antiviral treatments;
- Variation in approaches employed to model secondary complications and associated mortality, including the use of proxy estimates given the lack of direct evidence from the RCTs.

As previously noted, 7 of the 22 studies were undertaken from a UK perspective. 4 of these (including the submission from Roche) were published after the evaluation by Turner (2003)⁴⁶ undertaken as part of the previous NICE appraisal. All of the studies published after the Turner report, including the submission by Roche, are largely derived from the same source – the SAVE (Simulating Anti-influenza Value and Effectiveness) model. Given the overlap in approaches between these studies, only the more recent submission by Roche is considered in detail, alongside the earlier report by Turner (2003).⁴⁶

The ICER estimates reported in Table 7.1 reveal important differences between these two sources in terms of the subsequent results. The approaches, assumptions and results are therefore contrasted to identify key differences and issues in relation to their relevance to current NHS practice and also to assist in the development of the new model reported in Section 7.2.

7.1.2.1 Summary of Turner (2003)⁴⁶

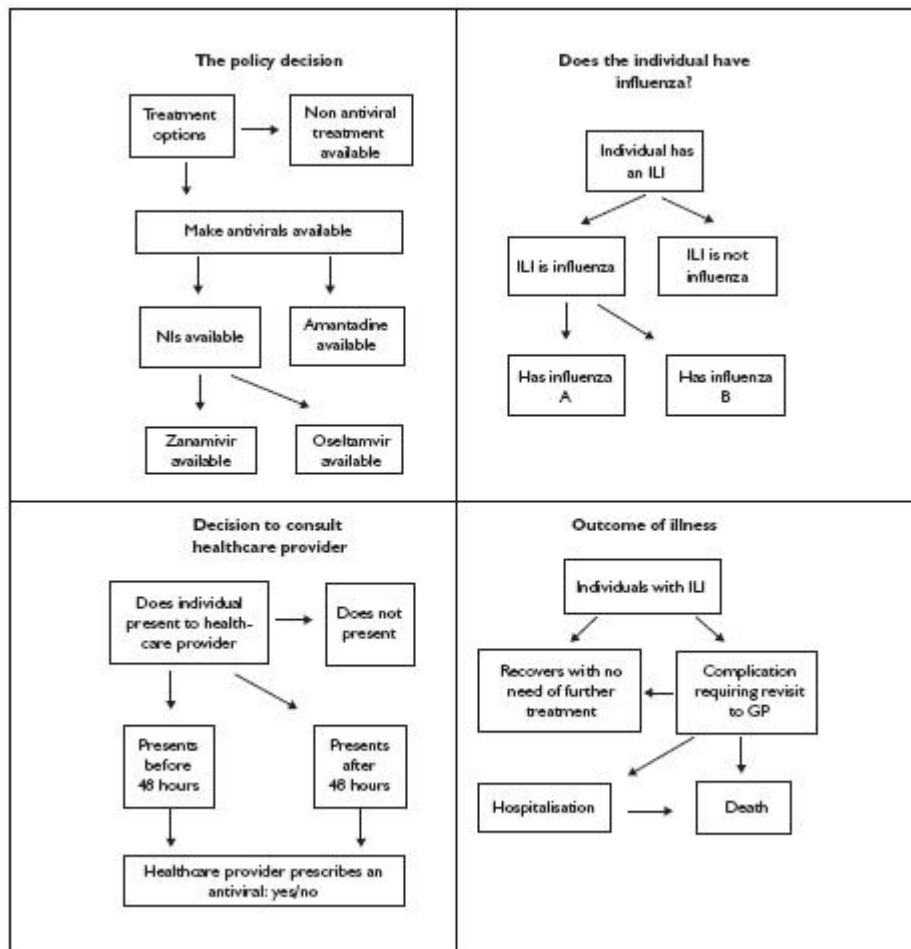
Overview

The study was designed to compare alternative options for the treatment and prophylaxis of influenza in four separate patient groups: (i) otherwise healthy adults, (ii) high-risk adults, (iii) children, and (iv) elderly in residential care. The treatment model compared four alternative strategies in each of the patient groups: usual care (i.e. no use of antivirals) and treatment with antivirals (amantadine, zanamivir, oseltamivir). The analysis adopted an NHS perspective, although the impact of incorporating productivity costs was addressed in the sensitivity analysis. A range of scenarios were undertaken to reflect alternative assumptions for key inputs. In addition, probabilistic sensitivity analysis using second-order Monte Carlo simulation was used to reflect parameter uncertainty in the model. Results were expressed as a series of pairwise estimates in terms of the incremental cost per QALY gained for each antiviral relative to usual care. A lifetime time horizon was adopted, although all influenza related events were assumed to take place within a single season and a lifetime horizon was employed solely to capture quality-adjusted life years lost due to influenza mortality.

The treatment model took the form of a decision tree, outlined in Figure 7.1. The model considered all patients in each group with ILI during periods when influenza was reported by surveillance schemes to be ‘circulating in the community’ (i.e. when the rate of ILI referrals exceeded 50 per 100,000 of the population, based on the definition in use at the time of the study). Progression through the model was dependent upon a series of separate considerations reflecting a broad range of policy, behavioural and epidemiological issues. These included: (i) the policy decision (e.g. whether antivirals were routinely available to healthcare providers and the potential impact this may have on subsequent consultation rates and other model parameters such as the probability ILI is influenza); (ii) the disease status of the patient (i.e. whether patient had influenza or other ILI; the proportion of influenza cases which were due to influenza type A or B); (iii) behavioural aspects related to the individual with an ILI (i.e. whether they present to a healthcare provider and timing of presentation) and

the healthcare provider themselves (e.g. compliance to recommendations on the use of antivirals, inappropriate prescription of antivirals and antibiotics etc) and (iv) the outcome of the illness and the impact of alternative treatments (in terms of symptomatic relief and also subsequent influenza related complications comprising both minor and major events and potentially mortality).

Figure 7.1: Schematic of model (Turner 2003)⁴⁶



The antivirals (amantadine, zanamivir or oseltamivir) were assumed to provide additional benefits relative to usual care alone only for those individuals who: (i) have influenza A or B (only influenza A in the case of amantadine), rather than an alternative ILI; and (ii) present to a GP within 48 hours of the onset of symptoms (with some exceptions: see below).

In each scenario, it was assumed that the patient would either recover directly from treatment without experiencing complications (in which case the benefits of antivirals were based on quality of life gains associated with symptomatic relief alone), or would encounter complications (either minor or severe) and subsequently recover (non-fatal) or not (fatal).

Minor complications were assumed to result in additional consultations with a GP only (and potentially additional use of antibiotics), whereas more severe complications resulted in hospitalisation and potentially mortality.

In the base-case analysis, the authors assumed that antivirals conferred additional benefits, relative to usual care, only in terms of symptomatic relief and reductions in minor complications requiring a revisit to a GP (and subsequent use of antibiotics). Hence, the base-case analysis assumed that the antivirals had no additional impact on major complications associated with influenza requiring hospitalisation or leading to premature mortality. The sensitivity analysis considered an alternative scenario (termed the ‘extrapolated’ model) in which the use of NIs only (oseltamivir and zanamivir) also resulted in reductions in major complications requiring hospitalisation and an associated reduction in influenza-related mortality. The adverse events associated with the use of NIs were considered to be sufficiently minor not to impact the model and hence were not included. However, an additional probability of adverse events was assigned to amantadine due to the more serious nature of these events. Issues of resistance to the use of antivirals were not considered.

The model assumed that all patients with ILI presenting to a GP within 48 hours of the onset of symptoms would be prescribed an antiviral in the relevant treatment strategies. However, due to difficulties in accurately gauging the timing of symptom onset, a small proportion of these were assumed to actually have had symptom duration in excess of 48 hours (i.e. in those presenting within the last 12 hours of the 48 hour period and with “insidious onset of influenza symptoms” as opposed to an abrupt onset, p.224). It was argued that such patients “would be presenting within 48 hours of apparently developing symptoms but would actually be outside 48 hours from onset”. For this proportion of individuals, it was assumed that, although antivirals would be prescribed, they would confer no additional benefits compared to usual care alone. Meanwhile, it was assumed that those presenting to a GP after 48 hours would not be prescribed any antiviral treatment except in cases where the patient falsely reports the time of onset of symptoms, could not recollect the time of onset accurately (more likely when the onset is “insidious” rather than “abrupt”) or where the GP inappropriately prescribes an antiviral treatment as a means of satisfying the patient’s wish to leave with a prescription.

Summary of effectiveness data

Estimates of the proportion of all ILIs in individuals presenting to a healthcare provider which are influenza (47.5% in the children group, 46% in all other groups) were based on national

surveillance data over a 10-year period (1992/03 – 2000/01) from the RCGP obtained through personal communication. Estimates for the children group were based on data for the <15 age group, all other groups were derived from the population aged ≥ 15 years for periods in which the threshold for ‘circulating in the community’ had been reached. For amantadine treatment it was necessary to distinguish between influenza A and B; the probabilities that influenza is type A (68.4% for healthy adults, 79.9% for high-risk adults and the elderly, 70.5% for children) were estimated from surveillance data for the period 1992 to 2001. The distinction between influenza A and B was only important in estimating the proportion of individuals in whom amantadine was assumed to be effective. No distinction was made in terms of subsequent differences in prognosis, costs or QoL for the different influenza types, and the NIs were assumed to be equally effective in both types.

The probabilities that a patient with ILI presents to a GP (28.2% for healthy adults, 32.5% for high-risk adults and the elderly, 15.5% for children) were derived from estimates of the size of the population, excess influenza consultations and attack rates obtain from a variety of separate sources. The probability that this presentation occurs within 48 hours of the onset of symptoms (17.8% for healthy adults, 12.2% for high-risk adults and the elderly, 57.2% for children) was derived from Ross (2000),¹¹⁸ adjusted according to the proportion of persons experiencing abrupt onset of influenza using data derived from a meta-analysis of studies reporting rates of abrupt onset in subjects with influenza A. Estimates of the proportion of those presenting within 48 hours of onset of symptoms that do not receive a drug treatment (4.8% for all groups) and the proportion of those presenting after 48 hours that do receive a drug treatment (2.8% for healthy adults, 1.1% for high-risk adults and the elderly, 12.1% for children) were also derived from Ross (2000).

The beneficial health effects of drug treatments were assumed to arise from improved quality of life (QoL) resulting from shorter duration of illness and, in the sensitivity analysis, a reduction in probability of severe complications and associated mortality with the NIs. The probability of severe complications was proxied by the probability of pneumonia and (in the children group only) the probability of otitis media. For usual care and amantadine treatment the probability of pneumonia (1.3% for healthy adults and children, 2.87% for high-risk adults) was based on the pooled control arms of the oseltamivir and zanamivir trials, whilst for oseltamivir (0.2% for healthy adults and children, 2.19% for high-risk adults) and zanamivir (0.4% for healthy adults and children, 2.0% for high-risk adults) it was based on the treatment arms of the respective trials. Using data from Roche trials, the probability of otitis media complications in children was assumed to be 21.3% for usual care and 12.0% for

oseltamivir treatment; for zanamivir or amantadine treatment the probability associated with usual care was adopted due to lack of data.

Hospitalisations were only considered as part of the ‘extrapolated’ model. The probability of hospitalisation for usual care was based on UK data reporting excess hospital admissions, combined with estimates of influenza attack rates and population estimates to derive the estimated probability of hospital admission. The relative risk of pneumonia was applied to these estimates to obtain the hospitalisation rates associated with each NI. The probability of influenza-related mortality was derived from a large UK observational study¹⁵ for each patient group, and was assumed to be constant (0.039% for healthy adults, 0.7% for high-risk adults and the elderly, 0.0048% for children) across all treatment strategies in the base case. In the sensitivity analysis, it was assumed that the estimated relative risk reductions in pneumonia associated with oseltamivir or zanamivir treatment also reduced mortality by the same proportion.

Summary of resource utilisation and cost data

The mean costs of GP visits (£21.38 for healthy adults and children, £27.43 for high-risk adults) were derived from UK published sources, weighted by the proportion of patients receiving home visits.^{118, 148} The cost of zanamivir (£24.98) was taken from published sources, the expected cost of oseltamivir (£19.16) was obtained from Roche, whilst the cost of amantadine (£3.38) was taken from the 2001 Alliance Pharmaceuticals submission to NICE. The cost of antibiotics (£4.05) was derived from Davey (1994).¹⁴⁹ The drug costs were increased to take into account pharmacy prescribing fees and container allowances.

The cost of inpatient stays were based on estimates of mean length of stay and mean cost per diem. The mean duration of stay was assumed to be 2.3 days for children (Simons P, personal communication), 11.9 days for adults and 15 days for those > 65 years based on national hospital statistics. It was assumed that 4.9% of adults admitted with pneumonia received assisted ventilation in an intensive care unit; the length of Intensive therapy unit (ITU) stay and mechanical ventilation were 28 days and 21.5 days respectively.

The unit costs of hospitalisation were calculated with reference to the National Schedule for Reference Costs: the mean cost per day for adults was taken from Health Resource Group (HRG) code D14 (£189), HRG code D13 (£164) for elderly and HRG code P04 (£309) for children. The mean cost per diem for an intensive care unit was assumed to be £1193.

Summary of quality of life data

The estimation of quality of life benefits was expressed in terms of mean QALYs. The estimates of QALYs comprised a number of separate elements: (i) symptoms – based on the illness duration; (ii) minor complications; (iii) adverse events (amantadine only); (iv) major complications and (v) premature mortality and associated loss of remaining quality-adjusted life expectancy. The base-case analysis evaluated the differential QALYs between the antiviral treatments and usual care in terms of elements (i), (ii) and (iii). As part of the sensitivity analysis, termed the ‘extrapolated model’, differential QALYs were estimated for all separate elements; only the NIs were assumed to result in differential QALYs, compared to usual care, for elements (iv) and (v).

The QALY estimates representing symptomatic benefits were derived from the *mean* duration of the illness, for each treatment, and the associated QoL during this period. The base-case analysis derived estimates based on the time to resolution of symptoms; sensitivity analysis explored the robustness of the results to the inclusion of productivity costs based on time to return to normal activity. Since estimates of the symptom duration were mainly reported in terms of median estimates in the clinical trials, a parametric survival analysis approach was employed in order to estimate the mean values required for the economic model. The authors assumed that the survival curve for time to recovery followed an exponential distribution (i.e. assuming a constant hazard). Median estimates were thus extrapolated, assuming an exponential distribution, in order to obtain the required mean estimates, converted into days, for input into the model. Estimates for the length of influenza illness for patients receiving usual care and oseltamivir and zanamivir were obtained directly from the relevant trials; whilst the length of illness for those receiving amantadine was based on the observed length of fever in the Cochrane review of amantadine (modified to include only those trials using doses of 100mg per day, extrapolated to give length of influenza illness using meta-regression results based on the observed lengths of fever and length of influenza illness observed in the oseltamivir trials). This alternative approach to estimating the duration of illness for amantadine was due to the lack of comparable outcomes compared to data reported for the NIs (i.e. outcomes were expressed in terms of the duration of fever as opposed to resolution of symptoms or return to normal activities).

QALYs based on symptoms estimated for each of the four treatment alternatives were derived from the mean duration of illness with respect to data reported for influenza positive patient health valuations conducted alongside a number of randomised trials of oseltamivir. In these trials, a 10-point Likert scale was completed daily over a 21-day period; this was recalibrated

to mean visual analogue scale (VAS) scores from the Measurement and Valuation of Health (MVH) study, which were then converted to Time Trade Off (TTO) equivalent utility scores using an equation (Ref MVH Group 1995).¹⁵⁰ Separate scores were used for healthy and ‘at risk’ populations. The TTO values for those receiving placebo and oseltamivir were used directly in the model as the QoL values for the usual care and oseltamivir treatment strategies respectively. To derive the QoL values for the zanamivir treatment and amantadine treatment strategies, the QoL values for the oseltamivir treatment strategy were adjusted according to the respective length of influenza illness associated with zanamivir and amantadine treatment.

The QoL associated with minor complications was assumed to be reflected in the patient health valuations given alongside the trials, while the QoL associated with severe complications was estimated separately based on WHO disability weights for lower respiratory conditions.¹⁵¹ These were 0.724 in the healthy adult population and 0.72 in the other populations. In the children’s model, the QoL associated with otitis media was taken to be 0.977 from the same source. The valuation of adverse events resulting from amantadine (0.81 for healthy adults and children, 0.74 for high-risk adults) was based on an assumed EQ-5D status, and the length of illness from amantadine adverse events was assumed to be 5 days.

QALYs lost due to premature mortality were estimated according to the quality-adjusted life expectancy for the separate patient groups based on estimation of the mean age of influenza deaths, remaining life expectancy (based on standard lifetables), the discount rate (1.5%) and quality adjustment according to age (based on the mean EQ-5D values derived from UK population norms). This approach assumed that individuals who die from influenza would have otherwise had a normal life expectancy with an associated QoL similar to that of the general population. The authors noted that this approach may overstate the benefit of preventing influenza deaths since those who die of influenza may be a less healthy subgroup. As previously stated, the relative risk reduction reported for pneumonia for the separate NIs was employed as proxy for the relative risk reduction for mortality.

Summary of cost-effectiveness data

Base-Case

In each sub-group, the base case results show that all three treatments were more costly and more effective than usual care. The ICERs given for each of the antiviral treatment strategies were reported separately relative to usual care. Hence, the results are presented as a series of

pairwise comparisons as opposed to a simultaneous assessment of the full range of relevant alternatives. As such, the results indicate whether each individual treatment is cost-effective relative to standard care; they do not, however, indicate which of the alternatives is optimal on cost-effectiveness grounds (which would require the interventions to be ranked in terms of costs or QALYs and then ICERs estimated following the exclusion of any dominated or extendedly dominated alternatives). The base-case results are reported in Table 7.2.

Table 7.2: Base-case cost-effectiveness results from Turner (2003)⁴⁶

Population	Strategy	Incremental Cost	Incremental QALY	ICER
Healthy adults	Amantadine	0.107	0.0000173	£6,190
	Oseltamivir	0.895	0.0000474	£19,015
	Zanamivir	1.290	0.0000409	£31,529
High-risk	Amantadine	0.063	0.000014	£4,535
	Oseltamivir	0.712	0.0000317	£22,502
	Zanamivir	0.960	0.0000555	£17,289
Residential care elderly	Amantadine	0.077	0.000015	£5,057
	Oseltamivir	0.85	0.000039	£21,781
	Zanamivir	1.14	0.000068	£16,819
Children	Amantadine	0.229	0.0000375	£6,117
	Oseltamivir	1.661	0.0000854	£19,461
	Zanamivir	2.222	0.0000721	£30,825

Oseltamivir is therefore slightly more cost-effective in the healthy adult and children populations than in the high-risk and residential care elderly populations, and conversely zanamivir is substantially more cost-effective in the high-risk and residential care populations than in the healthy adult and children populations.

Sensitivity analysis

In the healthy adult sensitivity analyses, ‘extrapolating’ the base case to include the impact of treatment on hospitalisations and deaths substantially improves the ICERs of oseltamivir and zanamivir for each of the subgroups. This effect is most evident in the high-risk and residential care elderly populations where the baseline risk of hospitalisation and mortality are highest (and hence the absolute gain associated with treatment is potentially greater). The ICER for amantadine remains unaltered from the base-case since no additional effect was assumed, relative to usual care, for hospitalisations and mortality. The ICERs for each of the antivirals across the subgroups was below £20,000 per QALY. In the residential care model, both oseltamivir and zanamivir dominated (i.e. less costly and more effective) usual care. The results are summarised in Table 7.3.

Table 7.3: ‘Extrapolated’ cost-effectiveness results from Turner (2003)⁴⁶

Population	Strategy	Incremental Cost	Incremental QALY	ICER
Healthy adults	Amantadine	0.11	0.000017	£6,190
	Oseltamivir	0.88	0.00019	£4,729
	Zanamivir	1.28	0.00014	£8,884
High-risk	Amantadine	0.063	0.000014	£4,535
	Oseltamivir	0.505	0.00017	£3,016
	Zanamivir	0.696	0.0002296	£3,029
Residential care elderly	Amantadine	0.076	0.000015	£5,199
	Oseltamivir	-0.98	0.0013	Dominates usual care
	Zanamivir	-0.21	0.001	Dominates usual care
Children	Amantadine	0.23	0.0000375	£6,117
	Oseltamivir	1.66	0.00015	£11,381
	Zanamivir	2.230	0.00012	£19,127

A number of additional scenarios (presented as one-way and two-way sensitivity analyses) were explored to examine the robustness of the model assumptions. The results indicated that the results were particularly sensitive to the probability that patients presenting with ILI have influenza. The results of the one-way sensitivity analyses are summarised in Table 7.4. As expected, lower probabilities (i.e. akin to a higher false positive rate) resulted in marked deteriorations in the ICERs of anti-viral treatment and vice-versa for higher probabilities.

Table 7.4: One-way sensitivity analysis of ICER applying alternative probability estimates (ILI is influenza) to base-case model

Population	Strategy	Probability ILI is influenza (base case = 0.47)				
		0.1	0.3	0.5	0.7	0.9
Healthy Adults	Amantadine	£79,993	£10,389	£5,555	£3,791	£2,878
	Oseltamivir	£95,130	£29,998	£16,972	£11,389	£8,288
	Zanamivir	Zero effect	£62,500	£30,500	£20,000	£16,857
'At risk' population	Amantadine	Neg. effect	£9,830	£3,928	£2,455	£1,785
	Oseltamivir	£107,165	£34,123	£19,514	£13,253	£9,775
	Zanamivir	£82,102	£26,178	£14,993	£10,200	£7,536
Residential care elderly	Amantadine	Not reported	Not reported	Not reported	Not reported	Not reported
	Oseltamivir	Not reported	Not reported	Not reported	Not reported	Not reported
	Zanamivir	Not reported	Not reported	Not reported	Not reported	Not reported
Children	Amantadine	£55,921	£10,135	£5,573	£3,843	£2,932
	Oseltamivir	£96,079	£31,598	£18,702	£13,175	£10,104
	Zanamivir	£111,000	£44,000	£27,250	£19,636	£16,385

Two-way sensitivity analyses were also undertaken to link the probability that ILI is influenza to higher consultation rates that may arise if NIs became routinely available following a positive recommendation on the use of NIs (Table 7.5 and 7.6). The two-way analysis explored the hypothesis that a positive recommendation in favour of the use of NIs, in particular populations (health and high-risk adults), would subsequently lead to an increase in the proportion of individuals consulting with a GP. This, in turn, was assumed to potentially lead to a reduction in the probability that ILI is influenza.

The results indicate that the cost-effectiveness of antivirals appears sensitive to a number of important issues, in particular:

1. whether antivirals result in reductions in hospitalisation and mortality associated with influenza;
2. whether the impact on hospitalisation and mortality is more plausible in particular groups (e.g. high-risk and elderly);
3. the probability that ILI is influenza; and
4. the potential impact on consultation rates following a positive recommendation on the use of antivirals.

Table 7.5: Two-way sensitivity analysis of the ICER in the base-case and extrapolated models (health adults)

Probability that ILI is influenza		Probability of presenting to GP if NI available			
		0.28	0.32	0.36	0.40
Healthy adult base case					
0.46	Zanamivir	£30,096	£51,613	£67,363	£79,738
	Oseltamivir	£17,765	£36,049	£49,684	£61,325
0.41	Zanamivir	£34,688	£58,395	£76,714	£91,294
	Oseltamivir	£20,198	£40,279	£56,819	£69,170
0.36	Zanamivir	£39,501	£67,172	£86,735	£104,220
	Oseltamivir	£23,442	£46,680	£64,754	£79,213
0.31	Zanamivir	£44,100	£76,343	£99,703	£118,145
	Oseltamivir	£26,872	£53,758	£75,130	£90,422
Healthy adult extrapolated case					
0.46	Zanamivir	£8,120	£13,760	£18,217	£21,695
	Oseltamivir	£4,280	£8,791	£12,277	£15,063
0.41	Zanamivir	£9,127	£15,511	£20,370	£24,357
	Oseltamivir	£4,897	£9,925	£13,841	£16,904
0.36	Zanamivir	£10,493	£17,755	£23,403	£27,921
	Oseltamivir	£5,687	£11,435	£15,920	£19,420
0.31	Zanamivir	£12,188	£20,733	£27,250	£32,445
	Oseltamivir	£6,737	£13,349	£18,572	£22,644

Table 7.6: Two-way sensitivity analysis of the ICER in the base-case and extrapolated models (high risk adults)

Probability that ILI is influenza		Probability of presenting to GP if NI available			
		0.33	0.37	0.41	0.45
High-risk base case					
0.46	Zanamivir	£19,031	£38,967	£55,223	£67,776
	Oseltamivir	£26,250	£60,327	£87,230	£111,667
0.41	Zanamivir	£21,677	£44,432	£62,106	£76,465
	Oseltamivir	£29,456	£68,663	£100,741	£127,473
0.36	Zanamivir	£25,098	£50,476	£70,878	£87,637
	Oseltamivir	£33,464	£76,617	£114,972	£143,740
0.31	Zanamivir	£29,691	£59,829	£82,442	£102,533
	Oseltamivir	£40,549	£94,429	£133,756	£170,754
High-risk extrapolated case					
0.46	Zanamivir	£3,677	£8,674	£12,658	£15,973
	Oseltamivir	£3,918	£10,761	£16,216	£20,778
0.41	Zanamivir	£4,304	£9,907	£14,380	£18,047
	Oseltamivir	£4,615	£12,235	£18,439	£23,443
0.36	Zanamivir	£5,160	£11,537	£16,657	£20,858
	Oseltamivir	£5,512	£14,206	£21,292	£26,987
0.31	Zanamivir	£6,222	£13,619	£19,579	£24,357
	Oseltamivir	£6,643	£16,684	£24,894	£31,472

Although issues (3) and (4) are presented as separate issues, they are inevitably closely linked and the results from the two-way analysis suggest that relatively small changes to these estimates can have a significant impact on the ICER.

7.1.2.2 Critique of Turner (2003)⁴⁶

The approach, methodology and interpretation of both the data and results in the report appear to be generally of high-quality. Significant efforts were clearly made to populate the different component parts of the model in a systematic and transparent manner. The checklists and critical appraisal of the report did not identify any significant concerns related to the majority of approaches employed. Where assumptions were employed, extensive sensitivity analyses were used to highlight the robustness of the base-case model to a variety of alternative assumptions. This process was informative in identifying a number of key issues likely to be important determinants of the cost-effectiveness of the use of antivirals generally and specifically concerning the use of NIs (oseltamivir and zanamivir). Of all the published studies considered in the review, the report from Turner (2003) was considered to be the most comprehensive and most relevant study from the perspective of the UK NHS.⁴⁶

A number of limitations of the model are discussed by the authors themselves, including the uncertainty inherent in the derivation of the QALY values for zanamivir and amantadine (in addition to that incorporated in the probabilistic sensitivity analysis), the poor quality of the evidence base for amantadine, the insignificance of the differences in rates of pneumonia observed in trials and uncertainty over the ability of elderly people to use the Diskhaler for zanamivir. It was suggested that there may be merit in further subgroup analysis of children given the greater rate of severe complications in very young children. Finally, as previously noted, the approach to the extrapolated model assumed that individuals who die from influenza would have otherwise had a normal life expectancy (and QoL). The authors noted that this approach may overstate the benefit of preventing influenza deaths since those who die of influenza may be a less healthy subgroup. However, it should also be noted that the discounted quality-adjusted life expectancy calculations for the 'at risk' adult group and elderly in residential care population were based on the same estimate (4.1 QALYs) which was derived from the mean age of death for subjects aged 65 years (i.e. the average age of influenza mortality in this group was 84 years and hence the remaining life-expectancies are derived from an estimate from the general population of the expected remaining life years of someone who had survived to this age). Hence, concerns noted regarding the potential for this approach to overstate the benefits in particular groups need to be considered against the potential to understate the benefits in others (e.g. 'at risk' subjects aged <65 years).

The critical appraisal identified several other possible limitations and issues that need to be considered in relation to the subsequent interpretation of the results. Firstly, the model itself addresses a number of behavioural elements (i.e. whether health care providers adhere to guidance or not, prescription of antivirals to placate patients regardless of their subsequent effectiveness etc) which reflect more of a positive approach to the decision problem as opposed to a normative perspective that typically underpins many decision models. The positive and normative distinction is applied in economics to distinguish approaches which model "what is" (positive) as opposed to "what ought to be" (normative). Hence, the model incorporates a level of inefficiency which, while reflecting the reality of clinical practice, means that the subsequent cost-effectiveness estimates do not represent the cost-effectiveness of antivirals as they should be used i.e. in accordance with guidelines etc. As a result, the current estimates are likely to under-estimate the cost-effectiveness of antivirals used in accordance with their respective licenses and subsequent guidance. Lack of adherence to these aspects is primarily an implementation issue and is separable from establishing whether the correct use of antivirals is, in itself, cost-effective. Despite these concerns, it is unlikely that this aspect would have a significant effect on the cost-effectiveness results.

The second limitation concerns the presentation of cost-effectiveness results as a series of pairwise comparisons. Hence, the cost-effectiveness results are not fully incremental; the ICERs given for each treatment were incremental to usual care in every case, *not* the next most costly (or effective) non-dominated strategy. A related issue concerns the presentation of decision uncertainty in the form of cost-effectiveness acceptability curves (CEACs). The presentation of a series of CEACs representing each pairwise comparison is similarly misleading in relation to adequately reflecting uncertainty surrounding the relevant decision problem (which refers to all relevant alternatives and not to specific subsets of comparators).

While the model considered the potential impact of NIs on hospitalisation and mortality rates as part of the ‘extrapolated’ model, only two serious complications resulting from ILI (pneumonia and otitis media) were considered. Additional complications documented in Meier (2000) and modelled in other studies (e.g. bronchitis, as in the Roche submission) were not considered. Similarly, the impact on mortality applied in the ‘extrapolated’ model was proxied via the relative risk of the NIs in relation to pneumonia (hence assuming that all mortality is due to pneumonia). If the risk of mortality is attributable to a wider set of complications, it is unclear whether this approach is likely to over or under-estimate the potential impact of NIs.

Another potential concern relates to the distributional assumption employed to extrapolate median illness durations into mean estimates for the model. The authors assumed that the survival curve for time to recovery followed an exponential distribution (i.e. assuming a constant hazard). However, it is unclear whether illness duration is exponentially distributed, hence the validity of the methods of extrapolation to derive the mean duration of illness remains unclear. It should also be noted that the duration of illness estimated from the meta-analysis (and survival analysis) was only used to adjust the QoL data obtained from the VAS scores for amantadine and zanamivir (estimates were adjusted based on the differential duration of illness vis-à-vis oseltamivir). The QoL estimates applied for oseltamivir and usual care were taken directly from the VAS data reported in a sub-set of the oseltamivir trials. Hence, the differential QoL reported between oseltamivir and usual care does not necessarily reflect the difference in mean duration of illness from the broader set of studies considered in the review itself.

It should also be recognised that the modelling stage which considers the decision to consult the healthcare provider, evaluates the probability that an individual *presents* within 48 hours. However, this is not strictly in accordance with either the respective licenses or existing NICE

guidance, which stipulates that patients should *both* present to the healthcare provider *and* be able to start antiviral treatment within 48 hours (36 hours in the case of children for zanamivir). Hence, it is not strictly correct to model this probability in terms of presentation rates within the 48 hour period, due to potential delays which may arise in actually receiving the treatment itself. In terms of presentation times, in accordance with the respective licenses, this has previously been interpreted in adults as presenting within 36 hours of illness and who can thus begin treatment within 48 hours.¹⁵² As a result it may have been more appropriate to consider presentation rates within a 36 hour period which may also have obviated the need for the subsequent adjustment to the 48 hour presentation rates to account for “insidious” onset.

Finally, although the sensitivity analysis provides a useful approach to identifying the key drivers of the cost-effectiveness results, many of the proposed analyses appear to be based on arbitrary estimates (i.e. fixed increments or decrements to key probability estimates). In particular, the results of the one and two-way sensitivity analyses highlight that the probability that ILI is influenza and the potential impact on consultation rates following a positive recommendation on the use of antivirals (and the potential link between the two) are important determinants of cost-effectiveness. However, no evidence is provided which support the range of estimates applied in these scenarios or even that there is a link between these two elements. Consequently, it is difficult to interpret whether these are reasonable assumptions or not. It should also be recognised that uncertainty surrounding the probability that ILI is influenza and the probability of consultations are already, to a degree, characterised by the distributions assigned as part of the probabilistic analysis.

A key remaining uncertainty is whether the variability in the probability ILI is influenza has been adequately represented and more importantly, whether an increase in consultation rates would alter the case-mix of patients presenting to a GP. If the case-mix remains unaffected, such that the probability that ILI is influenza is the same in individuals who currently present to a GP as it is in those who do not, then a higher consultation rate should have no material effect on the estimates of the ICER. While the ICER would remain unaffected in this scenario, clearly there are important budgetary implications that may arise. This issue is revisited in Section 7.2.4.

7.1.2.3 Summary of Roche submission (2008)

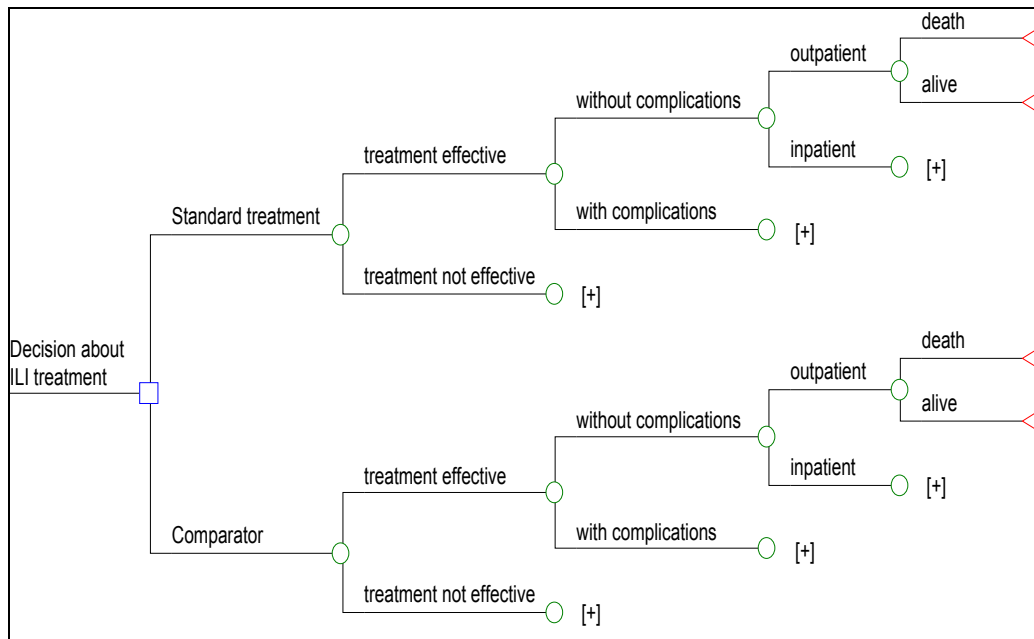
Overview

The study was designed to compare oseltamivir to zanamivir and usual care for the treatment of influenza in four separate patient groups: (i) otherwise healthy adults, (ii) ‘at risk’ adults (including all adults >64 years), (iii) otherwise healthy children 1-12 years, and (iv) otherwise healthy children 1-5 years. The model separately compared the strategy of oseltamivir treatment to those of usual care and zanamivir treatment across all patient groups (with the exception of otherwise healthy children 1-5 years, for whom only oseltamivir treatment was compared against usual care since zanamivir is not licensed for that age group).

The treatment model took the form of a decision tree outlined in Figure 7.2. The model considered all patients in each patient group presenting to a GP with an ILI during periods in which surveillance schemes reported influenza to be ‘circulating in the community’. A lifetime time horizon was adopted, although all influenza related events were assumed to take place within a single influenza season and so the lifetime horizon is employed solely to capture quality-adjusted life years lost due to influenza mortality. Quality-adjusted life years lost were discounted at 3.5% per annum, as per the NICE reference case; all other costs and health effects were captured within one year so were not discounted. The analysis primarily adopted an NHS perspective, although a societal perspective was considered in the sensitivity analysis. Probabilistic sensitivity analysis, using second-order Monte Carlo simulation, was used to analyse uncertainty in the model.

The overall structure of the Roche model reflects a narrower range of issues considered compared to the approach employed by Turner (2003).⁴⁶ Importantly, the Roche model starts at a later decision node; the decision problem considered by Roche starts at the point at which a patient has already presented to a GP. Hence, the probability that an individual will actually present to a healthcare provider (and the potential impact that a positive recommendation for NIs may have on this probability due to increased attendance rates) are not explicitly considered in the base-case analysis.

Figure 7.2: Roche model structure



The branches derived from the ‘treatment effective/no effective’ chance node are used to estimate the proportion of patients in whom NIs are assumed to provide additional benefits over and above those of usual care. In the base-case, this chance node is populated solely by the probability that ILI is influenza. Hence, issues related to inappropriate prescription of NIs and difficulties in gauging accurately the time of onset of symptoms (considered by Turner (2003)) are not part of the base-case analysis. Additional sensitivity analyses are, however, used to consider alternative factors which may alter the ‘treatment effective/no effective’ chance node, including the probability of developing resistance to the antivirals and the probability that patients present with 48 hours.

The base-case analysis of the Roche submission incorporates the benefit of NI in terms of both symptomatic improvements and reductions in minor complications, as well as their potential benefit in terms of preventing hospitalisations and mortality. As previously noted, this latter assumption formed part of the ‘extrapolated’ model reported by Turner (2003), but was not part of their base-case analysis. We have previously outlined that the inclusion/exclusion of the potential effectiveness of NIs in terms of hospitalisations and mortality were important drivers of cost-effectiveness in the report by Turner (2003).

The [+] sign in Figure 6.2 is used to simplify the graphical presentation and indicates that the pathways included in the branches above (e.g. death/alive after the outpatient pathway) are identical to those where the [+] sign is used. Hence, the model assumes that hospitalisations and mortality are not solely related to the onset of complications. In effect, this means that complications, hospitalisations and subsequent mortality are largely treated as independent events in the Roche submission.

The model compared oseltamivir with usual care and zanamivir using separate pairwise comparisons. For the pairwise comparison between oseltamivir and zanamivir, the submission assumed both NIs were equivalent in terms of their efficacy and so a cost-minimisation (rather than cost-effectiveness) approach was carried out for this particular pairwise comparison. However, it should be recognised from the outset that the premise for the cost-minimisation approach appears largely based on the differential costs reported in the Roche submission for the separate NIs. The total cost of a course of treatment for adults was assumed to be £16.36 for oseltamivir and £16.55 zanamivir – a difference of £0.19. The total cost of zanamivir reported in the Roche submission was “based on the new proposed price which has been approved by the Department of Health with effect from 1st February 2008” (p.67). However, the actual approved price of zanamivir is identical to that for oseltamivir (£16.36). Hence, in the case of the adult populations considered, any differences reported in the submission between oseltamivir and zanamivir are driven entirely by this error. For the children population, there remained a potential difference in the price of the two NIs due to the availability of an oral suspension form of oseltamivir (60mg/5mL, net price 75 mL=£16.36). In this instance, any difference between the cost of oseltamivir and zanamivir is reliant on the assumption that any remaining suspension can be re-used by the pharmacist. This appears to be an optimistic assumption and, hence, it might be more appropriate to assume identical costs for the NIs throughout, in which case there would be no difference in cost-effectiveness between the NIs based on the assumption of equivalent efficacy (and hence no reason on cost-effectiveness grounds to recommend one in preference to the other, assuming either are demonstrated to be more cost-effective than usual care without the use of antivirals).

Summary of effectiveness data

The previous review of the report by Turner (2003) indicated that the probability that ILI is influenza (akin to a measure of the true positive rate) was an important driver of cost-effectiveness, particularly when combined with assumptions related to increased consultation rates arising from a positive recommendation for the usage of NIs. In the Roche submission it

was assumed that the proportion of patients presenting to a GP with ILI who had influenza was 31%. This estimate was subsequently applied to all the separate populations. This contrasts with the approach used by Turner (2003) which applied separate estimates to the adult (46%) and children (47.5%) populations. It should also be noted that the estimate of 31% employed in the Roche submission is considerably lower than either of the estimates reported by Turner (2003). This assumption is referenced in the submission to NICE guidance (TA58), which in itself appears to be one of the alternative scenarios adopted in the sensitivity analyses undertaken by Turner (2003). This lower estimate appeared to be considered by the Appraisal Committee for TA58 to more appropriately reflect the potential impact that the availability of NIs may have in specific populations due to increased consultation following a positive recommendation. We have previously noted that the basis of this estimate appears largely arbitrary and, in addition, it remains questionable whether this assumption would be relevant to all populations (particularly since NIs have already been recommended in ‘high-risk’ populations).

The probability that influenza was type A (76%) was reported in the submission but was irrelevant to the reported outcomes since no distinction was made between the NIs in terms of their efficacy in terms of influenza types A and B. It was also assumed in the model that all patients presenting with ILI after 48 hours of the onset of symptoms were filtered out by the GP; that is, 100% of those diagnosed with ILI presented within 48 hours and so could benefit from treatment (this assumption was reconsidered in the sensitivity analysis by adopting the estimates used by Turner (2003), derived in turn from Ross (2000)).¹¹⁸

In each scenario it was assumed that a patient would either recover directly from treatment or encounter a single complication (one of three types): either bronchitis, pneumonia or – in the two children groups only – otitis media. The probabilities of developing bronchitis or pneumonia with usual care were taken from a large UK population based study by Meier (2000);¹⁵ the risk reductions resulting from NI treatment for healthy or ‘at risk’ adults were taken from a published meta-analysis of oseltamivir trials - Kaiser (2003),¹⁵³ whilst the risk reductions associated with children were taken directly from Roche trial data. For each of the children groups, the probability of developing otitis media with usual care was taken from the placebo arm from the Roche clinical trials of children, whilst the probability associated with either NI treatment was calculated by applying the risk reduction observed in the trial for oseltamivir to the probability associated with usual care.

It was assumed that there was a probability of hospitalisation resulting from ILI (without any complication), bronchitis or pneumonia, but not from otitis media. The probability of

hospitalisation from ILI with usual care was stated as being derived from US National Hospital Discharge Survey Data reported in Cox (2000),¹¹⁶ and was given as 1.93% for all patient groups; the risk reduction for NI treatment was sourced from Kaiser (2003),¹⁵³ resulting in a probability of hospitalisation following NI treatment of 0.97% in the ‘at risk’ adults group and 0.78% in all other groups. The probability of hospitalisation associated with bronchitis was assumed to be identical to that for ILI with usual care, whilst the probability of hospitalisation associated with pneumonia was stated as being taken from Cox (2000).¹¹⁶ NI treatment was assumed to reduce the probability of hospitalisation only in those patients who did *not* develop a complication.

It was assumed that there was a probability of mortality resulting from ILI (without any complication), as well as for bronchitis, pneumonia or otitis media. For ILI with usual care these were taken from Meier (2000) and were given as 0.0387% for otherwise healthy adults, 0.0271% for otherwise healthy children (of both age ranges) and 0.685% for ‘at risk’ adults. For either NI treatment the reduction in the probability of mortality from ILI was assumed to be equivalent to the reduction in hospitalisations associated with NI treatment reported in Kaiser (2003); for otherwise healthy adults the probability of mortality from ILI was 0.0157%, for otherwise healthy children this was 0.0109% (mistakenly given as 0.3445% in the printed submission) and for ‘at risk’ adults this was 0.3445%. The mortality associated with those who developed a complication was assumed to be identical to the ILI mortality for usual care, irrespective of the treatment strategy adopted or whether hospitalisation occurred (in common with the probability of hospitalisation, NI treatment was assumed to reduce the probability of mortality only in those patients who did not develop a complication). In effect there are two benefits being modelled in relation to mortality for the NIs: (i) a reduction in the complication rate – which means that subjects face the mortality rate from ILI (without any complication) as opposed to the mortality rate applied to the specific complication and (ii) a reduction in the mortality rate applied to patients entering the pathway represented by ILI (without any complication).

Summary of resource utilisation and cost data

The resource utilisation and costs associated with GP visits, diagnostic tests, antibiotics, treatments and hospital visits were derived from a variety of sources including the National Ambulatory Medical Care Survey (NAMCS) from the US and other US databases. These estimates were reported to have been reviewed by three clinical experts from the UK. The source of the drug costs for oseltamivir is not given; the total cost of treatment is assumed to be £16.36 for adults (tabs), £16.36 for children (small capsules), or £8.18 / £10.91 for children

1-5 years / 1-12 years (suspension). The costings reported for children assume no wastage or re-use of any remaining powder for the preparation of the oral suspension. The total cost of zanamivir (£16.55 for all patient groups) is “based on the new proposed price which has been approved by the Department of Health with effect from 1st February 2008” (p.67). We have previously noted the error regarding the cost of zanamivir and the assumptions employed with respect to the use of oral suspension.

The probabilities of hospitalisation given earlier are key drivers of the expected costs of each strategy. Inpatients were assumed to incur two GP visits costing £34 each (as opposed to between 1.20 and 2.50 visits for outpatients, depending on patient group and complication) and £107 of hospitalisation costs for each day spent in hospital. For children 1-5 years, the estimated length of stay is based on unpublished analysis by Watkins (Personal communication, 2008) (3 days), for children 1-12 years and otherwise healthy adults it is taken from the Assessment Group report for TA58 (8 days and 10 days respectively), whilst for ‘at risk’ adults it is taken from Nguyen-Van-Tam (2001) (12 days).¹⁵⁴ The expected cost of one day in an intensive care unit (£1,153) for 10% of patients developing a complication is considered in the sensitivity analysis, whilst the cost of hospitalisation per day is estimated to be £107, based on HRGs D14, D40 and D43. It was assumed that no costs were incurred as a result of any adverse events from either NI treatment, since these were expected to be minor and so any cost implications would be small.

Summary of quality of life data

The beneficial health effects of NI treatments were assumed to arise from improved QoL during the period of illness, a reduction in the probability of developing a complication following treatment and, for those who did not develop a complication, a reduction in the probability of mortality. As in Turner (2003), the QoL associated with minor complications was assumed to be reflected in the patient health valuations based on VAS reported alongside the trials for oseltamivir and so were not considered separately.

Utility weights associated with ILI (without complications), bronchitis, pneumonia and otitis media were assumed not to vary between patient groups. The utility value associated with ILI (without complications) for patients receiving usual care (0.840) was sourced from “Harvard utility scores” (no further reference given). The submission neither discusses nor justifies the use of the Harvard utility score for ILI (no complications). The relative improvement with either NI treatment was assumed to be 11.52% (resulting in a utility value of 0.937). This figure of 11.52% was calculated by converting the patient health valuations conducted

alongside the oseltamivir clinical trials into QoL scores (using the same methodology as Turner (2003)) and then deriving the percentage difference in the sum of expected QALYs between usual care and oseltamivir over the first 7 days of the valuation. Utility values associated with complications – bronchitis (0.990), pneumonia (0.900) or otitis media (0.910) – were based on a Dutch study (Stouthard (1997)¹⁵⁵) and assumed not to vary with the treatment strategy. All utility values were given triangular distributions.

These utility weights were applied to each day of illness – the duration of ILI was defined as the time to return to normal activities (this was considered in Turner (2003). only as part of the sensitivity analysis in order to calculate productivity losses). This was given separately for those patients who required hospitalisation and those who did not, and varied by patient group, complication, and, for those with no complication, treatment strategy.

The time to return to normal activities for outpatients was based on the data collected through the self-reported VAS instruments in the oseltamivir clinical trials: for patients without complications these were given as a single number of days and assumed to have gamma distributions, whilst for patients with complications these were given in two parts – days of illness before the complication occurred and days of illness with the complication – with each part assumed to have a triangular distribution. The durations of illness for those hospitalised were derived by adding the length of stay in hospital (given earlier for each patient group) to 50% of the respective outpatient duration of illness. As with outpatients, those who developed a complication were assumed to spend a number of days with ILI before developing the complication.

The QALYs lost through influenza-related mortality were derived for patients in each group by weighting the average life years lost by the EuroQoL tariff for that group. It was assumed that the average age of death for patients in each group was the mid-point of the group (3 years for children 1-5 years, 7 years for children 1-12 years, 38 years for otherwise healthy adults 13-64 years, and an assumed 45 years for ‘at risk’ adults 13-64 years and all those > 65 years); for this mid-point age, average remaining life expectancy was derived from life tables published by the UK government’s Actuary Department (76 years for children 1-5 years, 72 years for children 1-12 years, 42 years for otherwise healthy adults 13-64 years, and 36 years for ‘at risk’ adults 13-64 years and all those > 65 years). The mean EuroQoL tariff for all adults (0.85) was used for otherwise healthy adults and both children groups, whilst for ‘at risk’ adults the average of the EuroQoL tariffs for adults aged 65-74 years (0.78) and 75+ years (0.73) was used (0.76). All EuroQoL tariffs were assumed to have Beta distributions.

Although not mentioned in the printed report, the electronic model applied a utility weight of one (equivalent to perfect health) to each day within the first year of the model start-point spent without ILI or any of its complications.

Summary of cost-effectiveness data

The cost-effectiveness results for each sub-group are presented as pairwise comparisons of oseltamivir versus usual care and oseltamivir versus zanamivir (except for otherwise healthy children aged 1-5 years in whom zanamivir is not licensed). The base-case results are reported in Table 7.7. Given that oseltamivir and zanamivir are assumed to have identical efficacy and that oseltamivir is assumed to be less costly (particularly for children), it is unsurprising that in each of the pairwise comparisons oseltamivir is found to be cost-saving versus zanamivir (by £0.19, £5.65 and £0.19 per patient in the otherwise healthy adult, otherwise healthy children 1-12 years and ‘at risk’ adult groups respectively). The key results of interest are therefore the pairwise comparisons of oseltamivir versus usual care.

Table 7.7: Base-case cost-effectiveness results from Roche submission

Population	Strategy	Incremental Cost	Incremental QALY	ICER
Healthy adults	Oseltamivir vs. usual care	11.75	0.00216	£5,452
	Oseltamivir vs. zanamivir	-0.19	0	Oseltamivir dominates
Children 1-12	Oseltamivir vs. usual care	9.34	0.00156	£5,992
	Oseltamivir vs. zanamivir	-5.65	0	Oseltamivir dominates
Children 1-5	Oseltamivir vs. usual care	8.17	0.00174	£4,687
‘At risk’ adults	Oseltamivir vs. usual care	11.54	0.0177	£652
	Oseltamivir vs. zanamivir	-0.19	0	Oseltamivir dominates

A number of one-way sensitivity analyses were carried out to assess the sensitivity of the base-case results to variations in single parameters. Where a higher probability ILI is influenza (50%) is assumed (approximately the same as applied in the base-case analysis in the Turner (2003) model), the ICERs improve to £2567, £2904, £3333 and £301 per QALY in the otherwise healthy adults, otherwise healthy children 1-5 years, otherwise healthy children 1-12 years and ‘at risk’ adults groups respectively. Where the probabilities of patients presenting to a GP within 48 hours are taken from Ross (2000)¹¹⁸ (as opposed to the base-case assumption of 100% in all groups), these ICERs are less favourable: £35,821, £6090, £9677 and £4129 per QALY respectively. Assuming that 10% of patients incur one day in an intensive care unit substantially improves the ICERs to £3211, £4235, £4570 and £381 per

QALY, whilst assuming that children are prescribed the more expensive small-capsules rather than suspension raises the ICERs for children 1-5 years and 1-12 years to £9382 and £9496 per QALY respectively. The reported results do not appear to be particularly sensitive to variation made in relation to the number of years of life lost as a result of ILI mortality, the utility associated with usual care, whether a patient makes one or two GP visits or whether a 5% rate of resistance to antivirals is considered.

7.1.2.4 Critique of Roche submission (2008)

Overview

Perhaps the most important criticism of the submission by Roche was that there was no attempt to compare any of the results to those of other studies (such as Turner (2003)⁴⁶), despite the substantially lower ICERs calculated for oseltamivir versus usual care in particular patient groups. Hence, it is difficult to establish from the report itself what is driving these differences and the validity of the resulting ICER estimates.

Table 7.8 provides a comparison of the base-case results from Roche with the base-case estimates reported in Turner (2003) as well as the results from the ‘extrapolated’ model. These comparisons are based on the pairwise comparison between oseltamivir and usual care. As previously described, the assumptions employed in the base-case analysis of the Roche submission are more similar to the approach employed in the ‘extrapolated’ model reported by Turner (2003).⁴⁶ As expected, the differences between the estimates are smaller when the ICERs for Roche are compared to those from the ‘extrapolated’ model. However, important differences remain, particularly in the children and ‘at risk’ adult populations.

A comparison of the incremental cost and QALY estimates is problematic due to the different decision problems addressed by the separate models. The approach used by Turner (2003) focuses on all patients with ILI regardless of whether they subsequently present to a healthcare provider or, if they do present, whether they are considered eligible for treatment with antivirals. As a result, the reported mean differences in terms of the incremental costs and QALYs in the Turner (2003) model are actually only influenced by the relatively small proportion of patients who both consult and then receive antiviral therapy (i.e. within 48 hours). The incremental differences reported thus reflect the mean difference in the overall population of individuals with ILI, as opposed to the differences in the proportion of patients who are actually subsequently affected by treatment with NIs. This contrasts with the Roche submission which focuses specifically on the mean costs and QALYs in those patients who

are considered eligible (i.e. present to a healthcare provider) and are eligible to receive treatment with antivirals, as opposed to the wider population of people with ILI more generally. Given the different decision problems being addressed, it is difficult to identify whether the differences between the submission and the report by Turner (2003) are reflected in either the cost and/or the QALY estimates (and assumptions employed therein).

Table 7.8: Comparison of the results from Roche submission with Turner (2003)⁴⁶

Population	Strategy	Incremental Cost	Incremental QALY	ICER
Healthy adults	Oseltamivir vs. usual care (<i>Roche</i>)	11.75	0.00216	£5,452
	Oseltamivir vs. usual care (<i>Turner 'base case'</i>)	0.895	0.0000474	£19,015
	Oseltamivir vs. usual care (<i>Turner 'extrapolated'</i>)	0.88	0.00019	£4,729
Children 1-12	Oseltamivir vs. usual care (<i>Roche</i>)	9.34	0.00156	£5,992
	Oseltamivir vs. usual care (<i>Turner 'base case'</i>)	1.66	0.0000854	£22,502
	Oseltamivir vs. usual care (<i>Turner 'extrapolated'</i>)	1.66	0.00012	£19,127
'At risk' adults	Oseltamivir vs. usual care (<i>Roche</i>)	11.54	0.0177	£652
	Oseltamivir vs. usual care (<i>Turner 'base case'</i>)	0.712	0.0000317	£19,461
	Oseltamivir vs. usual care (<i>Turner 'extrapolated'</i>)	0.505	0.00017	£3,016

It should also be noted that neither the Roche submission nor the Turner (2003) model considered 'at risk' children as a separate patient group. Given that one of the key reasons for reviewing TA58 is the recent license extension for zanamivir to 5-12 year olds, and that currently NI treatments are currently recommended only for 'at risk' groups (adults and children), this was considered to be a potentially significant oversight in terms of patient groups considered within the submission.

In attempting to make a direct comparison between the different models, other important differences should also be noted that make a 'like for like' comparison problematic: (i) the current price of the NIs are now lower than those applied in the report by Turner (2003) (which should result in improvement to the ICER), (ii) the discount rates applied to outcomes are now higher (3.5% vs. 1.5%) applied to the quality-adjusted life years estimates associated with premature mortality (which should result in a deterioration of the ICER); (iii) the 'threshold' used to establish that influenza is circulating in the community is now lower

(unclear what effect this would have but it might be reasonable to hypothesise that this might worsen the ICER assuming that a lower threshold could result in a higher number of false positives); (iv) the probability that ILI is influenza is markedly lower in the Roche submission compared to the base-case analysis in Turner (2003) (which should result in a deterioration in the ICER) and finally (v) the new evidence available since Turner (2003).

Given these different issues, a direct comparison of the different ICERs may not be appropriate. However, some form of comparison clearly helps to identify possible areas of concern regarding differences in assumptions etc, even if this is just in terms of highlighting intuitive differences that appear to arise (e.g. why the results in the Roche submission are more favourable for particular groups, relative to those reported in the Turner (2003) model, but not for the healthy adult population).

In the absence of a clear explanation for the potential differences based on the reported data, the critical review focuses more closely on the specific assumptions and approaches employed within the Roche submission. These are contrasted with those used in the Turner (2003) model to attempt to highlight any major discrepancies between the two, in order to identify potential biases which may be causing these differences. A general checklist and more detailed checklist specific to decision models are reported in Appendix 10.5.

In general, the critical appraisal of the Roche submission was made more difficult due to a lack of transparency in both the printed submission and the electronic model, and a number of inconsistencies between the two. For example, the printed submission did not describe the distributions adopted for every parameter and a number of parameters adopted distributions without justification. A number of inconsistencies were identified in terms of references and data inputs between the report and the electronic model. However, most of the inaccuracies appeared to be in the report itself and the data reported for particular parameters, as opposed to the electronic model, hence it is unlikely that this would cause major issues with the results themselves.

There are a number of key assumptions made in the Roche submission that are likely to have an important effect on the relative cost-effectiveness of the alternatives considered. For ease of interpretation we have categorised these into a number of separate aspects: (i) structural issues; (ii) symptomatic benefits; (iii) resource utilisation and costs; (iv) complications and (iv) mortality. Each of these is considered in more detail below.

Structural issues

A key issue that arises from the Roche submission is the decision to start the decision model at a later point in the pathway compared to the earlier Turner (2003) model (at the point an individual presents to a GP, as opposed to an earlier stage which considers the probability that an individual actually presents to a GP). By starting at a later decision node, the issue of presentation rates to a GP are not considered in the base-case analysis. The Roche submission acknowledges that one of the concerns expressed by the Appraisal Committee about Roche's previous submission as part of the earlier appraisal (TA58) was that:

*“There was no assumed increase in GP consultations. The Committee considered it likely that more people with symptoms of ILI would consult their GP if they thought **they could be prescribed** an anti-influenza drug”* (p.47, emphasis added).

In the overview of the current model this concern is misrepresented:

*“The economic model begins when an individual presents to the GP with ILI. The model therefore doesn't address the issue of whether **existence** of a new technology will increase patient consultation rates. However, if the consultation rate does increase this will **not change the individual cost effectiveness estimates** as the cost of the initial GP consultation is included in the base case (sic) ICER”* (p.49. emphasis added)

Roche is correct in stating that any increase in the consultation rate caused by the *existence* of a new technology will have no effect on individual cost-effectiveness estimates, since the consultation rate will be increased irrespective of the strategy adopted. However, the question posed by the Appraisal Committee is whether the *availability* of an anti-influenza drug might increase consultation rates; if so, the consultation rate will increase if a strategy of NI treatment is adopted, but will not increase if the usual treatment strategy is adopted, and so the individual cost-effectiveness estimates may indeed be affected. Equally importantly, and a point which has already been raised during the report, is that regardless of whether an increased consultation is due to either the existence or availability of a technology, the critical aspect is whether this will lead to a change in the subsequent case-mix of patients consulting the GP (i.e. whether the additional patients who present following a change in policy have a lower probability that ILI is influenza than those who would presented prior to such a change). If the case-mix remains the same, then this should not have a material effect on the ICER itself, although the budgetary implications will clearly be different. As such, the

exclusion of this issue from the base-case analysis does not appear to have been adequately justified by the argument employed by Roche.

As we have previously noted, the potential link between the consultation rate and the probability that ILI is influenza is a key consideration. The Roche submission adopted a probability that ILI is influenza in patients presenting with ILI symptoms during periods in which influenza had been reported to be ‘circulating in the community’ of 31% in all patient groups, citing this as an assumption from TA58. As noted in the current submission by Roche, the Appraisal Committee at the time for TA58 considered the base case estimate of 46% (based on UK surveillance data) adopted by both Roche and the previous Assessment Group in the earlier appraisal as potentially being too high. As part of their sensitivity analysis, the previous Assessment Group considered other probabilities that ILI is influenza – 41%, 36% and 31% - which appear to have been chosen arbitrarily. In the published guidance for TA58, the Appraisal Committee discussed an ‘alternative case’ which appeared to favour the last of these, 31%. This probability appears to be the source of the 31% estimate adopted in the current submission by Roche.

There are a number of issues that arise from the estimate applied to the probability that ILI is influenza. Clearly the estimate applied by Roche is markedly lower than the base-case employed in the Turner (2003) model and more in line with the comments made by the previous Appraisal committee. Hence, the concerns noted previously about the decision to start at a later decision node in the Roche model are partially attenuated due to the more conservative estimate employed in the submission (although the costs of any additional visits to GP are not considered). Consequently, the more favourable ICER estimates reported in the Roche submission cannot simply be attributed to the structural alteration.

While the figure of 31% may be considered potentially conservative, there remain concerns about the reliability of this estimate in terms of both the Roche submission and the previous report by Turner (2003). We have previously outlined our concern regarding the arbitrary nature of this figure and the lack of data providing a robust link between a potential increase in the consultation rate and the probability that ILI is influenza. Focusing specifically on the Roche submission, it should also be noted that this estimate appears to have been related to specific populations in TA58 as opposed to the entire population (results employing this estimate in the Turner (2003) model are only reported for healthy adults and ‘at risk’ groups for these alternative scenarios). As such, the validity of this estimate remains unclear to the different populations considered. Furthermore, this figure is based on a sensitivity analysis reflecting the threshold used to determine that influenza is circulating in the community that

was applied at the time of the earlier appraisal (50 per 100,000 consultations), which may not adequately reflect the probability based on the current threshold (30 per 100,000 consultations). Finally, uncertainty surrounding this key probability was not considered in the probabilistic analysis and it was entered as a fixed input. As such, the subsequent results are likely to under-estimate the uncertainty surrounding the cost-effectiveness results. While alternative assumptions were employed as part of a range of one-way sensitivity analyses, the range of probabilities (10-50%) appears equally arbitrary.

Another structural difference relates to the proportion of those subjects presenting to a healthcare provider and who do so within the licensed period covered by the NI treatments. The base case assumption in the Roche submission assumes that 100% of those diagnosed with ILI present within 48 hours of the onset of symptoms (and so could benefit from treatment). This contrasts with the Turner (2003) model which assumes that a proportion of these will present after 48 hours or, amongst those who do, a proportion of these will not be able to adequately judge the timing of onset of symptoms. A sensitivity analysis was undertaken in the Roche submission, however, employing similar estimates adopted in the Turner (2003) model. This resulted in a deterioration of the ICERs in all subgroups (and in the case of otherwise healthy adults this increased to over £30k per QALY).

Finally, although not necessarily a structural issue, the Roche submission assumes equivalence in terms of relative efficacy between oseltamivir and zanamivir (in terms of symptomatic and other benefits). This assumption is not properly justified, and hence the basis for adopting a cost-minimisation (as opposed to cost-effectiveness) analysis for the two NI treatments appears unsubstantiated.

Symptomatic benefits

There are two main differences in terms of the Roche submission and the Turner (2003) model in relation to quantifying the potential symptomatic benefits with the NIs: (i) the primary outcome measure and (ii) the quality of life benefits assigned.

In terms of the primary outcome measure employed to reflect illness duration, Roche apply estimates based on the *median* time to return to normal activities. This contrasts with the Turner (2003) model which utilises the *mean* time to resolution of symptoms. This difference is potentially important since the time to return to normal activities is typically (though not always) longer than the time to resolution of symptoms. All other things being equal, the same relative effect (i.e. in terms of a relative reduction in symptom duration) applied to a

longer illness duration will result in higher absolute gains (and hence improvements in the subsequent ICER estimate). In the Turner (2003) model, return to normal activities was used as part of a sensitivity analysis considered to represent a wider societal perspective (using time return to normal activities as a basis for estimating productivity costs). However, it should also be recognised that the Turner (2003) model employed estimates of mean duration of illness as opposed to the median estimates used in the Roche submission. Given the censoring and skewed distribution of illness durations, the potential gains in symptom duration inherent in the decision to employ an estimate based on the time to return to normal activities will, partly or even wholly, be offset by the potentially shorter gains implied by utilising median as opposed to mean times.

Hence, it is unlikely that the analytic differences in the choice of outcome measure will lead to important differences in the ICER estimates. However, what is likely to be a more important distinction is the differences in the approaches subsequently employed to quality-adjust these durations as the basis for the calculation of the symptomatic gains in QALYs. In Turner (2003), the QoL values assigned to symptomatic benefits under usual care or oseltamivir treatment were taken directly from the TTO conversion of the VAS scores collected alongside the oseltamivir clinical trials; these suggested that, over 21 days, oseltamivir treatment was associated with an increase of 0.7225 quality-adjusted life days (QALDs) (5.28% greater than usual care) in otherwise healthy adults, and an increase of 0.5758 QALDs (5.59% greater than usual care) in high-risk adults.

In the Roche submission, these QoL values were not used in the model directly. Instead, the QoL values from the first 7 days of the TTO data were used to estimate the % difference in QoL between oseltamivir and usual care. This relative difference was then applied to a single, externally derived, literature based estimate of the QoL associated with influenza under usual care (0.84). These were then applied to the median duration of illness for each alternative. This approach differs in 2 important aspects to that reported in Turner (2003): (i) the prevailing QoL of a day of influenza was higher than the equivalent reported on the basis of the TTO data (the 7-day TTO values associated with usual care ranged from 0.1129 on day one to 0.7047 on day 7, whilst Roche assumed a utility of 0.84 for every day); (ii) the percentage increase was derived from only the first 7 of the 21 days of data based on otherwise healthy adults (resulting in a percentage increase of 11.52%, approximately double that based on the 21 day data).

The different approaches lead to important differences in the subsequent estimates of QALYs gained. All other things being equal, the same relative difference in QoL applied to a higher

baseline QoL value will result in proportionately higher gains in QALYs. In addition, the basis for the % difference in QoL were based on only 7-days in the Roche submission (vs. 21 in the base-case of Turner (2003)) and estimates for the otherwise healthy adult population were applied to all patient groups. Both of these assumptions lead to higher QoL gains than would have been derived from the approach employed in the Turner (2003) model. For example, the comparable % improvement reported for 'at risk' adults (over 7-days) was 7.82%. Hence, applying an estimate of 11.52% to the 'at risk' group will potentially over-estimate QoL gains in this particular group. However, the more pertinent issue is that the estimates based on 7-day differences are markedly higher than those based on the 21-days data.

Roche therefore estimate a higher QoL improvement of oseltamivir treatment during the period of illness in two key ways: by calculating a higher percentage increase in QALDs associated with oseltamivir (using 7 day as opposed to 21 day data), and then by subsequently applying this percentage increase to a much higher (baseline) QoL value for ILI with usual care than is suggested by the very same data used to calculate the percentage increase. By way of example, the TTO data derived by Roche (using the same methods as Turner (2003) but with an additional study included) suggest that, over 7 days, an otherwise healthy adult treated with oseltamivir instead of usual care would gain 0.3752 QALDs, with an average utility across the 7 days of 0.5190. By representing this as a percentage improvement over usual care (11.52%), and assuming that each day with usual care would instead have a utility of 0.84, Roche's model assumes that each day of ILI with oseltamivir treatment has a utility of 0.937, resulting in a gain over 7 days of illness of 0.679 QALDs (hence inflating the QALDs gained by 81%). Over a 21 day illness, the TTO data derived by Turner (2003) (21 day data is not given in the Roche submission) would suggest a gain of 0.72254 QALDs from oseltamivir treatment in an otherwise healthy adult; the assumptions adopted by Roche would inflate this gain by 182% to 2.037 QALDs.

In addition, Roche also potentially over-estimate the QoL improvement of patients receiving oseltamivir treatment immediately after illness. Although not mentioned in the printed submission, the model assumed that every day during the first year after presenting to a GP with ILI that is not spent in a state of ILI carries a utility weight of 1. Since oseltamivir treatment is assumed to result in a shorter period of illness than usual care, this utility weight is applied to a greater number of days in the oseltamivir arm of the model, lowering the ICER for oseltamivir vs. usual care (particularly for 'at risk' adults, for whom the difference in duration of illness between oseltamivir and usual care is most pronounced). This issue compounds the potential over-estimation already noted in relation to the use of TTO data.

It is clear that there are important differences between the approaches employed to estimate symptomatic improvements in QoL. In general, the approaches employed by Roche will result in significantly higher QoL gains. These gains do not appear to be substantiated and arise due to the potential selective use of data (i.e. 7 days as opposed to 21 days), application of a % improvement to a high baseline QoL (not referenced appropriately and potentially derived from a different valuation approach) and inappropriate assumptions (i.e. patients revert back to perfect health after influenza).

Resource utilisation and cost assumptions

As previously noted, the costs associated with GP visits, diagnostic tests, antibiotics, treatments and hospital visits were derived from NAMCS, a US database, and so may not reflect UK treatment patterns (although these were reported to have reviewed by three UK clinical experts).

The probabilities of hospitalisation are key drivers of the expected costs of each strategy. The estimates cited as being derived from Cox (2000)¹¹⁶ appear incorrectly referenced, so the probabilities of 1.93% for ILI with usual care or 14.86% for pneumonia (all treatment strategies) cannot be verified. According to Roche, the Cox (2000) study estimated excess pneumonia and influenza hospitalisations from US health care data, and it was assumed that these would not differ for UK patients. However, the estimate of 1.93% for those hospitalised under usual care may include both patients with complications and those without (this cannot be confirmed as the source is not properly referenced); if so, adopting a higher estimate for those patients with pneumonia suggests that the 1.93% figure is likely to be an over-estimate for patients without complications (i.e. pneumonia admissions may have been double counted). Furthermore, the assumption that the probability of hospitalisation under usual care is the same across all patient groups and is unaffected by whether complications occur or not appears unrealistic – the assumption that those with ILI and no complications require hospitalisation is an assumption adopted by very few other studies. Equally important is that the figure of 1.93% is applied to all patient groups; that is, the underlying hospitalisation rate is not considered to vary by age or risk status. This appears to be an important limitation of the data and the assumptions employed therein. It would seem reasonable to assume that hospitalisation rates are likely to differ according to these factors.

Table 7.9 provides a comparison of the probability of hospitalisation applied in the Roche submission (US data) against those used in the Turner (2003) model (UK data) to represent

usual care. The table demonstrates significant variation between the approaches, particularly in the healthy adult and children populations. The differences indicate that influenza appears to be associated with markedly high admission rates in the US and hence the generalisability of these estimates to UK practice is questionable. In terms of cost-effectiveness estimates, a higher baseline event rate (resulting in a higher absolute gain when combined with the relative risks of particular treatment) will result in improved estimates for the ICER.

Table 7.9: Comparison of the probability of hospitalisation

Source	Population		
	Children	Healthy Adults	High-risk adults
Roche*	1.95% (1 in 51)	1.97% (1 in 51)	2.03% (1 in 49)
Turner	0.029% (1 in 3448)	0.025% (1 in 4000)	1.2% (1 in 83) 14.8% for elderly in residential care (1 in 7)

* Estimates adjusted for proportion of patients with pneumonia

A relatively minor issue but one which highlights some of the concerns regarding the implementation of the model, relates to the assumption that children will not be hospitalised for otitis media. While this may be the case, it should also be noted that the model also assumes that children with ILI and no complications have a risk of hospitalisation. Due to the model structure, children who develop otitis media face a zero risk of hospitalisation, that is, they no longer face the comparable risk of children who do not develop this complication. As a result, there is an unanticipated (and illogical) potential beneficial effect associated with the development of otitis media.

Finally, in terms of the drug costs applied, the base case model assumes that all children offered oseltamivir treatment will be prescribed oral suspension rather than the more expensive small capsules, although this is not clear in the printed submission and no evidence is given to support this assumption. This lowers the cost of oseltamivir treatment substantially. We have already noted that the costings applied to oral suspension assumes no wastage and that any remaining powder for reconstitution can be re-used by other patients and the error in relation to the cost of zanamivir.

Complications

A number of separate issues relate to the approaches employed to handling the cost and quality of life associated with complications. These include: (i) the range of complications considered; (ii) the costs and QoL estimates applied to complications; (iii) the baseline

probability of major complications (usual care) and the relative effect estimates for oseltamivir.

In terms of minor complications, the approaches were broadly comparable. Minor complications were assumed to be mainly accounted for in the VAS TTO data in terms of QoL implications (with the exception of a number of particular complications) and costs were assumed to be related to additional GP consultations and use of antibiotics in both. There were slight differences in terms of the approaches used to quantify GP consultations and antibiotic use associated with minor complications, with Roche assuming additional (and complication specific estimates of) GP visits and antibiotic use for the three main complications considered (the rate of these complications were derived from a UK population based study,¹⁵ while the Turner (2003) model considered the overall complication rate (for all ILI complications) reported in the same study, assuming a single additional GP visit and the same proportion of antibiotic use in each. There were also differences in the source of relative risks applied to minor complications; estimates for Roche were derived from a previous meta-analysis (Kaiser (2003)¹⁵³) for pneumonia and bronchitis and individual trial data for children in relation to otitis media, while Turner (2003) applied a relative risk (estimated separately for the different subgroups) to minor complications derived from published RCTs reporting antibiotic usage.

The major differences in approaches between the two models relate to the approaches to quantifying the costs and benefits of major complications requiring hospitalisation and mortality (mortality is considered separately in the following section). We have previously outlined the different approaches and sources applied to estimate the probability of hospitalisation with usual care, leading to significantly higher hospitalisation rates in the Roche submission. In addition to differences in terms of the baseline event rates, there were also different approaches employed to estimating the relative effect of oseltamivir. The Roche submission employed estimates based on the relative risk of hospitalisation, whilst Turner (2003) applied the relative risk of pneumonia (citing a lack of evidence related to hospitalisation) as a proxy. The alternative approaches subsequently led to different estimates reported in Table 7.10. The estimates applied in the Roche submission were less favourable for the children and healthy adult population and more favourable in the high-risk population, compared to the estimates employed in the Turner (2003) model.

There were also differences between the approaches used to estimate the impact on QoL related to severe complications. In the Roche model, separate utility weights were applied to bronchitis (0.990 – not 0.913 as stated in the printed submission), pneumonia (0.900) and

otitis media (0.910) based on estimates reported in Stouthard (1997).¹⁵⁵ These utility values were applied to the expected duration of each complication derived from Roche clinical trial data (longer durations were assigned to patients subsequently hospitalised for a particular complication). However, it should be noted that the utility values were applied as absolute estimates in the Roche model as opposed to a decrement in relation to the QoL of an equivalent individual without a complication. Applying absolute values, as opposed to decrements, results in counter intuitive results such that a patient assigned usual care has a higher expected utility from developing bronchitis, pneumonia or otitis media than from remaining free of complications. In the model by Turner (2003), separate utility weights were applied to pneumonia (0.724 for healthy adults and 0.72 for high-risk and children) and otitis media (0.977) based on WHO disability weights. However, it was unclear how these estimates were subsequently applied in the model since the QALY values for pneumonia or otitis media presented in the parameters table do not define whether these are annual (which would not be correct) or daily estimates.

Table 7.10: Comparison of the relative risks of hospitalisation (oseltamivir)

Source	Population		
	Children	Healthy Adults	High-risk adults
Roche	0.41	0.41	0.50
Turner	0.15	0.15	0.76

Although differences were observed in relation to a number of separate aspects, the main difference likely to have an important impact on the ICER estimates is the underlying probability of hospitalisation and the associated relative risks applied to the different subgroups. Differences in the costs and benefits of minor complications were relatively unimportant and not considered to be an important driver of any subsequent differences in the reported ICER estimates. The approach used by Roche in relation to modelling the QoL impact of more severe complications appeared to lack face validity, whilst the approach employed by Turner (2003) lacked transparency and hence it was difficult to assess the validity of the final estimates employed in the model.

Mortality

In addition to the differences noted for complications, there were also important differences in the approaches employed to quantify the potential mortality benefits associated with the use of NIs. The probability of influenza-related mortality without antiviral treatment (usual care)

and the relative effectiveness estimates applied to oseltamivir are reported in Table 7.11. Although both Roche and Turner used the same source to estimate the baseline probability of influenza-related death (Meier (2000)¹⁵ based study), the estimates differ in the children population. Mortality estimates are significantly higher for this subgroup in the Roche submission. The difference is due to Roche applying mortality estimates obtained from Meier (2000)¹⁵ from the subgroup of ‘at risk’ children group, while Turner (2003)⁴⁶ combines the estimates for the healthy and ‘at risk’ children groups in the children population. Hence, it appears that Roche over-estimate the mortality probability in the children group.

Table 7.11: Probability of mortality for ILI; comparison between Roche and Turner (2003)⁴⁶

Parameter	Approach	Healthy adults	Children	‘At risk’ adults
Probability (usual care)	Roche	0.000387	0.00271	0.00685
	Turner	0.000387	0.000048	0.00685
Relative effect (oseltamivir)	Roche	60% reduction	60% reduction	50% reduction
	Turner	65% reduction	85% reduction	24% reduction
Absolute difference (oseltamivir vs. usual care)	Roche	0.000232	0.001626	0.003425
	Turner	0.000252	0.000041	0.001644

There are also differences in terms of the relative effects applied to reflect the impact of oseltamivir. Due to the absence of direct data on the impact of oseltamivir on the relative risk of mortality, both approaches used proxy estimates for relative risks derived from other events. Estimates from Turner (2003) were based on the relative risks reported in the trials for pneumonia (hence assuming that similar reductions would be observed in mortality and that mortality was primarily driven by pneumonia), while Roche employed the relative risks reported by Kaiser (2003) corresponding to the reduction in hospitalisations for lower respiratory tract infections. The different approaches result in relatively larger relative gains for healthy adults and children by Turner (2003) and ‘at risk’ adults by Roche. When the relative effects are applied to the baseline probabilities, differences in the probabilities assigned to the children population, result in larger absolute gains in the Roche model for the children (despite the lower relative risk reduction applied) as well as the ‘at risk’ groups, although the gains remain lower in the healthy adult population.

In addition to the different mortality probabilities employed, there are also major differences in terms of how the lost QALYs due to premature mortality are estimated. A comparison of the different estimates employed in the separate models is presented in Table 7.12. The lost QALYs employed in the two models are presented in italics. Clearly some of the differences simply reflect the different discount rates applied to outcomes that were relevant at the

different appraisal times (3.5 % for Roche, 1.5% for Turner (2003)). For ease of interpretation, we have also presented the equivalent estimates derived from the approach used by Roche for the same discount rate used by Turner (2003) (1.5%). These highlight those groups for which the different approaches appear to make a meaningful difference after adjusting for the variation in the discount rate itself.

Table 7.12: Comparison of quality-adjusted life expectancy

Patient group	Roche			Turner
	Life Years Lost	Discounted QALYs (3.5%)	Discounted QALYs (1.5%)	Discounted QALYs (1.5%)
Children (1-5)	76	23.30	38.9	NA
Children (1-12)	72	23.17	37.98	41.7
Healthy adults	42	19.21	26.74	19
'at risk' adults	36	17.18	23.91	4.1

The comparison reveals differences in the results attributable to the different approaches employed. In particular, the difference is most evident in the 'at risk' adult population, where the subsequent estimates of QALYs lost (discounted at a common rate of 1.5%) due to premature mortality are over 5 times greater in the Roche submission.

There are 2 assumptions central to this calculation: (i) the utility weights applied to each year of life lost and (ii) the expected number of life years lost. Both of these assumptions in the Roche submission appear to over-estimate the subsequent estimates representing the potential loss of QALYs. Firstly, Roche apply utility weights based on the mean weighted health state index value based on EuroQoL (EQ-5D) data representing UK population norms.¹⁵⁶ For otherwise healthy adults and children the estimates are reported to be based on the mean EQ-5D value based on all adults (0.85). However, this value is actually based on the value corresponding to adults aged 45-54; the corresponding value for all adults is 0.86. This value is then applied throughout the period of extrapolation and hence takes no account of the deterioration in QoL that the patient might expect as they become older. This approach appears to be optimistic for the adult and 'at risk' populations for whom the overall EQ-5D value will significantly over-estimate QoL in later years of life. This differs from the approach employed by Turner (2003) which employs the corresponding age-matched EuroQol tariffs for each group and thus allows for the expected deterioration in the quality of life in later years. Due to the lack of EuroQol values for children, Roche conservatively apply the EQ-5D value for all adults (0.85), whereas Turner (2003) assume perfect health (i.e. 1) in the analysis for children prior to 18 years of age, at which point the age-matched EQ-5D

value is applied based on UK norms. This difference in the approaches employed for children appears to be the main reason why the approach used by Roche results in lower discounted QALYs compared to Turner for this population. However, differences for the other groups are likely to be driven by the different approaches to quality-adjustment and also the lost years of life assumed.

In the Roche submission, the mid-point age of each of the groups considered is used as the basis for estimating the expected number of life years lost (i.e. the remaining life expectancy). Hence, the average age at premature death for children aged 1-12 is assumed to be 7 years, and for otherwise healthy adults aged 13-64, this is assumed to be 38 years. However, no justification is given for the estimate of 45 years as the mid-point age for the combined group of 'at risk' adults (13-64 years defined as being 'at risk' and those aged 65+ years). General population estimates from life-tables are then employed to estimate the average remaining life expectancy based on these ages. In contrast, Turner (2003) use data from the WHO annual mortality statistics to estimate the mean age at which influenza deaths *actually* occur in the different age groups – hence, assuming that the mid-point estimate from the group itself is not necessarily an accurate gauge of the age of patients in each respective group who actually die. Using this approach, Turner (2003) assume that the average age at premature death is 3 years for children, 51 years for otherwise healthy adults and 84 years for those aged >65 years. No separate estimate is reported by Turner (2003) for the 'at risk' population and it appears that estimates based on those aged >65 years are subsequently employed for both the 'at risk' adult group and the elderly residential care population. The differences in approaches to quantifying the expected number of life years lost is the main cause of the differences between the two models in the otherwise healthy adult and high-risk adult populations (the difference in utilities driving the difference in the children model), resulting in higher estimates being applied in the Roche submission. The general approach used by Turner appears to be more realistic, such that the Roche submission is likely to provide overly optimistic estimates of remaining life expectancy. However, legitimate concerns remain over the assumption employed in the 'at risk' population by Turner (2003) (i.e. applying estimates from a population aged >65 years).

7.1.2.5 Discussion of existing cost-effectiveness evidence

The review of cost-effectiveness evidence identified a large number of existing studies evaluating the cost-effectiveness of antivirals for the treatment of influenza. Of these studies, 2 were considered the most relevant from the perspective of the UK NHS: the previous report by Turner (2003) used in the earlier NICE appraisal and the new submission by Roche. A

number of important differences were identified with respect to the approaches and assumptions employed therein. These subsequently resulted in marked differences in the reported ICERs, particularly for the children and ‘at risk’ adult groups. Cost-effectiveness estimates for these groups were more favourable, in the Roche submission, than the comparable estimates reported by Turner (2003). A number of key differences between the models were identified in 5 aspects, summarised in Table 7.13. In conclusion, the main drivers for these differences were considered to be attributable to: (i) the reduction in the cost of antivirals since the earlier appraisal; (ii) the different approaches to quantifying symptomatic QoL benefits; (iii) the higher rate of hospitalisations assumed across each of the groups based on US hospitalisation data (Roche); (iv) the application of mortality data for ‘at risk’ children in the children analysis (Roche) and (v) approaches to quantifying QALYs lost due to premature mortality. With the exception of the first issue, all the remaining aspects were considered to provide optimistic estimates (Roche) of the subsequent cost-effectiveness of oseltamivir compared to the approaches employed in the previous report by Turner (2003). These factors also need to be considered against the more conservative estimate of the probability that ILI is influenza applied in the Roche submission. In addition to the observed differences between the models, a number of uncertainties remained related to the approaches employed in both sources. These aspects are now considered in more detail as part of the development of a new decision model to evaluate the cost-effectiveness of NIs for the treatment of influenza.

Table 7.13: Summary of main findings and remaining uncertainties

Aspect	Turner (2003) vs. Roche submission	Remaining uncertainties
Structural issues	The separate models commence from different points in the overall pathway. Turner (2003) focused on a broader decision problem, examining a range of behavioural and policy issues which influence the probability an individual presents to a healthcare provider, whereas Roche focus more specifically on the cost-effectiveness in those patients who actually present and are considered eligible to receive an NI. Despite these differences, both consider the potential relationship between consultation rates and the probability ILI is influenza via sensitivity analysis.	Unclear as to the whether the availability of NIs in particular groups would lead to an increased consultation rate with health care providers. More importantly, the link between an increased consultation rate and the probability that ILI is influenza remains unsubstantiated. Unclear whether this has implications in terms of budgetary implications and also cost-effectiveness estimates. Neither study provides an adequate representation of the probability that ILI is influenza based on the current threshold.
Symptomatic benefits	The separate models employ data from a similar source in terms of the QoL associated with influenza and the impact of treatment. However, the two models subsequently employ this data in a number of different ways. The duration of illness itself is based on different definitions (resolution of symptoms and return to normal activities) and different estimates of the appropriate input (e.g. median vs. mean times). The subsequent quality adjustment applied to these estimates also differs	A number of uncertainties remain due to the paucity of QoL data in this area. Firstly, the approach employed by Turner only utilises data on the mean duration of illness as a basis for adjusting QoL for zanamivir and amantadine. Data for oseltamivir and usual care are used directly and may not reflect the mean duration of illness based on the wider set of trials where QoL data was not collected. The extrapolation approach to obtain mean duration of illness assumes an exponential distribution which may not be appropriate.

	<p>markedly: with Turner applying QoL estimates direct from patient level data (21 days) for oseltamivir and usual care and using differences in mean illness times to adjust these estimates to obtain results for zanamivir. Roche employ the same data (restricted to the first 7-days) but use it as the basis for estimating a % decrement which is then applied to an external estimate of the QoL of influenza. This % decrement is then applied to the median duration of illness.</p>	<p>The approach employed by Roche is potentially more flexible, using the patient level data to estimate the relative QoL improvement associated with NI treatment, this estimate is then applied to the median duration of illness which is allowed to differ from that observed in the subset of oseltamivir trials reporting QoL data. However, the % improvements are obtained from a selective period and the absolute QoL gains are influenced by the underlying QoL associated with influenza which is not adequately justified.</p> <p>A number of uncertainties remain: including the outcome of interest (resolution of symptoms, return to normal activities); application and approach to estimating the duration (e.g. mean vs. median) as well as the appropriate approach to characterising QoL gains (i.e. employing the patient level data directly or considering the duration of illness and the implied decrement associated with influenza more directly).</p>
Resource utilisation and costs	<p>The major difference between the approaches relates to the probability of hospitalisation associated with influenza assigned to usual care. Estimates from Roche are derived from US sources and the same estimates are used for each of the different groups. Turner employs separate estimates for the different groups based on UK data but base their calculation on a number of uncertain links in the data (i.e. size of the population, attack rates and excess hospitalisations rates). Reductions in the probability of hospitalisations are only considered in the sensitivity analysis in the model by Turner, whereas these form part of the base-case in the Roche submission.</p>	<p>The probability of hospitalisation is potentially a key driver of cost-effectiveness. There remains significant uncertainty as to the underlying probabilities of hospitalisation used as a baseline (usual care) and as well as the relative effects assumed for the NIs. These uncertainties also relate to the separate subgroups considered.</p>
Complications	<p>Linked to the issues described for 'resource utilisation and costs'.</p>	<p>Linked to the issues described for 'resource utilisation and costs'. Also uncertainty as to the QoL implications of major complications.</p>
Mortality	<p>The separate models employ different markedly different estimates for the remaining life-expectancy of patients in the 'at risk' group. In general, the approach employed by Roche appears likely to over-estimate the potential gains in life years. Both approaches apply QoL weights from UK population norms, although the approach by Roche does not allow for QoL to deteriorate in later years of life. Both approaches based the life-expectancy calculation on lifetable data from national statistics which may not be generalisable to the 'at risk' groups. The life expectancy for the 'at risk' group in the Turner (2003) model is taken from patients aged > 65 years and it is unclear how representative this is for 'at risk' patients aged <65. Reductions in the probability of mortality are only considered in the sensitivity analysis in the model by Turner, whereas these form part of the base-case in the Roche submission. Both approaches use proxy estimates related to either the reduction in pneumonia (Turner) or hospitalisations (Roche).</p>	<p>There remain a number of uncertainties in relation to the potential loss in QALYs due to premature mortality. These relate to a number of separate aspects: (i) the different life-expectancies associated with the separate groups (and, in particular, the impact of 'at risk' status); (ii) the relative effect of NI treatments (i.e. whether the NIs have an effect or not and, if they do, whether this differs by subgroup and treatment).</p>

7.2 York Economic Assessment

7.2.1 Overview

The review of cost-effectiveness studies in Section 7.1 alongside the more detailed critique of Turner (2003)⁴⁶ and the submission by Roche, identified a number of remaining uncertainties regarding the existing cost-effectiveness estimates for the treatment of influenza with NIs in the UK National Health Service (NHS). A new decision analytic model was therefore developed to more formally address these issues and to re-evaluate the cost-effectiveness of NIs in different populations, incorporating the more recent evidence reported in earlier sections. This model provides a framework for combining data from the Bayesian synthesis of symptom outcomes, complication data and other relevant parameters required for cost-effectiveness considerations. The model was developed using Microsoft Excel with particular parameters estimated using WinBUGs.

The review of cost-effectiveness studies provided the basis for developing a preliminary model structure and initial set of assumptions. The final structure of the model was agreed following a discussion with a clinical expert (Dr John Watkins) to provide feedback on structure, data inputs and assumptions. Additional literature searches were also undertaken to inform the quality of life weights applied to symptoms and complications in the model. In common with both Turner (2003) and Roche, the model considers events within a single influenza season with a lifetime horizon employed to appropriately quantify lost QALYs associated with premature mortality. The model evaluates costs from the perspective of the NHS and Personal Social Services (NHS & PSS), expressed in UK £ sterling at a 2006/07 price base. Outcomes in the model are expressed in terms of QALYs. Costs are not discounted since only resource generating events occurring within a single season are considered; quality-adjusted life expectancy estimates over the lifetime horizon are discounted using a 3.5% annual discount rate according to the NICE reference case.¹⁵⁷

The model is probabilistic in that input parameters are entered into the model as probability distributions to reflect uncertainty in the mean estimates.¹⁵⁸ Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis can also be presented with their uncertainty. However, since the model is linear the mean estimates of the ICER are identical to those undertaken using deterministic approaches, although probabilistic simulations are needed in order to appropriately characterise the uncertainty surrounding these results. Results from a 'base-case' analysis are presented alongside a broad range of scenarios considering alternative assumptions.

The following sections outline the decision problem, the structure of the model and also provide an overview of the key assumptions and data sources used to populate the model in more detail.

Treatment strategies and populations

The decision problem addressed by the model relates to the cost-effectiveness of oseltamivir and zanamivir for the treatment of influenza compared to standard care without antiviral treatment. The model considers this in the context of individuals presenting to a healthcare provider who are also considered eligible for treatment according to the respective licenses for each of the NIs (i.e. patients presenting with symptoms typical of influenza, when influenza virus is circulating in the community, and who are able to start antiviral treatment within 48 hours of symptom onset). Although the separate NIs are considered together in the overall decision problem, the differences in their respective licenses (zanamivir is only licensed in children aged ≥ 5 years who can receive treatment within 36 hours of time of symptom onset, while oseltamivir is licensed in children in children aged ≥ 1 year who can receive treatment within 48 hours of symptom onset) are reflected in the subsequent interpretation of the cost-effectiveness results.

Cost-effectiveness estimates for influenza treatment are presented for 5 separate subgroups: (i) otherwise healthy children aged 1-14 years, (ii) 'at risk' children aged 1-14 years, (iii) otherwise healthy adults aged 15-64 years; (iv) 'at risk' adults aged 15-64 years and (v) elderly (aged 65 years or over). No separate analyses are presented for an 'at risk' elderly population, since age itself is considered a risk factor according to existing definitions for 'at risk' groups. Consequently, all subjects aged 65 years or over are considered together, regardless of whether other pre-existing co-morbidities are present or not.

The distinction between otherwise healthy subjects and 'at risk' subjects, in terms of the alternative age groupings, are principally driven by the different underlying baseline rates of complication and mortality and the remaining life expectancy associated with these different populations. However, differences between otherwise healthy adults, otherwise healthy children and 'at risk' groups (as a whole) are also informed by subgroup specific estimates of the relative effectiveness of each NI in terms of symptom duration and reductions in complications (proxied by the reduction in antibiotic use).

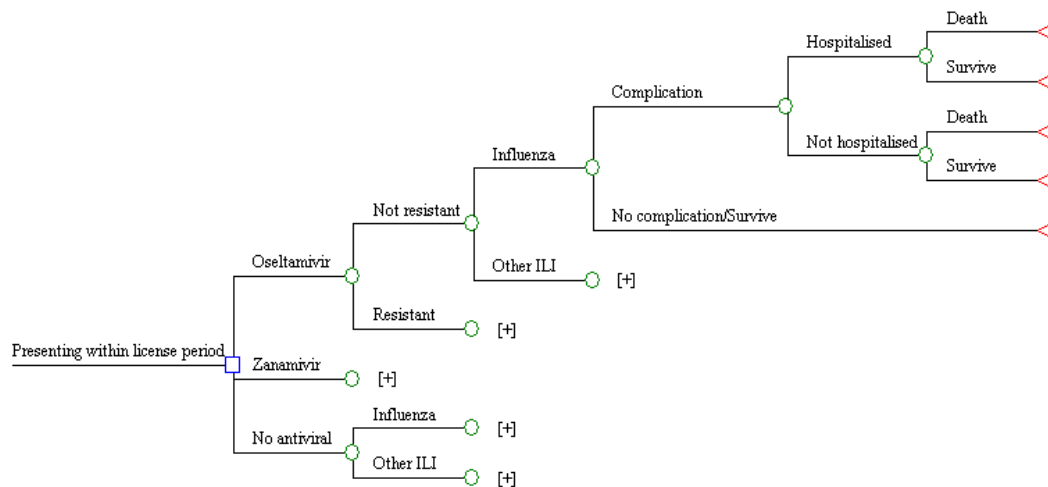
7.2.2 Model Structure

The model is based on a decision-analytic approach employing a decision-tree structure. The decision-tree is used to map the range of potential pathways an individual may follow depending on particular decisions (e.g. whether an NI is administered or not) and uncertain events (e.g. whether a particular individual is resistant to a particular NI treatment or experiences a secondary complication). A simplified schematic of the overall model structure is presented in Figure 7.3, together with a more detailed schematic of the full range of pathways considered for those patients experiencing a secondary complication in Figure 7.4

The model starts at the point an individual patient presents to a healthcare provider and is considered eligible for treatment with an NI. The initial decision node (represented by a square) corresponds to the decision faced by the healthcare provider: whether to prescribe an NI (oseltamivir or zanamivir) or not. Following this decision, subsequent pathways are characterised by a series of uncertain events (called ‘chance’ nodes and represented by a circle), such as whether an individual patient experiences a secondary complication and is subsequently hospitalised or not. Chance nodes are populated by probability estimates which may be influenced by the initial decision (and hence vary by treatment) such as the probability of experiencing a complication, or which may be considered to be unaffected by the treatment at a particular chance node. For example, the probability of mortality in a patient who has been hospitalised, termed a ‘conditional’ probability, may not be affected by the initial treatment received.

The decision tree represents the complete set of pathways considered within the scope of the model. For each treatment alternative a number of possible pathways are considered, each potentially associated with unique resource use, cost and quality of life implications. The end points of the tree are characterised by terminal nodes (represented by a triangle). These terminal nodes are used to evaluate the costs and quality of life implications (e.g. QALYs) of each of the respective pathways. These estimates are subsequently weighted according to their respective probabilities of arising (which will both vary by treatment and subgroup) and summed to provide the mean cost and QALY estimates, subsequently used to evaluate the relative cost-effectiveness of each of the alternatives considered.

Figure 7.3: Simplified schematic of decision model



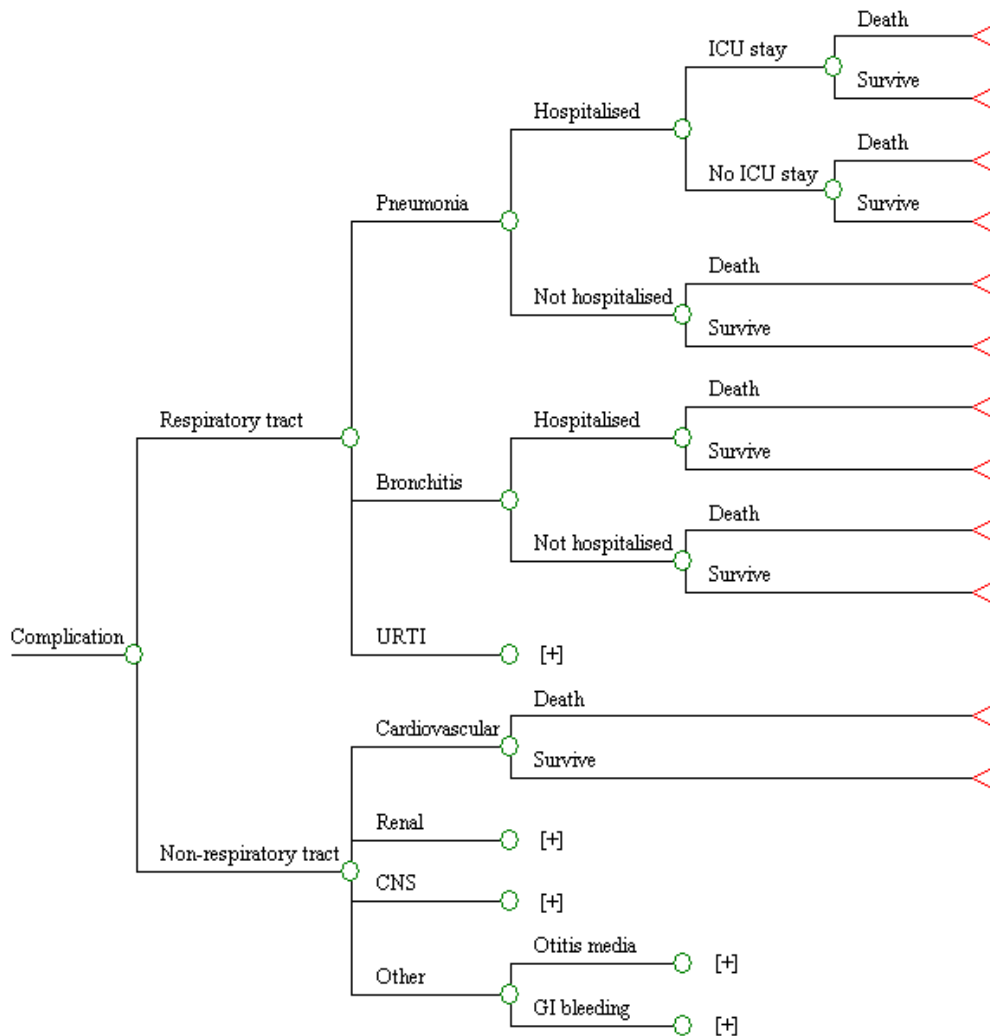
[+] is used to simplify the schematic. This is used to avoid repeating similar pathways of the model and means that the same pathways represented above the [+] are also applied here.

The overall schematics represent the main pathways considered within the tree. Following the initial decision node there are five main uncertain events considered for each NI: whether an individual (i) is resistant to an NI or not (not considered in the base-case); (ii) has true influenza or other ILI; (iii) experiences a complication or not; (iv) is hospitalised or not due to the complication and (v) either dies as a result of a complication (in both patients who are hospitalised and those not) or survives. Patients experiencing an uncomplicated illness are assumed to both survive and require no hospitalisations. A similar set of pathways are considered for patients not receiving NIs, although the issue of resistance to NIs is not relevant in this situation and hence not considered.

The more detailed schematic of complications shows the full range of potential pathways modelled for patients progressing down the complication branch for each of the treatment alternatives considered. A total of eight complications are considered in two main groupings (respiratory tract and non-respiratory tract). This distinction is important since hospitalisations are only considered in the model in relation to respiratory tract complications. Respiratory complications are further subdivided into three sub-categories: (i) pneumonia; (ii) bronchitis and (iii) other upper respiratory tract infections. Each of the three main respiratory tract infections considered may also subsequently lead to hospitalisation (and in the case of pneumonia, a stay in an intensive care unit (ICU)). Non-respiratory tract complications are assumed to be either: cardiovascular; central nervous system (CNS); renal or other (otitis media or gastrointestinal (GI) bleeding). Hospitalisations are not modelled for these events.

Patients experiencing any of the six complications are assumed to incur additional GP consultation costs (and potentially antibiotic costs) and reduced quality of life. Although hospitalisations are only considered for respiratory tract infections, patients experiencing any complication are assumed to face an elevated risk of mortality.

Figure 7.4: Detailed schematic of complications



The overall model considers patients with true influenza as well as those with other ILI (such as Respiratory Syncytial Virus (RSV)). This is important since at the point of the decision as to whether to administer an NI, a decision maker cannot perfectly discriminate between individuals with true influenza and those with other ILI. Consequently, both the costs and outcomes of true influenza and other ILI are considered. It should also be noted that much of the epidemiological literature relating to the consequences of influenza is derived from

studies related to ILI (not specifically influenza).¹⁵ However, the distinction between true influenza and other ILI is clearly important since the NIs are assumed to be effective only in those individuals with true influenza (and hence no effect on the costs and consequences associated with other ILI is considered).

The decision model includes both the acquisition costs of the NIs themselves as well as the costs of managing secondary complications (in terms of additional GP consultations and antibiotic use, as well as the costs of hospitalisation for respiratory tract complications). Outcomes are evaluated using QALYs, based on symptom duration (in all individuals), complications (type and duration) and premature mortality due to secondary complications.

7.2.3 Key model assumptions

The cost-effectiveness of NIs from an NHS perspective will be determined by a number of factors. These factors relate to the potential impact on symptom duration, as well as complications and associated mortality, and also to the generalisability of the existing clinical and epidemiological evidence base to an NHS setting. In addition, as outlined in earlier review of cost-effectiveness studies, there are also a number of important considerations related to wider context in which NIs are likely to be used, including: (i) the probability ILI is influenza during periods in which NI treatment is considered and (ii) the potential impact that the availability of NIs may have on the subsequent probability an individual is likely to consult a healthcare provider and whether (specifically) this could also alter the underlying probability ILI is influenza.

In contrast with Turner (2003), our model focuses on a more constrained decision problem (more similar to the approach employed by Roche) – specifically focusing on the decision at the point at which an individual has already presented to a healthcare provider and is considered eligible to receive an NI treatment. Hence, the probability a patient actually presents to a healthcare provider is not considered in the base-case analysis. The decision to start the model at this decision node was based on a number of separate considerations. Firstly, this appears to more closely reflect the decision problem actually faced by the healthcare provider in relation to the treatment of influenza. Secondly, there remains a lack of clarity as to what the probability represented by an earlier node should actually represent. As previously stated in the review section, this has commonly been interpreted as the probability that an individual consults with a GP within 48-hours of symptom onset, with no reference to their ability to start treatment.⁴⁶ However, this assumption does not actually reflect the current license or existing guidance on the use of NIs which refer to an individual both

presenting within a particular time period *and* being able to start treatment. Similarly, it should also be recognised that for children there is a difference between the respective licenses of oseltamivir and zanamivir which further complicates matters since these refer to different symptom durations (i.e. within 48-hours of onset of symptoms for oseltamivir and 36-hours for zanamivir).

Thirdly, and most importantly, this decision should not alter the cost-effectiveness results in ‘at risk’ groups for whom NIs are already recommended. Furthermore, even for those otherwise healthy populations in whom NIs are not currently recommended, estimates of the ICER would only be affected by considering an earlier decision point if two other conditions subsequently hold; namely, that following a positive recommendation: (i) individual behaviour in these groups will actually be influenced by a positive recommendation, and (ii) even if individual behaviour is influenced and consultation rates increase, that this will also lower the probability that ILI is influenza based on current presentation rates. In other words, the underlying probability for otherwise healthy populations who do not present would have to be lower than the estimates for an equivalent population do currently present. As previously stated, the evidence to support these assumptions and to quantify appropriately in a decision model is limited. However, given the potential importance of this issue as part of the earlier appraisal – a number of separate scenarios are considered to ensure consistency with the scenarios employed previously by Turner (2003).⁴⁶

In addition, the model also makes a number of separate assumptions (as part of a base-case analysis) in considering the cost-effectiveness of NIs to the UK NHS. These include the assumption that:

- NIs would only be used for treatment when influenza is known to be circulating in the community at the current threshold (based on 30 ILI consultations per 100,000 population).
- The probability that ILI is influenza based on national surveillance programs obtained from sentinel practices, during periods in which influenza is circulating in the community, is representative of national practice.
- Amantadine is not a relevant comparator on the basis that it is neither widely used (nor recommended for use) nor is it likely to be ever considered a relevant treatment option in the UK NHS in non-pandemic situations. In addition, it is also assumed that the existing evidence base regarding amantadine is too limited to improve the overall precision of the estimates associated with the NIs as part of a wider Bayesian ‘network’.

- NIs are only assumed to be effective in patients with true influenza and have no impact on other ILI.
- The relative effectiveness of NIs is assumed to be the same for both influenza A and B and hence no distinction between these types is made in the model.
- The relative effectiveness of NIs in terms of symptom and complications for patients with true influenza is most appropriately derived from the ITTI population from the trials (i.e. those with true influenza). In terms of *relative* effectiveness estimates applied in the model, the relative differences between NIs and placebo based on the ITTI trials are transferable to a UK setting.
- The relative effectiveness estimates from the ITTI populations are assumed to be independent of prior vaccination status or prophylactic use of NIs (or equally that prior exposure to these would be similar in practice to the patients recruited to the trials).
- The average delay from the timing of the onset of symptoms to patients receiving NIs in routine practice (i.e. for those who both consult a healthcare provider and are able to start treatment according to the license for each NI) is similar to the average delay reported in the trials.
- Differences in symptom durations are most appropriately quantified and valued, for decisions based on cost-effectiveness considerations, in terms of mean durations as opposed to median durations. From an NHS perspective, time to resolution of symptoms is assumed to be more relevant than time to return to normal activities.
- Adverse events associated with NIs are mild and self-limiting and have no additional impact on quality of life or costs.
- Patients eligible to receive NI treatments for influenza develop complications after their initial consultation with a healthcare provider. All patients who develop complications due to influenza and ILI subsequently present to a healthcare provider for treatment and may be prescribed antibiotics. Only complicated cases are assumed to lead to hospitalisation and death. Premature death due to influenza is assumed to only occur following a secondary complication (irrespective of whether a patient is hospitalised).
- Given limitations in the evidence base it is assumed that hospitalisations only occur as a result of respiratory tract infections (or equally that the NI treatments themselves will have no additional effects on reducing hospitalisations associated with non-respiratory complications compared to standard care. In which case, the exclusion of these hospitalisations from the scope of the model would not alter the incremental cost-effectiveness estimates for the NIs).
- In the absence of robust estimates of the relative treatment effects in relation to complications as a whole (including hospitalisations and mortality), estimates of the

relative effectiveness of reducing all of these events are driven by a single estimate of the relative effect – the relative risk of antibiotic use.

Clearly there exists significant uncertainty in relation to a number of these separate assumptions. Consequently, in addition to the base-case analysis, a series of separate scenarios are considered, exploring a range of alternative assumptions and their impact on the subsequent cost-effectiveness results.

7.2.4 Parameter estimates for inclusion in the York economic model

The complete list of model parameters for each subgroup is presented in Appendix 10.9. The following sections provide a description of the main model inputs and the main assumptions. These are outlined in terms of four key elements: (i) the probability ILI is influenza; (ii) symptoms; (iii) complications and (iv) mortality.

Probability ILI is influenza

The probability ILI is influenza is derived from national surveillance data provided by the RCGP (personal communication, Dr Alex Elliot). The probability was based on an analysis of swabs taken from individuals with symptomatic ILI collected during routine surveillance across the influenza seasons 2003/04 to 2006/07. These data are shown in Table 7.14. The analysis of swabs provides data from which it is possible to establish the proportion of ILI consultations that were positive for influenza. Across all weeks (and years) the overall probability that ILI is influenza is approximately 0.495 (622/1256).

However, the estimate of 0.495 represents a rather crude approximation of the ‘average’ probability since it ignores variability both within and across different seasons and also ignores subgroups (e.g. age). Additional data was therefore supplied on request from the RCGP to more formally consider different age groups (Dr Alex Elliott, RCGP, personal communication). The number of swabs and the total number with influenza were provided according to different age groups. Separate analyses were then undertaken to consider the variability of this estimate across alternative age groupings. This formed part of a more explicit consideration of the variability both within and across the different seasons.

Table 7.14: Influenza and ILI consultations during weeks in which the threshold for ‘circulating in the community’ is reached

Season	Week	ILI consultation rate	Number of swabs	Number influenza A	Number influenza B	Influenza total
2003/4	44	36.42	7	1		1
	45	47.24	73	35		35
	46	61.79	120	60		60
	47	54.69	58	36		36
	48	52.79	43	20		20
	49	57.86	78	31		31
	50	36.96	53	18		18
	51	41.20	25	9		9
	2	33.03	23	4		4
2004/5	1	38.91	15	5		5
	2	34.89	27	13		13
	3	33.26	16	4		4
	4	30.45	29	14	1	15
	5	34.26	27	15	2	17
	6	32.28	31	14	1	15
2005/6	5	36.90	81	10	42	52
	6	41.60	89	8	43	51
	7	42.21	63	10	19	29
2006/7	6	37.64	120	69	1	70
	7	43.85	153	82		82
	8	38.17	125	55		55
All weeks/ years			1256	513	109	622

Using a similar approach to that employed in the Bayesian analysis of symptom data, a separate Bayesian ‘hierarchical’ model was fitted to the data using WinBUGs. The model is reported in Appendix 10.10. This approach was used to synthesise the surveillance data in order to obtain more appropriate probability estimates (and their associated uncertainty) accounting for variability attributed to the different seasons as well as the variability due to different age groups. Three main age categories were initially considered: aged <15, 15-64 and 65+ years (corresponding to children, adult and elderly populations). No data was available to separately consider risk status, with the exception of the elderly. However, due to the limited number of swabs obtained in the elderly (only 93 of the swabs were in this group), the results of the base-case model are derived from a final analysis combining the adult and elderly population into a single category.

Results from the model estimated the probabilities to be 0.56 (95% CrI: 0.26 to 0.79) in subjects aged <15 years and 0.41 (95% CrI: 0.21 to 0.66) in subjects aged 15 and over,

respectively. The wide credibility intervals clearly reveal the high uncertainty surrounding these estimates reflecting the variability observed both within and across the separate seasons. An analysis ignoring the separate subgroups and the seasonal variability would not clearly adequately reflect this. To illustrate this more clearly, a simple application of a Beta (622, 634) distribution to the entire data, hence ignoring subgroups and seasonal variability, would result in a mean of 0.495 (95% CI: 0.468 to 0.522). These results clearly show that such an approach would not appropriately reflect the level of variability and uncertainty considered using a hierarchical approach. Uncertainty in the estimates obtained from the hierarchical model was subsequently reflected in the probabilistic analysis by applying the simulated output directly from WinBUGs.

Symptoms

There are two elements considered in the economic model: (i) the overall duration of symptoms themselves and how these vary across both subgroups and treatments; and (ii) the quality adjustment of these durations required in order to estimate QALYs.

The overall duration of symptoms for the different subgroups applied in the model were taken directly from the ITTI results from the Bayesian multi-parameter evidence synthesis model reported in Section 6. The summary estimates applied in the model are reported in Table 7.15. A separate scenario was undertaken to address the inconsistent data noted in the previous section. As part of the Bayesian synthesis, the separate ‘at risk’ populations (‘at risk’ children, ‘at risk’ adults and elderly) were combined into a single group. Consequently, the same mean duration of symptoms is applied to each of the separate ‘at risk’ populations considered in the economic model.

To maintain correlation between the symptom durations, the simulated output (20,000 iterations) from WinBUGs was exported directly into Excel.

Scenario analyses were also undertaken using output based on the ITTI populations employing median estimates as well as estimates based on different symptom definitions (return to normal activities).

Table 7.15: Duration of symptoms with 95% credibility intervals (CrI) applied in the economic model (ITTI analysis based on resolution of symptoms)

Subgroup	Treatment	Median (days) (95% CrI)	Mean (days) (95% CrI)
Healthy adults	Placebo	5.36 (2.47, 10.12)	8.96 (4.11, 16.89)
	Zanamivir	4.58 (2.09, 8.64)	7.66 (3.49, 14.46)
	Oseltamivir	4.12 (1.86, 7.86)	6.88 (3.12, 13.15)
'at risk'	Placebo	8.28 (3.84, 15.84)	13.83 (6.41, 26.45)
	Zanamivir	5.47 (2.48, 10.53)	9.13 (4.14, 17.59)
	Oseltamivir	7.34 (3.33, 14.24)	12.27 (5.53, 23.70)
Healthy children	Placebo	5.80 (2.32, 12.03)	9.69 (3.88, 20.22)
	Zanamivir	4.74 (1.83, 10.13)	7.92 (3.07, 16.86)
	Oseltamivir	4.22 (1.61, 9.04)	7.06 (2.69, 15.18)

The durations were then used as the basis for estimating the potential QALY gains associated with the reduction in symptom durations reported for each individual NI compared to usual care. In order to inform this aspect of the model, a separate systematic search of the literature was also undertaken in order to identify studies reporting preference-based valuations of the impact of influenza in different risk groups. These are summarised in Appendix 10.1. Although a number of studies were identified, none of these presented comparable estimates for different risk groups. In addition, even within the populations that were considered, there were a number of limitations related to the methods themselves (e.g. retrospective data collection) as well as the selection of respondents (e.g. small numbers of patients or experts). In the absence of more appropriate data from studies published since the earlier appraisal, quality-weights are applied to the periods of symptom duration based on those previously applied by Turner (2003) and reported in Table 7.16.

estimates were not available for zanamivir. Separate values are reported for otherwise healthy adults and 'at risk' adult populations. In the absence of comparable estimates for otherwise healthy children and 'at risk' children, the values corresponding to the equivalent adult populations are applied in the model.

Table 7.16: Utility values over a 21-day period

Day	Healthy adults			'at risk' groups		
	Placebo	Oseltamivir	Difference	Placebo	Oseltamivir	Difference
1	0.067543	0.082757	0.015214	0.117313	0.111745	-0.005568
2	0.244658	0.369697	0.125039	0.197075	0.213862	0.016787
3	0.396576	0.513446	0.116870	0.270045	0.311437	0.041392
4	0.526019	0.611720	0.085701	0.348902	0.384854	0.035952
5	0.611720	0.693377	0.081657	0.401373	0.436523	0.035150
6	0.658876	0.738223	0.079347	0.432902	0.460356	0.027454
7	0.704713	0.760151	0.055438	0.460299	0.483436	0.023137
8	0.757784	0.784536	0.026752	0.463900	0.509715	0.045815
9	0.778053	0.792279	0.014226	0.494421	0.543382	0.048961
10	0.787365	0.804462	0.017097	0.502314	0.547231	0.044917
11	0.795763	0.812164	0.016401	0.532226	0.565495	0.033269
12	0.797749	0.817108	0.019359	0.543382	0.576452	0.033070
13	0.798634	0.817179	0.018545	0.561641	0.594872	0.033231
14	0.802947	0.817715	0.014768	0.572611	0.601892	0.029281
15	0.807632	0.820322	0.012690	0.576452	0.615933	0.039481
16	0.809530	0.821819	0.012289	0.612671	0.619619	0.006948
17	0.809846	0.824986	0.015140	0.616314	0.637228	0.020914
18	0.811355	0.823955	0.012600	0.626906	0.651299	0.024393
19	0.811705	0.824773	0.013068	0.640805	0.658247	0.017442
20	0.813527	0.824702	0.011175	0.651299	0.665139	0.013840
21	0.864840	0.864840	0.000000	0.668569	0.678469	0.009900
Total QALD	14.456835	15.220211	0.763376	10.291420	10.867186	0.575766
Total QALY	0.002223	0.002257	0.000035	0.001718	0.001784	0.000067

It has previously been outlined that these values were derived based on the transformation of VAS data reported in a number of the oseltamivir trials into TTO utilities. Comparable The values reported over a 21-day period were used directly in the previous model by Turner (2003) to estimate QALY gains for oseltamivir compared to standard care. The respective QALY gains associated with zanamivir and amantadine were then estimated by comparing the differences in symptom duration with oseltamivir (with an adjustment applied to account for the relative difference between these treatments). In the earlier critique section of previous models, we highlighted the potential limitations of this approach, in particular that the QALY gains estimates for oseltamivir were derived directly from the subset of trials in which the VAS data were reported (as opposed to the wider set of trials considered in the review of symptom data). This represents an important source of uncertainty since the use of these estimates directly in the model reported here would make no use of any additional RCT evidence that has become available since the previous review. Hence, the QALY gains associated with oseltamivir would not differ from those reported previously despite the existence of new evidence.

In order to address this potential limitation, and to more appropriately reflect differences in symptom duration across the full range of RCTs included in the evidence synthesis sections, data from the placebo arms in the healthy adult and ‘at risk’ populations were used to establish a ‘baseline’ quality of life for the period of influenza without NI treatment. These data were then used to estimate the additional QALY gains associated with oseltamivir and zanamivir respectively based on the different symptom durations obtained from the Bayesian multi-parameter synthesis approach. This approach ensures that the respective QALY gains are subsequently informed by the complete set of RCT evidence with respect to both NI treatments.

For each simulated estimate of the mean duration of illness associated with standard care (i.e. placebo) derived from the WinBUGs simulation, the model derives the corresponding utility decrements based on the average VAS score over this particular duration from the TTO data for standard care (i.e. assuming these scores reflect the QoL anchored to an upper bound representing the normal health for someone of a similar age). These data represent the ‘baseline’ which is then used to estimate the average decrements over the period represented by standard care. This, in turn, provides the basis for estimating the associated QALY gains with oseltamivir and zanamivir. For each simulated estimate of the mean duration of illness with standard care, the corresponding estimates of the mean duration of illness with oseltamivir and zanamivir are then estimated. The difference between the two individual NI treatments and standard care subsequently reflect the reduction in the number of symptom days associated with each subgroup. The QoL decrements estimated from the mean duration of illness reported for standard care are then used as the basis for estimating the incremental QALY gains with each NI treatment (i.e. the QALY gains reflect the additional days valued at the average decrement reported across the duration of the ‘baseline’).

The aforementioned approach makes the assumption that the reduction in mean symptom durations for zanamivir and oseltamivir arise across the entire distribution of the equivalent symptom duration represented by standard care. Consequently, the utility weights reflect the average decrement reported across the average symptom duration for standard care. However, it is plausible that the differences relate to either the later periods of illness for which the associated decrement of QoL could be considerably lower than the associated average (or indeed, that these differences are attributed to reductions in symptoms at an earlier stage in which case the average decrement would be an under-estimate). In the absence of reliable data on when these differences arise, or alternative more robust QoL estimates from other

sources, a series of scenarios are subsequently employed reflecting a wide range of potential decrements.

Complications

Baseline probabilities

The model assumes that all patients with ILI (whether influenza or an alternative ILI) had a probability of developing a complication. Estimates of the baseline probabilities of developing each complication (and mortality subsequently) were derived separately for each subgroup from data reported in a large UK population based study.¹⁵ Meier (2000) was selected after detailed consideration of a number of potential UK based studies identified as part of the clinical effectiveness searches.¹⁵ This study was selected as it was the only study to report relevant data in relation to both age and 'at risk' status.¹⁵ Meier (2000) was also previously used to derive similar baselines by Turner (2003) and also Roche as part of their submission. The model inputs were derived in a number of stages:

- The data for the 15-49 years age group was combined with that given for the 50-64 years age group to form a pooled 'adult' group more appropriate to the present analysis (with the distinction between 'healthy' and 'predisposed' patients maintained, representing healthy and 'at risk' patients respectively). In addition, the data for 'healthy' patients 65+ years was combined with that for 'predisposed' patients 65+ years to form a single pooled 'elderly' group.
- In each sub-group, the mean probability of a patient developing a complication was derived by dividing the number of patients with a complication by the number of patients with ILI. A beta distribution was fitted to each probability for the probabilistic sensitivity analysis.
- Where a patient developed a complication, this was assumed to fall into one of five categories (as reported in Meier (2000): respiratory tract infection (RTI), cardiovascular, CNS, renal or 'other'. The mean conditional probability of the complication falling under each category was then derived by dividing the number of complications in that category by the total number of complications in all five categories. A dirichlet distribution was assigned to each probability for the probabilistic sensitivity analysis.¹⁵⁹
- Where a patient developed an RTI, this was assumed to fall into one of three sub-categories: bronchitis, pneumonia or upper respiratory tract infection (URTI). As before, the mean conditional probability of the complication falling under each sub-category was derived by dividing the number of complications in that sub-category

by the total number of complications in all three sub-categories, with a dirichlet distribution assigned to each probability for the probabilistic sensitivity analysis.

- Where a patient developed an ‘other’ complication, this was assumed to be either otitis media or GI bleeding – the mean conditional probability of developing otitis media was derived by dividing the number of otitis media complications by the total number of otitis media and GI bleeding complications, with a beta distribution assigned for the probabilistic sensitivity analysis.

These probabilities are reported in Table 7.17.

Table 7.17: Probability of a complication

	Healthy children (1-14yrs)	‘at risk’ children (1-14yrs)	Healthy adults (15-64yrs)	‘at risk’ adults (15-64yrs)	Elderly (65+ yrs)
Probability of any type of complication					
Probability of complication	0.1344 (n=2,311)	0.1759 (n=650)	0.0755 (n=6437)	0.1217 (n=2142)	0.1092 (n=1917)
Total patients	17,201	3,695	85248	17597	17552
Probability of a specific type of complication					
RTI complication	0.7021 (n=1697)	0.7692 (n=520)	0.8612 (n=5636)	0.7521 (n=1941)	0.7625 (n=1573)
Cardiovascular complication	0.0000 (n=0)	0.0000 (n=0)	0.0017 (n=11)	0.0133 (n=29)	0.0329 (n=68)
CNS complication	0.0070 (n=17)	0.0000 (n=0)	0.0154 (n=101)	0.0069 (n=15)	0.0213 (n=44)
Renal complication	0.0008 (n=2)	0.0000 (n=0)	0.0014 (n=9)	0.0023 (n=5)	0.0082 (n=17)
‘Other’ complication	0.2900 (n=701)	0.2308 (n=156)	0.1203 (n=787)	0.0880 (n=192)	0.1770 (n=366)
Total complications	2,417	675	6511	2166	1844
Probability of an RTI complication					
Bronchitis	0.0701 (n=113)	0.0633 (n=21)	0.1916 (n=1057)	0.2613 (n=370)	0.3446 (n=529)
Pneumonia	0.0180 (n=29)	0.0271 (n=9)	0.0430 (n=237)	0.0438 (n=62)	0.1322 (n=203)
URTI	0.9119 (n=1,470)	0.9096 (n=302)	0.7655 (n=4224)	0.6949 (n=984)	0.5231 (n=803)
Total RTI complications	1612	332	5518	1416	1535
Probability of ‘other’ complication					
Otitis media	0.9757 (n=684)	0.9871 (n=153)	0.6649 (n=500)	0.6250 (n=110)	0.2162 (n=32)
GI bleeding	0.0243 (n=17)	0.0129 (n=2)	0.3351 (n=252)	0.3750 (n=66)	0.7838 (n=116)
Total ‘other’ complications	701	155	752	176	148

It was noted that the possibility exists for a patient to develop more than one complication – consequently the additional costs and utility decrements attributable to each complication were inflated by the mean number of complications estimated per patient in each subgroup.

The model assumes that patients who develop RTI face a (conditional) probability of hospitalisation due to the complication. This conditional probability was taken from hospitalisation rates for lower respiratory tract infections reported within a meta-analysis of ten trials of oseltamivir reported by Kaiser (2003).¹⁵³ For healthy adults and healthy children, the mean probability of hospitalisation, conditional upon developing a complication, was estimated to be 0.1087 (5/46), whilst for ‘at risk’ groups this was estimated to be 0.1579 (15/95). Due to limitations in the data, these conditional probabilities could not be further divided by age. Beta distributions were fitted to the conditional probabilities for the probabilistic sensitivity analysis.

The model also assumed that, of those patients hospitalised for pneumonia, approximately 5% (22/453) would require ITU care with or without mechanical ventilation. This figure was derived from Turner (2003) in the absence of any alternative evidence identified. Again, a beta distribution was assigned to this conditional probability.

Relative risk of a complication

For each of the NI treatment strategies, the baseline probability of a complication was adjusted according to the relative risk (versus placebo) of requiring antibiotics, as given in Table 7.18 for each sub-group. However, it was assumed that when a complication did occur, receiving NI treatment did *not* affect the conditional probabilities of a complication falling into each category or sub-category, *nor* did it affect the conditional probabilities of a complication resulting in hospitalisation or mortality (discussed in more detail below); reductions in hospitalisations and mortality associated with NI treatments were therefore driven structurally by the model by the lower probability of developing a complication itself.

The decision to relate hospitalisations and mortality structurally to complications as a whole as opposed to treating these as potentially independent events and/or applying separate relative risks to each element was made on several grounds. Firstly, it appears to make clinical sense to relate these issues, since it is unclear why an uncomplicated illness would require either hospitalisation or would subsequently result in death. Secondly, the evidence on the relative effectiveness of the NIs in relation to hospitalisation and mortality is either

limited (hospitalisation data reported in earlier sections is highly variable and only reported in a small number of potentially selective studies) or entirely absent (mortality). However, it equally needs to be recognised that the current RCTs are themselves are not adequately powered on these particular outcomes, so the lack of suitable estimates is not sufficient evidence in itself that these events are not potentially reduced by the use of NI treatment. Consequently, the model structurally relates these aspects and applies the most robust ‘proxy’ estimate of the relative effectiveness of the NIs derived from the results of the clinical effectiveness review, namely the relative risk of a reduction in the use of antibiotics. Clearly there remains significant uncertainty surrounding this assumption and hence a number of alternative scenarios are subsequently explored.

Table 7.18: Relative risks applied to complications (based on reduction in antibiotic use)

Subgroup	Comparison	Relative risk (95% CI)
Healthy adults	Zanamivir vs. placebo	0.71 (0.34 to 1.45)
	Oseltamivir vs. placebo	0.57 (0.24 to 1.35)
'at risk'	Zanamivir vs. placebo	0.74 (0.35 to 1.57)
	Oseltamivir vs. placebo	0.69 (0.50 to 0.93)
Children	Zanamivir vs. placebo	0.78 (0.45 to 1.35)
	Oseltamivir vs. placebo	0.56 (0.36 to 0.87)

Resource use and costs of complications

The model assumes that each patient developing a complication requires a single GP visit and faces a higher probability of requiring antibiotics than patients who did not develop a complication. The estimated cost of a GP visit was derived in a similar manner to that of Turner (2003): unit costs for surgery visits (£30) and home visits (£48) were taken from published sources;¹⁶⁰ these were then weighted by an estimate of the proportion of patients in each subgroup receiving home visits, for the elderly group (25%) and for the adult and children groups (7%).⁴⁶

The probabilities that patients required antibiotics were taken directly from Meier (2000)¹⁵ and assumed to vary by subgroup and presence of complications. Beta distributions were assigned to each probability for the probabilistic sensitivity analysis. The costs of these antibiotics were taken from Roche’s submission: the costs for patients without complications and those with all non-RTI complications (including otitis media) were assumed to be those given by Roche for patients with ILI, whilst the costs for all RTIs were assumed to be those given by Roche for patients with bronchitis and pneumonia (Roche did not consider URTI). Where separate costs were given by Roche for children aged 1-5 years and children aged 1-12

years, the costs for children aged 1-12 were used to inform the 1-14 year age groups in the York analyses. These data are reported in Table 7.19.

Table 7.19: Probability and costs of antibiotic use

	Healthy children (1-14yrs)	'at risk' children (1-14yrs)	Healthy adults (15-64yrs)	'at risk' adults (15-64yrs)	Elderly (65+ yrs)
No RTI complication	0.279 (£0.21)	0.279 (£0.21)	0.420 (£0.46)	0.420 (£0.46)	0.547 (£0.46)
RTI complication	0.737 (£2.39)	0.737 (£2.39)	0.814 (£3.71)	0.814 (£5.66)	0.797 (£5.66)

Estimates for length of hospital stay were derived from national hospital episode statistics for 2006/7 – these were used to calculate both the duration of utility decrements resulting from complications as well as the costs of hospitalisation (Table 7.20). Length of stay estimates varied by subgroup and by complication. For pneumonia, national data for diagnosis chapters J12 to J18 was used to estimate a mean length of stay for children (0-14 years, 2.93 days), adults (15-74 years, 7.41 days) and elderly (75+ years, 14.51 days) - these were derived by weighting the mean length of stay given by sex, age-group and diagnosis chapter by the corresponding number of finished consultant episodes. For bronchitis, a similar method was used across diagnosis chapters J20 and J21 to derive estimates of mean length of stay for children, adults and elderly of 2.47, 2.51 and 6.58 days respectively, whilst for URTI a similar method was employed across diagnosis chapter J22 to derive estimates of mean length of stay for children, adults and elderly of 2.15, 3.77 and 11.46 days respectively. Unit cost per diems were derived from the respective Health Resource Group (HRG) costs estimates obtained using per diem estimates derived from 'excess bed' estimates (Table 7.20).

Table 7.20: Length of hospitalisation and cost per diem

Complication	Children (0-14)	Adults (15-74)	Elderly (75+)	Cost per diem
Pneumonia	2.9292	7.4115	14.5126	£166
Bronchitis	2.4664	2.5077	6.5828	£172
URTI	2.1467	3.7665	11.4650	£182

Quality of life implications of complications

The model assumes that those patients who develop a complication receive a reduction in their QoL for a particular duration. As part of the review of economic models, a number of sources were identified that reported utility values for particular complications. These were assessed and considered in relation to whether they provide values derived from preference-based methods for the range of RTI and other particular complications considered. No single study was identified which addressed the full range of estimates required. However, the final estimates were derived from a study reporting utility values from the Health Utility Index (HUI) and decrements assumed are reported in Table 7.21.¹⁶¹ For RTI complications, these decrements were applied for a time equivalent to the estimated length of hospital stay for the respective complication, irrespective of whether the patient was hospitalised for the complication or not, whilst for non-RTI complications the appropriate decrement was applied for a time equivalent to the estimated length of hospital stay for bronchitis (in the absence of any more appropriate data).

Table 7.21: Utility decrements applied to complications

Complication	Utility decrement
Bronchitis	0.15
Pneumonia	0.25
URTI	0.15
Cardiovascular	0.37
CNS	0.15
Renal	0.15
Otitis media	0.15
GI bleeding	0.15

The model assumed that hospitalisation itself did not result in any further decrement in patients' utility, with the exception of those admitted to an ITU with pneumonia who received a further utility decrement of 0.13 in addition to the decrement of 0.25 associated with pneumonia.¹⁶¹ This additional decrement was applied for a length of time equivalent to the estimated length of hospital stay for pneumonia.

Mortality

The model assumed that all patients who develop a complication face a subsequent probability of mortality. This (conditional) probability was assumed to vary by subgroup but *not* by whether a patient was hospitalised (due to a lack of suitable data) *nor* by treatment

strategy (although, as with hospitalisation, the *unconditional* probability of mortality for a typical patient with ILI was lower with NI treatment than with usual care due to the lower probability of developing a complication in the first instance).

As with the baseline probabilities of developing a complication, estimates of the conditional probabilities of mortality were derived separately for each subgroup from data provided in Meier (2000).¹⁵ Since it was assumed that all patients whose ILI resulted in mortality experienced at least one other complication, the mean conditional probability of mortality given a complication was derived by dividing the number of deaths in each subgroup by the number of patients experiencing a complication. These conditional probabilities are given in Table 7.22.

Table 7.22: Probability of mortality (conditional upon a complication)

	Healthy children (1-14yrs)	'at risk' Children (1-14yrs)	Healthy Adults (15-64yrs)	'at risk' Adults (15-64yrs)	Elderly (65+ yrs)
Probability of mortality <i>given</i> a complication	0.0000 (n=0)	0.0015 (n=1)	0.0051 (n=33)	0.0075 (n=16)	0.1168 (n=224)
Total patients with complication	2,311	650	6437	2142	1917

Mortality was assumed not to incur any cost; however, it was assumed to result in potential loss of QALYs. In each age group (children, adults, elderly), the expected age of death from ILI-related complications was derived from data from the national statistics reporting influenza deaths (J10-J18) by age group.¹⁶² For each age group, the remaining life expectancy at this age of (premature) death was then derived from general population life-table statistics,¹⁶³ with these estimated remaining years of life quality weighted according to age-matched UK population norms reported using EQ-5D.¹⁵⁶ The utility estimates derived from EQ-5D were also adjusted in the model to reflect the increasing age of particular populations in later years of life. The resulting quality-adjusted life expectancy was then discounted at 3.5% per annum. The resulting discounted estimates applied in the model are reported in Table 7.23.

Cost of antivirals

The acquisition costs of oseltamivir (£16.36) were derived from national sources,⁴⁵ with identical estimates applied for zanamivir based on the revised price agreement. It was also

assumed that any remaining powder related to the use of oral suspension (oseltamivir) in children would not be re-used and hence the full cost £16.36 was assumed throughout in each subgroup.

Table 7.23: Quality-adjusted life expectancies applied to premature mortality

	Children	Adults	Elderly
Expected age of death (years)	4.75	53.66	86.76
Life expectancy at this age (years)	75.02	28.01	5.29
Quality-adjusted life expectancy (years)	65.95	22.54	4.59
Discounted (3.5%) QALE (years)	24.95	14.66	4.20

Validation

The validity of the model was considered in detail. An initial structure and set of assumptions were developed from the review of previous cost-effectiveness models. These were discussed extensively by the group and reviewed by a clinical expert. Through this process the final model structure and associated assumptions were finalised. Detailed reference was also made to Turner (2003) and the Roche submission in order to identify possible areas of uncertainty to be considered using separate scenarios. As part of an overall quality assurance process for the final model, the internal model validity was explored extensively exploring logical consistency throughout. Model inputs were cross checked against the source data.

Base-Case Analysis and Scenarios

The model results are presented according to a particular set of assumptions employed as part of a base-case analysis. The impact of employing alternative assumptions to those proposed in the base-case analysis is then explored using detailed scenario analysis.

Table 7.24 summarises the alternative scenarios considered. For each element, the position in the base-case analysis is outlined, alongside the alternative assumption applied. The scenarios are undertaken to assess the robustness of the base-case model results to variation in (i) the sources of data used to populate the model and (ii) alternative assumptions related to key parameters in the model.

7.2.5 Results of the York Economic Assessment

The results of the model are presented in two ways. Firstly, mean costs and QALYs for the various comparators are presented and their cost-effectiveness compared using standard decision rules and estimating ICERs as appropriate.¹⁶⁴ The ICER examines the additional costs that one strategy incurs over another and compares this with the additional benefits. When more than two interventions are being compared the ICERs are calculated using the following process:

- The strategies are ranked in terms of cost (from the least expensive to the most costly).
- If a strategy is more expensive and less effective than any previous strategy, then this strategy is said to be dominated and is excluded from the calculation of the ICERs.
- The ICERs are calculated for each successive alternative, from the cheapest to the most costly. If the ICER for a given strategy is higher than that of any more effective strategy, then this strategy is ruled out on the basis of extended dominance.

Secondly, the results of the probabilistic analysis using Monte Carlo simulation is then used to calculate the combined impact of the model's various uncertainties on the overall uncertainty surrounding the cost-effectiveness results themselves. Tabulated results are presented for the base-case and select scenarios values of the probability each intervention is cost-effective at a threshold of £20,000 and £30,000 per additional QALY.

7.2.5.1 Results of the Base-Case Analysis

Table 7.25 reports the base-case results according to the separate populations. In each population, the ICER for either oseltamivir or zanamivir (relative to standard care) appears well below conventional thresholds applied to determine cost-effectiveness. Across the separate populations there is variability in terms of the ICER itself (ranging from between £563 to £7,038 per additional QALY) and also which particular NI is considered optimal according to cost-effectiveness considerations.

Table 7.24: Details of the key elements of the base-case analysis and how these are varied in the separate scenarios

Scenario	Element	Position in base-case analysis	Variation considered in scenario analysis
1	Inclusion of potential hospitalisation and mortality benefits with NIs	Included for all populations, treatment effects based on subgroup and treatment specific estimates of the relative risk reduction in antibiotic use.	Hospitalisation and mortality benefits excluded across all populations
2	Complications and mortality	Included for all populations, treatment effects based on subgroup and treatment specific estimates of relative risk reduction in antibiotics.	Treatment effects specific for individual treatments but not subgroup specific. Separate scenarios considered including and excluding hospitalisation and mortality.
3	Definition of symptoms	Mean time to resolution of symptoms	Mean and median estimates (time to resolution of symptoms and time to return to normal activities)
4	RCTs and subgroup data used in Bayesian synthesis	All RCTs and subgroups where data on median and SE are reported included.	Excluding 'at risk' children RCT data
5	Probability ILI is influenza	Derived from surveillance data, 'hierarchical' model to estimate estimates for children (<15) and adults (15+)	Alternative, common estimates applied (probabilities between 0.1 and 0.9) to all groups. Separate scenarios considered including and excluding hospitalisation and mortality.
6	Probability ILI is influenza & increased GP consultations (otherwise healthy populations only)	As above for probability ILI is influenza. Additional GP consultations not considered.	2-way analyses combining alternative reductions in the probability ILI is influenza (-5% to -15%) and increased GP consultations (+5% to + 15%) consistent with Turner (2003).
7	Viral resistance	Not considered for either oseltamivir or zanamivir.	Alternative resistance rates modelled for oseltamivir only (range 1%-10%).
8	Quality of life decrements associated with symptom duration	Derived from VAS TTO data from oseltamivir trials	Alternative decrements applied (range between 0.1 and 0.9)
9	Training costs associated with use of zanamivir (Diskhaler)	Not considered. Assumed to be £0.	Alternative costs applied (range £7-£21 per patient)
10	Quality-adjusted life expectancy in 'at risk' groups	Derived from equivalent age-matched estimates from general population.	Quality-adjusted life expectancy reduced (range 10%-50%)
11	Baseline complication and mortality rates	Derived from UK source related to ILI (i.e. includes influenza and other ILI)	Adjustment made to adjust for potential differences in an influenza population (adjustment made using influenza/RSV data)
12	Relative efficacy of NIs	Derived from Bayesian synthesis. Mean estimates both treatment and subgroup specific.	Assume equivalent efficacy between the NIs. Best and worst case analyses undertaken including and excluding hospitalisation and mortality benefits.

In general, estimates of the ICER appear more favourable in the ‘at risk’ groups than in the otherwise healthy populations. This appears to be driven by the slightly higher reductions in symptom duration derived from the Bayesian synthesis for the ‘at risk’ groups, relative to the healthy populations, and the higher baseline risks of complications and their sequela (higher hospitalisation and mortality estimates), resulting in higher absolute gains attributed to these populations. Within the ‘at risk’ populations, the ICER estimates are most favourable for the elderly population principally due to this group having the highest baseline complication rate. Zanamivir was consistently reported as the most cost-effective treatment in each of the ‘at risk’ groups (oseltamivir was ruled out on the grounds of extended dominance in each of the ‘at risk’ groups). This reflects the higher reductions in symptom duration for zanamivir in these groups estimated on average compared to both standard care and oseltamivir derived from the Bayesian synthesis. However, this also needs to be considered in relation to the current licences since zanamivir is not currently licensed in ‘at risk’ children aged <5 years.

Table 7.25: Base-case results for the different populations

Strategy	Mean Cost	Mean QALY	ICER	Prob. CE for Max WTP*	
				£20,000	£30,000
Healthy children					
Usual care	£5.03	24.9629	NA	0.04	0.02
Zanamivir	£18.60	24.9641	D	0.23	0.25
Oseltamivir	£18.21	24.9647	£7,035	0.72	0.74
‘at risk’ children					
Usual care	£8.60	24.9600	NA	0.02	0.02
Zanamivir	£20.04	24.9666	£1,752	0.85	0.85
Oseltamivir	£19.89	24.9638	ED	0.13	0.13
Healthy adults					
Usual care	£3.29	14.6671	NA	0.00	0.00
Zanamivir	£17.83	14.6692	D	0.23	0.23
Oseltamivir	£17.68	14.6697	£5,521	0.77	0.77
‘at risk’ adults					
Usual care	£6.82	11.0038	NA	0.00	0.00
Zanamivir	£19.36	11.0093	£2,270	0.90	0.90
Oseltamivir	£19.25	11.0073	ED	0.10	0.10
Elderly					
Usual care	£13.13	4.1939	NA	0.00	0.00
Zanamivir	£22.07	4.2098	£562	0.64	0.64
Oseltamivir	£21.84	4.2081	ED	0.36	0.36

D= Dominated, ED = Extendedly dominated

* Probability each intervention is cost-effective for a maximum willingness to pay of £20,000 or £30,000 per additional QALY

The uncertainty surrounding the results in ‘at risk’ populations, based on the probability statements related to cost-effectiveness, appears higher in those groups with higher baseline complication rates such as the elderly. In these instances, the relative difference between zanamivir and oseltamivir in terms of mean reduction in symptom duration are partly attenuated by the more favourable relative risks reductions assumed for oseltamivir in terms of complications. However, even in these groups, zanamivir remains the most cost-effective intervention taking both symptomatic benefits and complications into consideration.

In the otherwise healthy populations (both adults and children), oseltamivir dominated zanamivir (i.e. oseltamivir is associated with higher QALYs and lower costs overall). The ICER estimates for oseltamivir compared to standard care are between £5,522 (adults) and £7,038 (children). The slightly more favourable ICERs in the healthy adult population are partly explained due to the zero mortality rate applied to the healthy children population based on data from Meier (2000).¹⁵

At a threshold of £20,000 per QALY there appears very little uncertainty that an NI treatment is cost-effective. In the otherwise healthy populations the probability that usual care (without an NI treatment) was optimal on cost-effectiveness grounds was 0.04 or less (i.e. only on 4% or less of simulations did usual care appear to be cost-effective), similarly in the ‘at risk’ populations this was lower still (0.03 or less). In the otherwise healthy populations, oseltamivir had a probability of being cost-effective at a threshold of £20,000 of between 0.72 and 0.78. In the ‘at risk’ populations the probability that zanamivir is optimal was highest in the ‘at risk’ adult population (0.9) with less certainty in the children (0.84) and elderly (0.64) populations. Again, the results in ‘at risk’ children need to be considered in relation to current licenses.

7.2.5.2 Results of the Scenario Analysis

Scenario 1: Exclusion of potential hospitalisation and mortality benefits with NIs

As part of the base-case analysis potential reductions in associated hospitalisations and mortality benefits related to the NIs are included. This position more closely reflects the approach considered in the ‘extrapolated’ model by Turner (2003) as opposed to their original base-case approach which excluded these elements. Our updated clinical effectiveness review identified limited RCT data in relation to hospitalisations and no evidence in relation to mortality reductions. Consequently, the base-case analysis employs a ‘proxy’ estimate based on the relative risk of antibiotic usage which, via the structure of the model, feeds through

into similar reductions in hospitalisations and mortality. Clearly this is an important assumption which may also be considered more plausible in particular populations (e.g. ‘at risk’ and elderly compared to otherwise healthy populations). This concern is already partially reflected in the base-case analysis, since the absolute benefit associated with the use of NIs attributed to hospitalisation and mortality benefits will ultimately be driven by two related issues: (i) the baseline risk of hospitalisation and mortality, as well as (ii) the relative effectiveness of NI treatment. As previously demonstrated, the baseline risk of hospitalisation and mortality is clearly lower in the otherwise healthy population and is highest in the elderly. However, given the remaining uncertainty related to the relative effectiveness applied to oseltamivir and zanamivir, a separate scenario was considered excluding these benefits.

Given that these elements are structurally driven in the current model, it is not possible simply to ‘switch off’ the relative effects for these benefits without major structural alterations. Hence, the results presented here are obtained by setting the conditional probability of hospitalisation following a complication to zero and excluding the probability of influenza related mortality. Although this approach will alter the resulting mean values of the costs and QALYs, the subsequent ICER estimates are identical to those that would be obtained by excluding the relative risks of these separate elements. The results of this scenario are presented in Table 7.26.

As expected the exclusion of hospitalisation and mortality benefits results in less favourable ICERs across each of the subgroup. The differences are most evident in the otherwise healthy adult population for whom the ICER increases to £13,988 per QALY (compared to the base-case results of £5,522). The subgroup least affected is the otherwise healthy children population with an associated ICER of £7,854 per QALY (compared to £7,038 in the base-case). The smaller effect observed for the otherwise healthy children population is mainly due to the fact that mortality benefits are not actually different to those from the base-case analysis, since the probability of mortality was already assumed to be zero in this population in the base-case.

Despite the higher estimates of the ICER obtained all subgroups, the estimates remained below £20,000 per QALY in each of these. In addition, in each subgroup, the same strategies were excluded on the grounds of dominance and extended dominance as occurred in the base-case analysis. The associated probability that no antiviral treatment was the most cost-effective strategy was 0.12 in the healthy adult population and 0.05 or lower in the other subgroups.

Table 7.26: Scenario 1- Excluding mortality and hospitalisation benefits

Strategy	Mean Cost	Mean QALY	ICER	Prob. CE for Max WTP	
				£20,000	£30,000
Healthy children					
Usual care	£2.63	24.9629	NA	0.05	0.02
Zanamivir	£17.55	24.9641	D	0.24	0.25
Oseltamivir	£17.35	24.9647	£7,852	0.72	0.73
'at risk' children					
Usual care	£3.42	24.9639	NA	0.00	0.00
Zanamivir	£17.84	24.9682	£3,327	0.99	0.99
Oseltamivir	£17.78	24.9653	ED	0.01	0.01
Healthy adults					
Usual care	£1.25	14.6694	NA	0.12	0.01
Zanamivir	£16.99	14.6701	D	0.09	0.12
Oseltamivir	£16.94	14.6705	£13,985	0.79	0.87
'at risk' adults					
Usual care	£1.97	11.0079	NA	0.00	0.00
Zanamivir	£17.31	11.0111	£4,850	0.99	0.99
Oseltamivir	£17.28	11.0090	ED	0.01	0.01
Elderly					
Usual care	£1.90	4.2159	NA	0.00	0.00
Zanamivir	£17.31	4.2192	£4,763	0.99	0.99
Oseltamivir	£17.28	4.2171	ED	0.01	0.01

Scenario 2: Further considerations of complications and mortality

Two additional analyses were undertaken to further examine the robustness of the base-case results to alternative assumptions related to the relative risks of complications and mortality. These are reported in Table 7.27. Only the ICERs for these analyses are reported for ease of presentation.

For the first of these issues, it was previously reported in the clinical effectiveness review section that no significant heterogeneity was observed between the different subgroups in terms of the pairwise estimates of the relative treatment effects for each NI in terms of antibiotic use. Consequently, we apply common (but treatment specific) estimates of the relative risks to antibiotic use (and hence also to hospitalisation and mortality). The results of this analysis did not have an important effect on the ICER estimates and the same strategies remained ruled out on the grounds of dominance and extended dominance.

As part of Scenario 1, the potential impact on the ICER estimates excluding reductions in both hospitalisation and mortality was explored. Given the differences in the ICER noted for

particular populations (e.g. healthy adults), it remains unclear how each of these individual elements was contributing to these differences and whether this varied across the respective subgroups. A separate analysis was therefore undertaken to exclude the benefits of just mortality, hence leaving the potential reduction in hospitalisations still in place.

The exclusion of mortality appeared to have the largest effect on the ICER for the otherwise healthy adult population, suggesting that the mortality benefits for this subgroup are proportionately more influential in terms of the base-case ICER estimates than they are for the other subgroups.

Table 7.27: Scenario 2 - Complications, hospitalisations and mortality

Subgroup	ICER	
	Oseltamivir	Zanamivir
Application of 'all patient' results for the relative risk of complications		
Healthy children	£7,203	D
'at risk' children	ED	£1,766
Healthy adults	£5,879	D
'at risk' adults	ED	£2,288
Elderly	ED	£571
No effect of NIs on mortality		
Healthy children	£7,035	D
'at risk' children	ED	£2,639
Healthy adults	£12,828	D
'at risk' adults	ED	£3,968
Elderly	ED	£2,764

Scenario 3: Definition of symptoms

Scenario 3 considers the robustness of the base-case results to both alternative definitions of symptoms (return to normal activities) and alternative measures of the difference in symptom duration based on the median estimates. Each of these analyses was directly informed by the different outputs reported from the Bayesian synthesis. These results are reported in Table 7.28.

Overall the conclusions remained robust to both the use of different symptom definitions and alternative measures of the difference in duration. As expected, the ICER estimates were slightly more favourable when the mean time to return to normal activities was employed instead of resolution of symptoms. This is primarily due to the longer overall durations of illness reported using this measure as opposed to major differences in the relative

effectiveness estimates. Similarly, employing estimates of the median durations (as opposed to mean duration) results in less favourable estimates ICER. Again this is not unexpected since the absolute gains in symptom benefits (assuming a similar relative effect) for each NI relative to usual care will be higher based on the extrapolation required to estimate the mean estimate. However, these differences did not appear to result in marked differences in the subsequent estimates of the ICER.

Table 7.28: Scenario 3 - Alternative definitions of symptoms

Subgroup	ICER	
	Osetamivir	Zanamivir
Mean time to return to normal activities		
Healthy children	£5,965	D
'at risk' children	ED	£1,485
Healthy adults	£5,198	D
'at risk' adults	ED	£1,965
Elderly	ED	£533
Median time to resolution of symptoms		
Healthy children	£9,245	D
'at risk' children	ED	£2,254
Healthy adults	£6,139	D
'at risk' adults	ED	£2,808
Elderly	ED	£602
Median time to return to normal activities		
Healthy children	£8,175	D
'at risk' children	ED	£2,020
Healthy adults	£5,859	D
'at risk' adults	ED	£2,562
Elderly	ED	£585

Scenario 4: RCTs and subgroup data used in Bayesian synthesis

Given the inconsistency identified in Hedrick (2000) related to 'at risk' children and the limited data in general in 'at risk' children, a separate scenario was considered using the results from the revised synthesis excluding the 'at risk' children data from the model. These results are reported in Table 7.29 The ICERs in each population increased marginally compared to the base-case analysis.

Table 7.29: Scenario 4 – Exclusion of ‘at risk’ children data

Subgroup	ICER	
	Oseltamivir	Zanamivir
Including hospitalisations and mortality		
Healthy children	£7,428	D
‘at risk’ children	ED	£2,059
Healthy adults	£5,671	D
‘at risk’ adults	ED	£2,604
Elderly	ED	£588
Excluding hospitalisations and mortality		
Healthy children	£8,292	D
‘at risk’ children	ED	£4,290
Healthy adults	£14,902	D
‘at risk’ adults	ED	£6,251
Elderly	ED	£6,098

Scenario 5: Probability ILI is influenza

The base-case analysis utilises data from national surveillance data, employing a ‘hierarchical’ model to account for variability across influenza seasons and separate age groups. Clearly there remains potential uncertainty in relation to the generalisability of these estimates and also whether the variability is adequately reflected in the approach used. It is also worth re-iterating that the probability estimates were markedly higher in the group aged <15 than those aged 15 and over. In order to explore the robustness of the base-case results to variations in this probability, a detailed series of analyses were undertaken employing a range of common estimates applied to each of the separate populations (ranging from 0.1 to 0.9). A two-way scenario analysis is also considered both including and excluding the potential benefits of reductions in hospitalisation and mortality. These results are presented in Tables 7.30 and 7.31. Given the large number of comparisons presented, only the ICER of the non-dominated strategy (or strategies) is presented together with an indication of what the optimal NI strategy is in each scenario.

In each of these analyses, the same strategies that were excluded from the ICER calculations in the base-case analysis were also ruled out here. Hence, altering the probability ILI is influenza did not affect the relevant comparison providing the basis for the ICER estimate for each subgroup. In all cases (with the exception of the elderly subgroup when the probability ILI is influenza was 0.8 or higher) the ICER represents the comparison between the non-dominated NI strategy (oseltamivir in healthy adults and healthy children and zanamivir in ‘at risk’ populations) and no antiviral treatment. As the results indicate, the ICER estimates are sensitive to alternative estimates of the probability that ILI is influenza. This was most

apparent in the otherwise healthy populations, with ICER estimates exceeding £20,000 per QALY when the probability was reduced to 0.2 in both children (regardless of whether hospitalisation and mortality benefits were considered or not) and adults (when hospitalisation and mortality benefits were excluded). Results in the 'at risk' populations remained more robust to this source of variation, with ICERs consistently lower than £20,000 per QALY in all scenarios except the most extreme considered i.e. when the probability ILI is influenza is reduced to 0.1 and hospitalisation and mortality benefits are excluded. These results can also be interpreted alongside the 95% credibility intervals associated with this probability in both children (CrI: 0.26 to 0.79) and adults (CrI: 0.21 to 0.66). These represent the variability in the probability ILI is influenza both within influenza seasons and across seasons according to the current threshold used to determine that influenza is circulating in the community.

Scenario 6: Probability ILI is influenza and increased GP consultations

Although the results of Scenario 5 indicate that the overall ICER results appear quite robust to relatively large deviations from the estimates employed in the base-case analysis, the strength of these conclusions need to be related to another core assumption of the model. That is, that a positive recommendation in particular populations would not result in any additional GP consultations or, if consultations did increase, this would not lead to a reduction in the associated probability ILI is influenza (and hence would not alter the ICER estimates). However, the results of Turner (2003) demonstrated that relatively small changes to both the probability ILI is influenza and the underlying GP consultation rate can have important impacts on the subsequent ICER estimates. Although the evidence related to this link remains highly uncertain, a number of separate scenarios are considered. These scenarios are only undertaken in those populations in which NI treatment is not currently recommended by existing guidance, namely otherwise healthy adults and healthy children.

In the absence of suitable data to inform the estimates considered in these scenarios, we employed comparable ranges to those reported by Turner (2003), representing absolute increases of between 5-15% in terms of the proportion of the populations presenting to a GP and similar associated absolute reductions in the probability ILI is influenza. The absolute reductions in the probability ILI is influenza are applied to the base-case estimates applied to children (0.56) and adults (0.41). Consequently, nine possible combinations are considered in two separate scenarios (including and excluding hospitalisation and mortality benefits). Again, for ease of presentation, only the ICER of the non-dominated NI is presented based on a comparison with standard care.

In common with Turner (2003) these results reported in Tables 7.30 to 7.33 indicate that relatively minor changes in the probability ILI is influenza when combined simultaneously with changes in the probability an individual consults a GP lead to more marked variation in the subsequent ICER estimates. This was most evident in the adult population, primarily due to the fact that while the same absolute decrements were applied to both populations, in terms of the probability ILI is influenza, the baseline estimate to which these were applied remains higher in the subgroup of healthy children (0.56 versus 0.41).

Clearly the key question here is whether these differences in the probability ILI is influenza estimated for children and adults are meaningful or not, and ultimately what the actual probability ILI is influenza is at a national level for the separate populations. Clearly, if the difference between healthy adults and healthy children is not considered reasonable, then the subsequent ICERs for these separate populations should be carefully considered.

Furthermore, if the 'true' probability that ILI is lower in both groups than the estimates derived from routine surveillance data, then the estimates presented in Scenario 6 are likely to under-represent the potential variability in the subsequent ICER estimates and also over-state the potential cost-effectiveness of NIs across these scenarios. For example, reducing the probability ILI is influenza in healthy children from the base-case estimate (0.56) to 0.3 in itself approximately doubles the ICER estimate (£14,696 versus £7,038 - including hospitalisation and mortality benefits). Clearly if the 0.3 estimate was then applied as the base-case probability to which the absolute decreases in the probability ILI is influenza are applied, then the ICER estimates would increase more dramatically.

Scenario 7: Viral resistance

The base-case analysis assumes that viral strains are not resistant to either oseltamivir or zanamivir. We have previously described in Section 3.3.3 that potential concerns are emerging related to issues of viral resistance and also that the different profiles of the separate NIs means that resistance could conceivably be higher for oseltamivir. In order to examine the robustness of the base-case ICER to this issue, a number of alternative resistance rates were applied to oseltamivir in the model. Since oseltamivir was ruled out on the grounds of dominance/extended dominance in 'at risk' groups, this scenario was only undertaken in the otherwise healthy populations (on the basis that the ICER estimates in 'at risk' groups would not be affected by this alteration).

Table 7.30: Scenario 5 – ICER estimates for alternative probabilities that an ILI is influenza in individuals presenting to a GP; including hospitalisation and mortality

Subgroup	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Healthy children	£47,573 (O)	£22,939 (O)	£14,727 (O)	£10,621 (O)	£8,158 (O)	£6,515 (O)	£5,342 (O)	£4,463 (O)	£3,778 (O)
'at risk' children	£13,384 (Z)	£6,316 (Z)	£3,960 (Z)	£2,781 (Z)	£2,075 (Z)	£1,603 (Z)	£1,267 (Z)	£1,014 (Z)	£818 (Z)
Healthy adults	£25,023 (O)	£12,133 (O)	£7,837 (O)	£5,689 (O)	£4,400 (O)	£3,540 (O)	£2,926 (O)	£2,466 (O)	£2,108 (O)
'at risk' adults	£11,469 (Z)	£5,389 (Z)	£3,363 (Z)	£2,349 (Z)	£1,741 (O)	£1,336 (Z)	£1,047 (Z)	£829 (Z)	£661 (Z)
Elderly	£3,756 (Z)	£1,645 (Z)	£941 (Z)	£589 (Z)	£378 (Z)	£238 (Z)	£137 (Z)	£53 (O) £136 (Z)*	£136 (Z)*

Table 7.31: Scenario 5 - ICER estimates for alternative probabilities that an ILI is influenza in individuals presenting to a GP; excluding hospitalisation and mortality

Subgroup	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Healthy children	£48,390 (O)	£23,755 (O)	£15,544 (O)	£11,438 (O)	£8,974 (O)	£7,332 (O)	£6,159 (O)	£5,279 (O)	£4,595 (O)
'at risk' children	£20,845 (Z)	£10,199 (Z)	£6,651 (Z)	£4,877 (Z)	£3,812 (Z)	£3,102 (Z)	£2,595 (Z)	£2,215 (Z)	£1,919 (Z)
Healthy adults	£59,300 (O)	£29,349 (O)	£19,366 (O)	£14,374 (O)	£11,379 (O)	£9,382 (O)	£7,956 (O)	£6,887 (O)	£6,055 (O)
'at risk' adults	£20,928 (Z)	£10,302 (Z)	£6,960 (Z)	£4,989 (Z)	£3,926 (Z)	£3,218 (Z)	£2,711 (Z)	£2,332 (Z)	£2,037 (Z)
Elderly	£20,472 (Z)	£10,090 (Z)	£6,629 (Z)	£4,898 (Z)	£3,860 (Z)	£3,168 (Z)	£2,674 (Z)	£2,303 (Z)	£2,014 (Z)

O=oseltamivir, Z=Zanamivir; * ICER of zanamivir vs oseltamivir

Table 7.32: Scenario 6 - ICER estimates for alternative probabilities that an ILI is influenza and increased GP consultations; including hospitalisation and mortality

Subgroup	Prob. ILI=flu (-5%)			Prob. ILI=flu (-10%)			Prob. ILI=flu (-15%)		
	GP(+5%)	GP (+10%)	GP (+15%)	GP(+5%)	GP (+10%)	GP (+15%)	GP(+5%)	GP (+10%)	GP (+15%)
Healthy children	£8,798 (O)	£9,711 (O)	£10,625 (O)	£9,928 (O)	£10,940 (O)	£11,951 (O)	£11,331 (O)	£12,465 (O)	£13,959 (O)
Healthy adults	£7,023 (O)	£7,754 (O)	£8,436 (O)	£8,332 (O)	£9,124 (O)	£9,915 (O)	£10,076 (O)	£11,019 (O)	£11,962 (O)

Table 7.33: Scenario 6 - ICER estimates for alternative probabilities that an ILI is influenza and increased GP consultations; excluding hospitalisation and mortality

Subgroup	Prob. ILI=flu (-5%)			Prob. ILI=flu (-10%)			Prob. ILI=flu (-15%)		
	GP(+5%)	GP (+10%)	GP (+15%)	GP(+5%)	GP (+10%)	GP (+15%)	GP(+5%)	GP (+10%)	GP (+15%)
Healthy children	£9,614 (O)	£10,528 (O)	£11,441 (O)	£10,744 (O)	£11,756 (O)	£12,768 (O)	£12,147 (O)	£13,281 (O)	£14,415 (O)
Healthy adults	£17,590 (O)	£19,174 (O)	£20,757 (O)	£20,518 (O)	£22,356 (O)	£24,195 (O)	£24,568 (O)	£26,759 (O)	£28,950 (O)

O=oseltamivir, Z=Zanamivir; * ICER of zanamivir vs oseltamivir

Table 7.34 reports the impact on the ICER results for the healthy populations, applying estimates of resistance between 1% and 10% across all individuals (and viral subtypes). These ranges cover the potential ranges derived from the most recent UK data surveillance data from 2007/08, where the proportion of H1N1 viruses was high, as well as earlier years in which the proportion of H1N1 viruses was lower as reported in Section 3.3.3.

Table 7.34: Scenario 7 - ICER estimates for alternative rates of resistance to oseltamivir (%)

Subgroup	1%	2.5%	5%	7.5%	10%
Healthy children	£7,123 (O)	£7,259 (O)	£7,495 (O)	£7,743 (O)	£8,005 (O)
Healthy adults	£5,584 (O)	£5,682 (O)	£5,851 (O)	£6,030 (O)	£6,218 (O)

The results demonstrate that the ICER results from the base-case analysis appear robust to this issue. However, the issue of resistance also needs to be considered in a wider context that is not considered within the model presented here. Clearly, the more widespread use of NIs in otherwise healthy populations could increase the overall resistance levels and this, in itself, could have related implications for the overall cost-effectiveness in other ‘at risk’ groups, as well as in other indications (e.g. prophylactic use). Hence, while the results appear robust, they also need to be interpreted with a degree of caution, given the scope of the decision problem addressed here.

Scenario 8: Quality of life decrements applied to symptom duration

The model inputs section has previously described in detail the use of the VAS TTO data to estimate QALY gains due to shorter symptom duration as part of the base-case analysis. This is based on a relatively complex calculation which takes account of uncertainty both in terms of the underlying duration of illness for the different populations as well as in the difference in symptom duration for the NI treatments. However, uncertainty inherent in the utility values is not considered. These are two sources of uncertainty which therefore need further consideration. The first relates to the uncertainty in the utility values themselves (i.e. the actual decrement in QoL applied to characterise the impact of influenza). The literature search that was undertaken in relation to QoL did not identify alternative estimates that were considered to provide more robust estimates than those adopted here. However, such a search may not actually address what could be considered an equally important source of remaining uncertainty. This second source of uncertainty relates to what this decrement should actually represent. That is, should this decrement reflect the “average” impact on QoL over the course of the influenza illness, or alternatively should this represent the “worst” day of the illness or even the period close to the end of the illness? This source of uncertainty is important since it

is closely related to the assumption about where over the course of an influenza illness the reduction in symptom durations reported for the NIs are being achieved.

Tables 7.35 and 7.36 report the results of a detailed series of scenarios which are used to address these issues. The approach employed in the base-case is equivalent to applying a utility decrement in the region of 0.4 to 0.5 over the entire duration of illness for otherwise healthy adults and children and 0.5 to 0.6 for 'at risk' groups. In terms of the first source of uncertainty considered, the table presents alternative estimates representing larger and smaller decrements compared to those employed in the base-case.

As expected, the ICERs become more (less) favourable when higher (lower) decrements are applied. However, interestingly the results demonstrate that the ICERs remain relatively stable when higher decrements are applied but appear much more sensitive to lower decrements. This finding is particularly important in terms of the second source of uncertainty that needs to be considered. That is, at which point over the distribution of the duration of influenza illness is the duration of symptom reduction being achieved? This is also potentially important, in particular subgroups, in terms of which NI is considered optimal. For example, applying a smaller decrement in the order of 0.1-0.2 results in oseltamivir no longer being ruled out on the grounds of dominance or extended dominance by zanamivir in elderly patients. This is because, while zanamivir is associated with higher reductions (on average) in mean symptom duration in the model, oseltamivir is assumed to have more favourable (on average) relative risk reductions associated with complications. As the decrements applied to symptoms become smaller, the relative contribution of hospitalisation and mortality becomes more important in particular risk groups, such that applying decrement of 0.1 for symptoms results in zanamivir actually becoming dominated by oseltamivir in the elderly group.

The approach employed in the base-case is akin to assuming that the gains in symptom duration are occurring across the entire distribution of illness durations. Hence, the decrements in QoL assigned reflect the "average" QoL impact of influenza over its entire course. However, in the absence of more reliable data, it might equally be assumed that any gains in symptom duration achieved with the use of NIs may actually occur at the start or tail end of the distribution of illness duration. The previous results have demonstrated that if these gains are occurring earlier in the distribution, implying that a higher decrement than the average applied might be more appropriate, the subsequent ICERs do not appear markedly affected. However, if these gains are being achieved closer to the end of the influenza illness, where lower decrements than the "average" may be appropriate, then this may have a more marked effect on the subsequent results.

Table 7.35: Scenario 8 – Alternative QoL decrements applied during the period of influenza; including hospitalisation and mortality

Subgroup	QoL decrements								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Healthy children	£29,115 (O)	£15,369 (O)	£10,440 (O)	£7,904 (O)	£6,360 (O)	£5,320 (O)	£4,573 (O)	£4,010 (O)	£3,570 (O)
'at risk' children	£3,843 (Z)	£3,088 (Z)	£2,581 (Z)	£2,217 (Z)	£1,943 (Z)	£1,729 (Z)	£1,558 (Z)	£1,417 (Z)	£1,300 (Z)
Healthy adults	£8,234 (O)	£7,269 (O)	£6,506 (O)	£5,888 (O)	£5,377 (O)	£4,948 (O)	£4,582 (O)	£4,267 (O)	£3,992 (O)
'at risk' adults	£4,266 (Z)	£3,615 (Z)	£3,136 (Z)	£2,769 (Z)	£2,479 (Z)	£2,244 (Z)	£2,050 (Z)	£1,887 (Z)	£1,747 (Z)
Elderly	£652 (O)	£643 (O) £732 (Z)	£622 (Z)	£599 (Z)	£579 (Z)	£560 (Z)	£542 (Z)	£525 (Z)	£509 (Z)

Table 7.36: Scenario 8 - QoL decrements applied during the period of influenza; excluding hospitalisation and mortality

Subgroup	QoL decrements								
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
Healthy children	£32,495 (O)	£17,053 (O)	£11,651 (O)	£8,822 (O)	£7,098 (O)	£5,938 (O)	£5,104 (O)	£4,475 (O)	£3,984 (O)
'at risk' children	£18,402 (Z)	£9,541 (Z)	£6,440 (Z)	£4,861 (Z)	£3,903 (Z)	£3,261 (Z)	£2,800 (Z)	£2,453 (Z)	£2,183 (Z)
Healthy adults	£59,684 (O)	£31,691 (O)	£21,573 (O)	£16,352 (O)	£13,166 (O)	£11,019 (O)	£9,474 (O)	£8,309 (O)	£7,399 (O)
'at risk' adults	£26,606 (Z)	£13,863 (Z)	£9,373 (Z)	£7,080 (Z)	£5,689 (Z)	£4,754 (Z)	£4,084 (Z)	£3,579 (Z)	£3,185 (Z)
Elderly	£23,691 (Z)	£13,057 (Z)	£9,012 (Z)	£6,881 (Z)	£5,564 (Z)	£4,671 (Z)	£4,025 (Z)	£3,536 (Z)	£3,152 (Z)

For a scenario based on the tail end of the distribution, there remains a question over what an appropriate decrement might be in these instances. One approach might be to consider the mean symptom durations applied to no antiviral treatment (approximately 9-10 days in healthy populations and 14 days in the 'at risk' populations) and consider the TTO decrements from the VAS scores for the days immediately preceding these. The equivalent decrements for healthy populations for these times are clearly lower than the average, with a decrement of about 0.22-0.23 for healthy populations and 0.45 for 'at risk' populations. Application of these decrements would not significantly alter the ICER estimates for the 'at risk' groups, however, the decrements applied to healthy populations leads to marked increases in the ICERs (even increasing to >£20,000 per QALY in the otherwise healthy adult population). Consequently, the results appear more sensitive in otherwise healthy populations, compared to the 'at risk' groups, to the uncertainties that were not considered within the base-case approach to modelling the QoL associated with symptomatic benefits.

Scenario 9: Additional training costs associated with the use of zanamivir

In terms of the specific costs associated with the NIs, the base-case analysis only considers the acquisition costs of the drugs themselves. An important source of uncertainty is whether patients need training to administer zanamivir (Diskhaler) effectively. However, it remains unclear who would provide training to an individual patient (e.g. GP, practice nurse, pharmacist), the duration of training required or whether this would represent a cost to the NHS or not. In the absence of a clear perspective on this issue, a separate scenario was undertaken assuming that the GP would provide guidance to the patient. The cost of this was quantified by considering the cost difference between a routine GP consultation and one requiring an extended consultation (£14).¹⁶⁰ Given the various uncertainties which remain, this estimate is varied by 50% in either direction (£7 and £21). Separate scenarios are only presented in those populations for which zanamivir was not ruled out previously on grounds of dominance or extended dominance (since imposing an additional cost in this instance would simply strengthen this finding).

Table 7.37 reports the results from this scenario. The results indicate that oseltamivir is no longer ruled out in the majority of scenarios considered for the separate 'at risk' population. This contrasts with this base-case results in which oseltamivir was consistently ruled out by zanamivir. In these scenarios, the additional value attributed to the reduction in symptom benefits assumed for zanamivir (relative to both oseltamivir and usual care) are becoming partly offset by the increased cost of training.

Table 7.37: Scenario 9 - Variation to Base-Case: Additional training costs associated with the use of zanamivir (Diskhaler)

Subgroup	Additional costs		
	£7	£14	£21
'At risk' children	£2,824 (Z)	£3,016 (O)	£3,016 (O)
		£5,079 (Z)	£7,591 (Z)
'At risk' adults	£3,529 (O)	£3,529 (O)	£3,529 (O)
	£3,551 (Z)	£7,044 (Z)	£10,537 (Z)
Elderly	£612 (O)	£612 (O)	£612 (O)
	£4,291 (Z)	£8,447 (Z)	£12,603 (Z)

Scenario 10: Reduced quality-adjusted life expectancy in 'at risk' groups

In the absence of more appropriate data for the 'at risk' populations, the remaining life-expectancy estimates and quality of life estimates used to populate the base-case analysis are derived from general population estimates. The generalisability of both of these aspects to an 'at risk' population may be subject to uncertainty and it might be reasonable to consider that both the remaining life expectancy and/or quality of life would be lower in 'at risk' groups compared to the general population. Hence, a separate scenario was employed to more formally consider the robustness of the base-case results to reductions in the estimates used to value the QALYs lost due to premature mortality in these groups.

In both the 'at risk' children and adult populations, the quality adjusted life expectancy was reduced by between 10% and 50%. These results are reported in Table 7.38. The revised ICERs remained robust to this adjustment.

Table 7.38: Scenario 10 - Reduced quality-adjusted life expectancy in 'at risk' groups

Subgroup	Reduced quality adjusted life expectancy		
	-10%	-25%	-50%
'At risk' children	£1,813 (Z)	£1,913 (Z)	£2,106 (Z)
'At risk' adults	£2,372 (Z)	£2,542 (Z)	£2,888 (Z)

Scenario 11: Adjustment to (baseline) complication and mortality rates to adjust for influenza and other ILI

In common with both Turner (2003) and the Roche submission, the baseline rates of complications were derived from a large UK population based study using the GPRD – Meier (2000).¹⁵ It should be noted that that this includes subjects with a diagnosis of influenza or other ILI. The underlying assumption of the model is, therefore, that while the NIs are only

effective in terms of true influenza, the baseline complication and mortality rates are similar in true influenza and other ILI (e.g. RSV). However, recent studies have demonstrated that influenza may contribute proportionally more to overall mortality than RSV in particular populations.¹⁶

In order to consider this uncertainty in the model, a separate scenario was undertaken by applying the relative proportion of mortality reported for pneumonia and influenza deaths attributed to influenza and RSV respectively reported by Thompson (2003).¹⁶ This proportion was used as the basis for adjusting both the complication and mortality rates assigned to true influenza and other ILI in the model. The results of this are reported in Table 7.39. In each subgroup, the ICER was more favorable than equivalent result from the base-case analysis, although the ICERs were not markedly different.

Table 7.39: Adjustment to (baseline) complication and mortality rates to adjust for influenza/other ILI

Subgroup	ICER	
	Oseltamivir	Zanamivir
Healthy children	£6,448	D
'At risk' children	ED	£1,366
Healthy adults	£3,752	D
'At risk' adults	ED	£1,469
Elderly	£231	£232

Scenario 12: Equivalent effectiveness for NIs (best case and worse case scenarios)

In both the base-case analysis and each of the scenarios considered to this point, the model has applied treatment specific estimates for oseltamivir and zanamivir in relation to estimates of both symptom duration and also the relative risk of antibiotic use (and hence structurally also hospitalisations and mortality). However, these estimates are derived on the basis of indirect evidence. Furthermore, the results of the Bayesian synthesis in terms of symptom duration showed that the 95% CrI obtained from an indirect comparison of oseltamivir and zanamivir consistently overlapped. In the absence of direct evidence from head-to-head studies reporting the relative effectiveness of oseltamivir and zanamivir, an important source of uncertainty is whether a decision maker would consider it appropriate to make separate recommendations regarding each individual NI.

To address this uncertainty, a separate scenario was undertaken assuming that oseltamivir and zanamivir are equivalent in terms of clinical effectiveness. These scenarios then consider

“best case” and “worse case” assumptions related to the mean differences in symptom duration and the relative risks of antibiotic use. In the best-case scenario, the model applies the highest mean reduction in symptoms from the separate NI results and also the highest relative risk reduction (and equally the lowest for both in the worse-case scenario).

These results are presented in Tables 7.40 and 7.41 including and excluding hospitalisation and mortality benefits. In all scenarios, except otherwise healthy adults, the range of ICERs remained below £20,000 per QALY. However, the range of ICERs for otherwise healthy adults exceeded this threshold in the worse-case analysis (£5,537 to £22,364).

Table 7.40: Scenario 12 - Equivalent effectiveness for NIs (best case and worse case scenarios for symptoms and complications), including hospitalisation and mortality

Subgroup	ICER for NI	
	Best-case	Worse-Case
Healthy children	£7,035	£10,656
'At risk' children	£1,711	£3,114
Healthy adults	£5,521	£7,007
'At risk' adults	£2,219	£3,639
Elderly	£534	£646

Table 7.41: Scenario 12 - Equivalent effectiveness for NIs (best case and worse case scenarios for symptoms and complications), excluding hospitalisation and mortality

Subgroup	ICER for NI	
	Best-case	Worse-Case
Healthy children	£7,852	£11,711
'At risk' children	£3,312	£9,745
Healthy adults	£13,985	£22,161
'At risk' adults	£4,838	£14,157
Elderly	£4,749	£13,317

7.2.6 Discussion

The results from the base-case analysis demonstrated important variation across the separate populations in terms of the cost-effectiveness results. In general, the ICER estimates were lower (and hence more favourable) in ‘at risk’ populations compared to otherwise healthy populations. This finding partly reflects the inclusion of potential benefits attributed to reductions in hospitalisation and mortality and the higher underlying baseline rates of these events in ‘at risk’ populations. However, it is also worth noting that differences in mean

symptom duration were also assumed to be larger for ‘at risk’ populations, than those for healthy populations, based on the results from the Bayesian synthesis of symptom data (with the highest gains estimated for zanamivir).

Within each of the separate ‘at risk’ populations considered, zanamivir appeared the optimal NI treatment based on cost-effectiveness considerations. This reflects the higher reduction in the mean duration of symptoms obtained with zanamivir for the ‘at risk’ populations, rather than differences attributed to a reduction in complications (which on, average, were assumed to favour oseltamivir in both the ‘at risk’ and healthy populations).

In contrast, oseltamivir was considered the optimal NI treatment for healthy populations (both adults and children). This reflects the higher (on average) reduction in the mean duration of symptoms for oseltamivir estimated from the Bayesian synthesis, as well as the higher (on average) reduction in complications assumed in the economic model for this NI.

The strength of these conclusions also needs to be considered in the context of the findings from the earlier sections, as well as the range of scenarios subsequently considered employing alternative assumptions. In particular, the estimates applied in the economic model for both symptom reduction and reduction in complications are derived from indirect comparisons made in the absence of head-to-head RCT evidence. In terms of symptom reductions, the 95% CrI for the individual NIs derived from the Bayesian synthesis were found to consistently overlap each other. The only exception to this related to the ITTI analysis for the ‘at risk’ group in terms of the time to resolution of symptoms and return to normal activities (both median and mean estimates). For these outcomes, and within this population, the 95% CrI for the difference between zanamivir and oseltamivir did not include zero, suggesting a statistically significant difference (with an associated probability that zanamivir was optimal of 0.99).

The result for the ‘at risk’ group from the Bayesian synthesis of symptom data is particularly important since these estimates are applied directly in the base-case analysis of the economic model. This also largely explains why zanamivir is identified as the optimal intervention in the ‘at risk’ populations and not in the otherwise healthy populations. The strength of this finding also needs to be considered in relation to the potential inconsistency noted in the RCT data in the ‘at risk’ children group. When this group was excluded from the synthesis, the associated 95% CrI for the difference between zanamivir and oseltamivir included zero, suggesting a finding of no significant treatment difference. However, even after the potential inconsistency in evidence was excluded, zanamivir remained the optimal intervention in the

‘at risk’ group based on both symptom data (probability of zanamivir being optimal = 0.95) and in terms of subsequent cost-effectiveness considerations. Finally, it should be noted that there remains uncertainty regarding whether patients require training to administer zanamivir and the potential additional costs that this may accrue. When additional training costs were included as part of a separate scenario, oseltamivir was no longer ruled out by zanamivir based on grounds of either dominance or extended dominance in ‘at risk’ populations.

In terms of the otherwise healthy populations, the mean reductions in terms of symptom duration between the NIs were comparatively small. Hence, although one or other of the NIs was consistently found to be the optimal treatment in the cost-effectiveness model, the resulting differences in terms of the absolute estimates of mean costs and QALYs for the separate NIs were relatively minor. A similar finding also eventually emerged in terms of the cost-effectiveness results in the ‘at risk’ population. While more favourable results were assumed in terms of symptom benefits for zanamivir, these were partly (or even wholly in particular scenarios) offset by the more favourable reduction in complications assumed for oseltamivir. Consequently, differences in terms of the absolute estimate of the mean costs and QALYs for the two separate NIs were, as a whole, relatively small across all populations.

The overall difference between the cost-effectiveness results for the separate scenarios including and excluding potential hospitalisation and mortality benefits also needs to be put in the context of the conclusions from the review of clinical effectiveness. In general, the data related to complications were considered limited and while the results appeared relatively strong in terms of reduction in antibiotic use with both NIs, there was limited data with which to conclude that this would be generalisable to the reductions in hospitalisation and mortality subsequently assumed in the economic model. Again, as with the symptom data, there was no head-to-head evidence to inform the relative effectiveness of the individual NIs and hence some caution is needed in interpreting the subsequent estimates based on the indirect evidence considered which, on average, appear to favour oseltamivir. The biological and clinical plausibility of the differences applied in the model in terms of symptoms and complications also needs to be considered.

Across the numerous separate scenarios undertaken, the overall conclusions and ICER estimates in the ‘at risk’ populations appeared remarkably robust to a wider range of alternative assumptions. However, in a limited number of scenarios, oseltamivir was no longer ruled out on the grounds of dominance or extended dominance. This demonstrates how the relative contribution of symptomatic benefits (which favoured zanamivir in the ‘at risk’

populations) and complications (which favoured oseltamivir) can alter the overall cost-effectiveness results as these separate aspects are varied across the alternative sets of assumptions.

The ICER results appeared more sensitive in the otherwise healthy populations. However, zanamivir remained consistently dominated by oseltamivir in both adults and children across the separate scenarios. The base-case estimate of the ICER of oseltamivir compared to standard care was sensitive to a number of key assumptions; namely:

- The exclusion of hospitalisation and mortality benefits with NI treatment.
- The probability ILI is influenza.
- The potential link between a positive recommendation, increased consultations with healthcare providers and the subsequent estimate that the probability ILI is influenza.
- The decrement applied to quantify the impact of influenza on quality of life and the assumption about where the mean reduction in symptom durations were being achieved (i.e. across the entire illness period or closer to the beginning or end of the illness) with NI treatment compared to standard care.

Finally, it is important to compare the results of the cost-effectiveness model presented here (referred to from this point onwards as the ‘York model’) with the key results from other relevant models (Turner (2003) and Roche (2008)) considered in detail earlier as part of the cost-effectiveness review section. This allows any major discrepancies to be identified and explained where possible. However, since the York model and Turner (2003) models were undertaken at different times, some of these differences will invariably simply reflect the guidance (e.g. choice of discount rate) or data (e.g. the costs of the NIs) relevant at a particular point, as opposed to different analytic approaches and/or assumptions.

Table 7.42 presents a comparison of results from the three different models in the particular populations considered in each. These are presented separately using the base-case set of assumptions in each and considering scenarios both including and excluding hospitalisation and mortality benefits. The ICER results from Turner (2003) have been re-estimated here employing similar decision rules to the York model, enabling a simultaneous comparison of both NIs and standard care. This contrasts with the separate pairwise comparisons originally presented by Turner (2003). Similarly, in the absence of results from the Roche model excluding hospitalisation and mortality benefits, these were re-estimated using the same

approach applied within the York model (i.e. by setting the probability of hospitalisation and influenza mortality to zero).

Table 7.42: Comparison of results from the different models, where results include hospitalisation and mortality benefits

Subgroup	ICER	
	Osetamivir	Zanamivir
York model		
Healthy children	£7,035	D
'At risk' children	ED	£1,752
Healthy adults	£5,521	D
'At risk' adults	ED	£2,270
Elderly	ED	£562
Turner (2003)		
Children	£11,381	D
'At risk' children	Not reported separately	Not reported separately
Healthy adults	£4,729	D
'At risk' adults	£3,205 vs. zanamivir	£3,016 vs. usual care
Residential care elderly	Dominated by zanamivir	Dominates usual care
Roche		
Children 1-5	£4,687	Not relevant comparator
Children 1-12	£5,992	D
'At risk' children	Not reported separately	Not reported separately
Healthy adults	£5,452	D
'At risk' adults	£652	D
Elderly	Not reported separately	Not reported separately

Despite the different structures and assumptions employed, the results of the York model and Turner (2003), including hospitalisation and mortality benefits, were broadly consistent in their findings for the comparable populations considered. Zanamivir was dominated by oseltamivir in both models in the healthy adult population. The subsequent ICERs for oseltamivir compared to standard care were also very similar for this population.

A similar finding was also observed in the healthy children population (York model) and the overall children population (Turner(2003)). The more favourable ICERs estimated in the York model were driven largely by the higher probability ILI is influenza applied therein (0.56 vs. 0.48), resulting in a higher proportion of children who are assumed to benefit from treatment with an NI.

The ICER estimates for the ‘at risk’ adult population also appeared very consistent across the two models. The more favourable results reported in the ‘residential care’ elderly population by Turner (2003) for zanamivir (which dominated both usual care and oseltamivir), compared to the ICER of £562 (zanamivir versus usual care) in the elderly population in the York model, is largely due to the higher underlying hospitalisation rate assumed in Turner (2003) for this specific setting (14% hospitalisation rate compared to 1.31% applied to the broader elderly population considered in the York model). No separate analysis of an ‘at risk’ children population was undertaken by either Turner (2003) or Roche.

Table 7.43: Comparison of results from the different models, where results exclude hospitalisation and mortality benefits

Subgroup	ICER	
	Osetamivir	Zanamivir
York model		
Healthy children	£7,852	D
‘At risk’ children	ED	£3,327
Healthy adults	£13,985	D
‘At risk’ adults	ED	£4,850
Elderly	ED	£4,763
Turner (2003)		
Children	£19,461	ED
‘At risk’ children	Not reported separately	Not reported separately
Healthy adults	£19,015	D
‘At risk’ adults	ED	£17,289
Residential care elderly	ED	£16,819
Roche*		
Children 1-5	£12,152	Not relevant comparator
Children 1-12	£18,144	D
‘At risk’ children	Not reported separately	Not reported separately
Healthy adults	£20,283	D
‘At risk’ adults	£8,937	D
Elderly	Not reported separately	Not reported separately

* Not presented by Roche – results based on Assessment Group re-analysis

Although Roche applied the most conservative estimate of the probability ILI is influenza (0.31 in all populations), their subsequent ICER results were the most favourable of the 3 models in each of the populations (with the exception of the ICER for otherwise healthy adults in which Turner (2003) reported the lowest ICER). Roche also consistently reported zanamivir to be dominated by oseltamivir in all populations considered, as opposed to the

York model and Turner (2003) which identified different NIs to be optimal depending upon the particular population.

The major set of assumptions leading to the more favourable ICERs reported in the Roche submission have previously been described in detail (e.g. in relation to QoL benefit related to symptoms, application of hospitalisation rates from the USA and estimates of the remaining life expectancy used in particular populations). These assumptions act in favour of NI treatment and more than offset the more conservative estimate applied to the probability ILI is influenza. The consistent finding that oseltamivir dominates zanamivir has previously been attributed to the assumption of equivalent clinical effectiveness for both oseltamivir and zanamivir and the error regarding the revised price of zanamivir.

The more favourable assumptions employed within the Roche submission in relation to particular aspects become more evident when the separate models are compared excluding the potential benefits of hospitalisation and mortality. In this scenario, the ICER estimates for the comparable populations based on the Roche model are now markedly less favourable than those from the equivalent set of results based on York model (demonstrating that the assumptions applied to these elements are key drivers of the base-case results presented by Roche).

The comparison between the York model and Turner (2003), excluding hospitalisations and mortality, reveals more marked variation between the ICER estimates than in the previous comparison. However, there is consistency in the optimal treatment identified across the separate populations at a threshold of £20,000 per QALY. Since hospitalisation and mortality benefits are excluded, the remaining differences in the ICER will largely be driven by the different approaches to quantifying the QALY gains due to symptomatic benefits (and also the lower cost of the NIs themselves based on current prices). There are 3 key elements which appear to explain the differences in the subsequent ICER estimates: (i) the higher estimate applied to the probability ILI is influenza in the York model for children (likely to lead to likely to lower ICERs in this population); (ii) the duration of symptoms and the data and methods employed; and (iii) the alternative approaches to valuing QALY gains due to symptomatic benefits.

In terms of the approaches used to estimate the mean symptom durations, there appear to be two main differences which may result in the subsequent differences in the ICERs. Firstly, the York model includes additional data published since the earlier appraisal. Secondly, different methods are employed within the separate reviews to estimate the mean duration of

symptoms. While the York model is based on a Bayesian synthesis of symptom data employing a Weibull distribution to estimate the mean duration from the median data reported in the RCTs, the model by Turner (2003) employs a more conventional meta-analysis with an exponential assumption to estimate mean durations. Despite the different approaches employed here, it is unlikely that differences in the alternative analytic approaches themselves are driving the resulting differences in the ICER. Rather, these differences are likely to be due to the approaches used to estimate the QALY gains attributed to reduction in the mean estimates of symptom duration.

We have previously noted that Turner (2003) use the TTO (VAS) data reported in a number of the oseltamivir trials as a direct input into their model. Hence, the overall differences reported across the entire 21-day TTO data are used to estimate the mean QALY gains associated with oseltamivir (compared to standard care). Consequently, the estimates of mean symptom duration synthesised from the wider set of RCTs are only used as a method to adjust the mean QALY gains estimated for oseltamivir in order to obtain the gains for zanamivir. Hence, while the relative differences in QALY gains between oseltamivir and zanamivir are informed by the wider set of RCTs considered in the earlier review, the absolute QALY gains associated with oseltamivir and standard care are derived entirely from the subset of the oseltamivir RCTs in which the VAS data was reported.

In contrast, the York model uses the results from the Bayesian synthesis as the basis for estimating the QALY gains for each of the NI treatments and standard care. This approach then employs the placebo TTO data as a 'baseline'. The mean duration of symptoms estimated from the synthesis for placebo is then used to estimate the corresponding 'average' decrement in utility over this period. The QALY gains for oseltamivir and zanamivir are then estimated based on the reductions in mean symptom duration reported for each treatment (i.e. the decrement is not applied to these additional days). Consequently the York model and Turner (2003) employ different assumptions and data to this aspect. In general, the York model will result in higher QALY gains, since invariably it will be based on mean symptom durations that are shorter than the 21-day data employed in the base-case analysis of Turner (2003). Consequently, the 'average' decrement will be greater than that considered by Turner (2003).

Hence, although the initial comparison of the York model and Turner (2003) including hospitalisation and mortality benefits, revealed largely consistent findings and also comparable ICER results, the differences observed in symptoms ultimately imply that these differences are offset by other assumptions in the Turner (2003) 'extrapolated' model. In the

children analysis this is likely to be due to the inclusion of complication data for both ‘at risk’ and healthy children in the population being considered by Turner (2003) resulting in a higher baseline risk than the ‘healthy’ children population considered in the York model. The remaining differences in the otherwise healthy and ‘at risk’ adult group are likely to be due to a number of different elements, including: the different probabilities that ILI is influenza (0.41 for adults in the York model and 0.46 in Turner (2003)); the different underlying hospitalisation rates assumed; the different relative risks employed as proxies for reduction in hospitalisation and mortality; and the different quality-adjusted life expectancies (QALE) applied to premature mortality.

Important differences were noted between the ‘at risk’ adult estimates for the remaining QALE. Although both approaches were based on general population estimates of remaining life expectancy – estimates applied in Turner (2003) (4.1 years; 1.5% discount rate) were markedly different from those employed by York (14.66 years; 3.5% discount rate). Indeed, the estimates used in Turner (2003) were more comparable to the estimates applied to the elderly population in the York model (4.20 years; 3.5% discount rate). In the earlier review section it was noted that the assumption employed in the ‘at risk’ population by Turner (2003) appeared to have derived from estimates from a population aged >65 years (estimates in the ‘at risk’ and residential care elderly populations were the same). Hence, the results for the ‘at risk’ group reported by Turner (2003) appear more representative of an elderly ‘at risk’ population.

Despite the differences noted in the modelling approaches, assumptions and data inputs, the results of the York model and those reported previously by Turner (2003) were consistent in their findings that the ICER estimates appear more favourable in ‘at risk’ populations compared to the otherwise healthy populations. Similarly, the various scenarios considered in both models demonstrate that the results in otherwise healthy populations were sensitive to a number of common issues and uncertainties.

8 Discussion

8.1 Statement of principal findings

8.1.1 Clinical evaluation

This review showed that treatment with zanamivir or oseltamivir, when compared to placebo, generally reduced the median duration of symptoms and median time to return to normal activity across all subgroups. Limited data were available on complication or adverse event rates, there is therefore considerable uncertainty around these effects, and little evidence of an overall impact of either drug on these outcomes. The most consistent data and strongest evidence related to antibiotic use, with both zanamivir and oseltamivir resulting in reductions in this outcome.

Comparisons with placebo

When compared to placebo, zanamivir reduced the median duration of symptoms by between approximately 0.5 and 1 day, and oseltamivir by between 0.5 and 1.5 days in healthy adults. The median reduction in the time taken to return to normal activity was about 0.5 days with zanamivir and 1.5 to 2.5 days with oseltamivir. Although these results were statistically significant, the absolute effects were small and their clinical significance in an otherwise healthy population questionable.

For the 'at risk' subgroups, effect sizes for differences in symptom duration were generally larger, and potentially more clinically significant, than those seen in healthy adults. However, there was greater uncertainty around these results with estimates often failing to reach statistical significance, although the direction of effect remained in favour of treatment with NIs. For the overall 'at risk' population, treatment reduced the median duration of symptoms by approximately 1 to 2 days with zanamivir, and by 0.5 to 0.75 days with oseltamivir. A similar pattern was seen in the time taken to return to normal activity, with the median time being between 1 and 2 days with zanamivir and 0.75 and 2.5 (data for 'at risk' adults only) days with oseltamivir.

Both this and the previous review by Turner (2003) found that zanamivir and oseltamivir generally reduced the median duration of symptoms and median time to return to normal activity when compared to placebo..

Data for adverse events and complication rates were inconsistently reported, and little overall difference between zanamivir or oseltamivir and placebo was observed. A considerable degree of uncertainty remains around these outcomes for all subgroups. The Turner (2003) review did not directly analyse data on complications or adverse effects.

We were unable to formally evaluate a number of associated clinical and implementation issues. Of primary importance is the impact of delayed initiation of treatment after the onset of symptoms, prior vaccination status, and the probability that a person presenting to their GP with an ILI had influenza (true positive rate (TPR)). Other issues that may also be important include the use of antipyretics and other symptomatic relief on the time to alleviation of fever and all symptoms, and antiviral resistance. There was insufficient evidence available to undertake a formal assessment of the impact of these on the clinical effectiveness of NIs and a thorough investigation of this would undoubtedly require obtaining individual patient data . While some of these factors have been explored further in the economic model (for example the impact of altering the TPR), additional investigation may be required.

A number of additional considerations that may also impact on the effectiveness and use of NIs became apparent during the course of the review. These included the incidence of bronchospams with zanamivir in people with underlying respiratory disease, the apparent emergence of resistance in the H1N1 influenza A subtype to oseltamivir over the 2007/8 influenza season, and the increase in neuropsychiatric events associated with oseltamivir that have been observed primarily in children which has resulted in a recent revision of the labelling of both oseltamivir and zanamivir for healthcare professional in the US. Furthermore, it has been suggested that during periods of increased influenza activity, the difficulty of obtaining a prescription within 48 hours could be addressed by community pharmacists assisting with dispensing medications, or the use of expectant treatment with NIs. While these particular issues were outside the scope of the review, some relate closely to the impact of delayed initiation of treatment after the onset of symptoms. A more formal evaluation of alternative management strategies should also be considered.

Bayesian multi-parameter evidence synthesis

In the absence of head-to-head trials comparing zanamivir and oseltamivir directly, and the lack of routinely available data on mean symptom duration required for the cost-effectiveness model, a separate Bayesian multi-parameter evidence synthesis of symptom data with indirect comparisons was conducted.

A comparison of the individual pair-wise results for active treatment versus placebo derived from the multi-parameter synthesis model with those from the standard meta-analyses indicated general consistency across the two approaches. However, the “borrowing of strength” and consideration of wider evidence provided by the multi-parameter synthesis model increased the precision of the subsequent estimates of effect sizes in particular populations.

Across all analyses and subgroups, the probability that an NI treatment was more effective than placebo was 100%. However, variation was observed across both clinical subgroups and the different sets of results (e.g. ITT vs. ITTI) in terms of which NI treatment had the highest probability of being ‘best’ (as measured by reduction in symptom duration). For healthy adults, oseltamivir consistently had a higher probability of being the better treatment, whilst for ‘at risk’ populations zanamivir consistently had a higher probability of being better. The results for the otherwise healthy children were more varied across the separate analyses due to the more limited data available. The strength of these findings needs to be considered against the overall findings of the clinical effectiveness review, the indirect nature of these comparisons and the clinical (and biological) plausibility of results.

8.1.2 Economic evaluation

The results from the Bayesian synthesis were combined with other relevant clinical effectiveness parameters (i.e. the relative treatment effect for complications) as well as other data related to costs and quality of life, in order to assess the cost-effectiveness of oseltamivir and zanamivir for the treatment of influenza.

The model considered the decision problem in the context of individuals presenting to a healthcare provider, who are eligible for treatment according to the respective licenses for each of the NIs. Cost-effectiveness estimates for influenza treatment were presented for 5 separate subgroups: (i) otherwise healthy children aged 1-14 years, (ii) ‘at risk’ children aged 1-14 years, (iii) otherwise healthy adults aged 15-64 years; (iv) ‘at risk’ adults aged 15-64 years and (v) elderly (aged 65 years or over). A base-case analysis was undertaken including both symptomatic benefits as well as potential benefits associated with reductions in hospitalisation and mortality. A series of scenarios were also employed to reflect a wide range of alternative assumptions (e.g. the exclusion of benefits attributed to reductions in hospitalisation and mortality).

The results from the base-case analysis demonstrated important variation across the separate populations in terms of the cost-effectiveness results. In general, the ICER estimates were more favourable in 'at risk' populations compared to the otherwise healthy populations. Within each of the separate 'at risk' populations considered, zanamivir appeared the optimal NI treatment based on cost-effectiveness considerations. This reflected the higher reduction in the mean duration of symptoms obtained with zanamivir for the 'at risk' groups, rather than differences attributed to a reduction in complications. In contrast, oseltamivir was considered the optimal NI treatment for healthy populations (both adults and children). This reflected the higher reduction in the mean duration of symptoms for oseltamivir, as well as the higher reduction in complications assumed in the economic model for this NI.

Despite the alternative parameters applied to estimate the relative effectiveness in terms of symptoms and complications for the individual NIs, the subsequent differences in terms of the absolute estimate of the mean costs and QALYs were relatively small across all populations.

Across the numerous scenarios considered, the overall conclusions and cost-effectiveness estimates in the 'at risk' populations appeared robust to a wider range of alternative assumptions. The ICER results appeared less robust in the otherwise healthy populations and cost-effectiveness estimates were potentially sensitive to a number of key aspects, including: whether hospitalisation and mortality benefits arise with NI treatment; the probability that a patient presenting to a health care provider actually has true influenza (since NI treatments were only assumed to be effective for these patients); the potential link between a positive recommendation, increased consultations with healthcare providers and the subsequent estimate of the probability that a patient has true influenza; and the assumptions related to the quality life impact attributed to a reduction in symptom duration.

The overall cost-effectiveness results appeared generally consistent with the findings reported in the earlier review by Turner (2003). Furthermore, the various scenarios considered in both models demonstrated a number of common issues and uncertainties leading to remaining uncertainties regarding the cost-effectiveness of NIs in the otherwise healthy populations. However, the ICER results for the 'at risk' populations reported here largely appeared more favourable overall and were more robust to alternative assumptions than in the earlier review. Indeed, the ICER estimates for the 'at risk' group remained below a threshold of £20,000 per QALY across all scenarios considered here with only one exception. In this instance, the probability that ILI is influenza in patients presenting to a GP had to be as low as 0.1 and potential benefits in terms of reductions in hospitalisation and mortality benefits had to be excluded.

The robustness of the overall cost-effectiveness results in the 'at risk' population and with particular reference to the underlying probability that ILI is influenza raises some important policy issues. Clearly the current model has considered the cost-effectiveness of NI treatment in accordance with the current licenses of the treatments and hence for periods in which influenza is reported to be 'circulating in the community' by appropriate surveillance schemes. Within the model considered here, this has been interpreted using the current national threshold of 30 per 100,000 consultations. Hence, the probability estimate applied in the economic model was derived from RCGP data (2003/04 to 2006/07) for those weeks in which this threshold was met or exceeded. However, it should be recognised that this threshold was only reached for a total of 21 weeks across the period 2003/04 to 2006/07 (i.e. an average of 5.25 weeks in each season). The robustness of the cost-effectiveness results in 'at risk' groups to markedly lower estimates of the probability that ILI is influenza clearly poses the question of whether adopting a lower threshold could be a cost-effective approach to the management of influenza with NIs in the 'at risk' population. Clearly, any alternative to the current 'threshold' approach would need to ensure that the probability that ILI is influenza remains sufficiently high to ensure that subsequent treatment is still cost-effective. However, re-analysis of the RCGP data for the period 2003/04 to 2006/07 across all weeks of the influenza season (i.e. not just those weeks in which the threshold had been met) using the same 'hierarchical' approach employed as part of the base-case analysis, revealed that the probability that ILI is influenza was, on average, 0.29 (ranging from between 0.26 and 0.34 in the separate populations considered). The cost-effectiveness results for the 'at risk' populations demonstrated that ICER estimates remained below £20,000 per QALY when these alternative probabilities were employed.

A formal consideration of the full range of potential strategies (including alternative thresholds) for the management of influenza was not possible within the constraints of this review. There remain a number of important issues, particularly related to the management of 'at risk' populations, which could be evaluated using cost-effectiveness analysis. A broader analysis could consider a wide range of possible strategies including those already highlighted such as the use of community pharmacists, near-patient testing and also 'expectant' treatment.

8.2 Strengths and limitations of the assessment

8.2.1 Strengths

We conducted a comprehensive and rigorous systematic review which addressed a clear research question using predefined inclusion criteria. Extensive literature searches were undertaken to locate all relevant studies, both published and unpublished, in any language. Efforts were made to contact authors and publishers to identify further studies and obtain additional information to ensure as many studies could be included in the meta-analyses as possible. The study selection, data extraction, and quality assessment were conducted in duplicate, reducing the potential for error and bias. Subgroups of interest were identified *a priori* and analyses were pre-planned.

Compared to the previous review by Turner (2003), the current review included a larger body of evidence. Data were sought from a wider range of sources (e.g. FDA medical reviews); fourteen additional studies were included, six RCTs of zanamivir (three in healthy adults, one in the elderly, one in ‘at risk’ adults and one in children which included a minority of ‘at risk’ participants) and eight of oseltamivir (four in healthy adults, one in an ‘at risk’ population of undefined age, one in ‘at risk’ children and two in adult populations which included both healthy and ‘at risk’ individuals). In addition, data on influenza-related complications and adverse events were systematically reviewed and meta-analyses were undertaken where appropriate.

In the absence of head-to-head evidence on the relative effectiveness of the alternative antiviral treatments, an indirect comparison was also undertaken using Bayesian approaches to characterise the joint distribution of the efficacy of the antiviral treatments in terms of symptom duration. These estimates were subsequently used to inform the independent economic model which provided an overall framework for combining data from the synthesis of symptom outcomes, with the wider data on complications and other relevant parameters required for cost-effectiveness considerations.

8.2.2 Limitations

By necessity, this appraisal is limited by the data that could be extracted from published reports or provided by companies. Although the majority of included studies were described as randomised, double blind, details of the methods of randomisation, allocation concealment, and particularly blinding, were poorly reported; two trials were reported being open label. Many trials were small and several recruited very small numbers of participants from each

participating centre, often spanning several countries or continents. Most trials had short follow-up periods of either 21 or 28 days, which were inadequate to fully assess the rates of complications, hospitalisation and mortality. Despite this, there was often incomplete follow up with losses to follow-up of more than 5% in approximately 25% of included studies. There is therefore uncertainty in the estimates of effectiveness in alleviation of symptoms and time to return to normal activity within some subgroups, particularly for the ‘at risk’ groups. Information on complications and adverse events was inconsistently reported and data were sparse. No trial recruited a population representative of the currently licensed population for the respective drug, limiting the ability to draw general conclusions about the use of antiviral drugs in the licensed population.

8.3 Uncertainties

The main areas of outstanding uncertainty are:

- The impact of NI treatments on the rates of complications, hospitalisation and mortality associated with influenza.
- The uncertainty surrounding the effect size of antiviral drugs in ‘at risk’ populations.
- The relative effectiveness of the separate NIs.
- The probability that a patient presenting to a healthcare provider has true influenza as opposed to other ILI and the impact of this upon clinical and cost-effectiveness of NIs.
- The impact on quality of life of influenza symptoms and the relative effect of NI treatments on this aspect.

8.4 Conclusions

8.4.1 Implications for service provision

The overall clinical and cost-effectiveness results appeared generally consistent with the findings reported in the earlier review by Turner (2003).

Zanamivir and oseltamivir reduced the median duration of symptoms and median time to return to normal activity, when compared to placebo, in all populations assessed, though effect size estimates were subject to greater uncertainty in ‘at risk’ subgroups. Where data were available for adverse events and complication rates, there was little overall difference associated with the use of either zanamivir or oseltamivir when compared individually to placebo; the most consistent data and strongest evidence related to antibiotic use, with both zanamivir and oseltamivir resulting in statistically significant reductions in antibiotic use.

In general, the cost-effectiveness estimates were more favourable in ‘at risk’ populations compared to the otherwise healthy populations, as well as being more robust to a range of alternative assumptions (e.g. variation of the probability that ILL is influenza and whether hospitalisation and mortality benefits arise with NI treatment). Within each of the separate ‘at risk’ populations considered, zanamivir appeared the optimal NI treatment based on cost-effectiveness considerations. In contrast, oseltamivir was considered the optimal NI treatment for healthy populations (both adults and children). However, the overall differences between the NIs, in terms of the absolute estimates of both costs and outcomes, were minor across all populations.

8.4.2 Recommendations for research

A well-designed, adequately powered head-to-head trial (with a placebo arm), in a representative ‘at risk’ population (with sufficient follow-up time to also evaluate complications) would reduce the uncertainty around the estimates of clinical effectiveness of antiviral drugs in this population. However, the conduct of such a trial would need to be carefully assessed in terms of the cost-effectiveness of the research itself, as well as the potential feasibility and ethical issues (i.e. the inclusion of a placebo arm) which may arise. Well-designed observational studies might also be considered to evaluate the impact of NI treatments on complications, hospitalisation and mortality as well as quality of life.

Additional detailed consideration of the existing evidence related to the impact of delayed initiation of treatment after the onset of symptoms would also be potentially valuable research. This could be undertaken in conjunction with a more formal evaluation of the clinical and cost-effectiveness of alternative management strategies that could be used to reduce this delay (e.g. expectant treatment).

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10 Appendices

10.1 Literature search strategies

10.1.1 Clinical effectiveness

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16. relenza\$.ti,ab.
17. (gg167 or gg 167).mp.
18. (gr121167 or gr 121167 or gr 121167x or gr121167x).mp.
19. 139110-80-8.mn.
20. or/14-19
21. oseltamivir\$.ti,ab,rn.
22. tamiflu\$.ti,ab.
23. (gs4104 or gs 4104).mp.
24. (gs4171 or gs 4171 or gs4071 or gs 4071).mp.
25. (ro-0796 or ro0796 or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802).mp.
26. or/21-25
27. Neuraminidase/
28. ((neuraminidase or sialidase) adj2 (inhibit\$ or antagonist\$)).ti,ab.
29. (NA adj2 (inhibit\$ or antagonist\$)).ti,ab.
30. or/27-29
31. Amantadine/
32. amantadin\$.ti,ab.
33. (symmetrel or symetrel).ti,ab.
34. lysovir.ti,ab.
35. aminoadamantane.ti,ab.
36. adamantylamine.ti,ab.
37. adekin.ti,ab.
38. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu).ti,ab.
39. amixx.ti,ab.
40. cerebamed.ti,ab.
41. endantadine.ti,ab.
42. (gen-amantadine or genamantadine or pms-amantadine or pmsamantadine).ti,ab.
43. (infecto-flu or infectoflu).ti,ab.

44. infex.ti,ab.
45. (mantadix or midantan).ti,ab.
46. symadine.ti,ab.
47. (viregyt or wiregyt).ti,ab.
48. virofral.ti,ab.
49. tregor.ti,ab.
50. 768-94-5.rn.
51. or/31-50
52. 8 and 13 and (20 or 26 or 30 or 51)
53. Animals/
54. Humans/
55. 53 not (53 and 54)
56. 52 not 55
57. (200110\$ or 200111\$ or 200112\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).ed
58. 56 and 57

Trials Filter:

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;94(2):130-6.

EMBASE (OVID gateway). 2001-2007/week 46. 23rd November 2007.
580 records were retrieved.

1. random.tw.
2. clinical trial.mp.
3. exp Health Care Quality/
4. or/1-3
5. exp Influenza/
6. influenza\$.ti,ab.
7. flu.ti,ab.
8. grippe.ti,ab.
9. or/5-8
10. Zanamivir/
11. zanamivir\$.ti,ab.
12. relenza\$.ti,ab.
13. (gg167 or gg 167).mp.
14. (gr121167 or gr 121167 or gr 121167x or gr121167x).mp.
15. 139110 80 8.rn.
16. or/10-15
17. Oseltamivir/
18. oseltamivir\$.ti,ab.
19. tamiflu\$.ti,ab.
20. (gs4104 or gs 4104).mp.
21. (gs4171 or gs 4171 or gs4071 or gs 4071).mp.
22. (ro-0796 or ro0796 or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802).mp.
23. or/17-22
24. Sialidase Inhibitor/
25. ((neuraminidase or sialidase) adj2 (inhibit\$ or antagonist\$)).ti,ab.
26. (NA adj2 (inhibit\$ or antagonist\$)).ti,ab.
27. or/24-26
28. Amantadine/
29. amantadin\$.ti,ab.
30. (symmetrel or symetrel).ti,ab.

31. lysovir.ti,ab.
32. aminoadamantane.ti,ab.
33. adamantylamine.ti,ab.
34. adekin.ti,ab.
35. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu).ti,ab.
36. amixx.ti,ab.
37. cerebramed.ti,ab.
38. endantadine.ti,ab.
39. (gen-amantadine or genamantadine or pms-amantadine or pmsamantadine).ti,ab.
40. (infecto-flu or infectoflu).ti,ab
41. infex.ti,ab.
42. (mantadix or midantan).ti,ab.
43. symadine.ti,ab.
44. (viregyt or wiregyt).ti,ab.
45. virofral.ti,ab.
46. tregor.ti,ab.
47. 768 94 5.rn.
48. or/28-47
49. 4 and 9 and (16 or 23 or 27 or 48)
50. Animal/ or Animal Experiment/ or Nonhuman/
51. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
52. or/50-51
53. exp Human/ or Human Experiment/
54. 52 not (52 and 53)
55. 49 not 54
56. (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).em
57. 55 and 56

Trials Filter:

Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association* 2006;94(1):41-7.

CINAHL (OVID gateway). 2001/Oct-2007/Nov week 2. 23rd November 2007.

61 records were retrieved.

1. exp prognosis/
2. exp study design/
3. random.mp.
4. or/1-3
5. Influenza/
6. influenza\$.ti,ab.
7. flu.ti,ab.
8. grippe.ti,ab.
9. or/5-8
10. zanamivir\$.ti,ab.
11. relenza\$.ti,ab.
12. (gg167 or gg 167).mp.
13. (gr121167 or gr 121167 or gr 121167x or gr121167x).mp.
14. 139110-80-8.mp.
15. or/10-14
16. oseltamivir\$.ti,ab.
17. tamiflu\$.ti,ab.

18. (gs4104 or gs 4104).mp.
19. (gs4171 or gs 4171 or gs4071 or gs 4071).mp.
20. (ro-0796 or ro0796 or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802).mp.
21. or/16-20
22. ((neuraminidase or sialidase) adj2 (inhibit\$ or antagonist\$)).ti,ab.
23. (NA adj2 (inhibit\$ or antagonist\$)).ti,ab.
24. 22 or 23
25. Amantadine/
26. amantadin\$.ti,ab.
27. (symmetrel or symetrel).ti,ab.
28. lysovir.ti,ab.
29. aminoadamantane.ti,ab.
30. adamantylamine.ti,ab.
31. adamantylamine.ti,ab.
32. adekin.ti,ab.
33. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu).ti,ab.
34. amixx.ti,ab.
35. cerebamed.ti,ab.
36. endantadine.ti,ab.
37. (gen-amantadine or genamantadine or pms-amantadine or pmsamantadine).ti,ab.
38. (infecto-flu or infectoflu).ti,ab.
39. infex.ti,ab.
40. (mantadix or midantan).ti,ab.
41. symadine.ti,ab.
42. (viregyt or wiregyt).ti,ab.
43. virofral.ti,ab.
44. tregor.ti,ab.
45. 768-94-5.mp.
46. or/25-45
47. 4 and 9 and (15 or 21 or 24 or 46)
48. (200110\$ or 200111\$ or 200112\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).ew.
49. 47 and 48

Trials Filter:

McMaster University. Health Information Research Unit (HiRU). Evidence-Based Informatics. Hedges Project.

Search strategies for CINAHL: therapy.

http://hiru.mcmaster.ca/hiru/HIRU_Hedges_CINAHL_Strategies.htm

Science Citation Index (Web of Science). 2001-2007/Nov 22nd. 23rd November 2007.
249 records were retrieved.

#1 TS=(clinical* SAME trial*)

#2 TS=(controlled SAME trial*) OR TS=(controlled SAME stud*)

#3 TS=(random OR randomisation OR randomization OR randomized or randomised)

#4 TS=(singl* or doubl* or tripl* or trebl*) SAME TS=(mask* or blind*)

#5 TS=placebo*

#6 #1 or #2 or #3 or #4 or #5

#7 TS=(influenza* or flu or grippe)

#8 TS=(zanamivir* or relenza*)

#9 TS=(oseltamivir* or tamiflu*)

#10 TS=(neuraminidase or sialidase or NA) SAME TS=(inhibit* or antagonist*)

#11 TS=(neuraminidase or sialidase) SAME TS=(inhibitor* or antagonist*)

#12 TS=(amantadin* or symmetrel or symetrel or lysovir)

#13 TS=(aminoadamantane or adamantylamine or adekin or aman or amanta*)
 #14 TS=(amixx or cerebramed or endantadine or infecto-flu or infectoflu or infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor)
 #15 #8 or #9 or #10 or #11 or #12 or #13 or #14
 #16 #6 and #7 and #15
 Timespan=2001-2007

CDSR and CENTRAL (Cochrane Library). 2001-2007:Issue 4. 23rd November 2007.

17 reviews were retrieved in CDSR and 56 records in CENTRAL.

- #1 MeSH descriptor Influenza, Human explode all trees
- #2 (influenza* or flu or grippe)
- #3 (#1 OR #2)
- #4 MeSH descriptor Zanamivir explode all trees
- #5 (zanamivir* or relenza*)
- #6 (gg167 or "gg 167" or gg-167 or gr121167 or "gr 121167" or gr-121167 or gr 121167x or gr121167x)
- #7 (139110-80-8 or 139110808 or "139110 80 8")
- #8 (#4 OR #5 OR #6 OR #7)
- #9 (oseltamivir* or tamiflu*)
- #10 (gs4104 or "gs 4104" or gs-4104)
- #11 (gs4171 or "gs 4171" or gs-4171)
- #12 (ro-0796 or ro0796 or "ro 0796" or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802)
- #13 (#9 OR #10 OR #11 OR #12)
- #14 MeSH descriptor Neuraminidase explode all trees
- #15 (neuraminidase or sialidase) NEAR/2 (inhibit* or antagonist*)
- #16 NA NEAR/2 (inhibit* or antagonist*)
- #17 (#14 OR #15 OR #16)
- #18 MeSH descriptor Amantadine explode all trees
- #19 (amantadin* or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin)
- #20 (aman or amanta or amanta-hci-azu or amanta-sulfate-azu or amixx or cerebramed or endantadine)
- #21 (gen-amantadine or pms-amantadine or genamantadine or pmsamantadine or infecto-flu or infectoflu or infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor)
- #22 (768-94-5 or 768945 or "768 94 5")
- #23 (#18 OR #19 OR #20 OR #21 OR #22)
- #24 (#3 AND (#8 OR #13 OR #17 OR #23)), from 2001 to 2007

DARE and HTA (CRD Internal Databases). 2001-2007/10. 23rd November 2007.

6 records were retrieved in DARE and 15 records were retrieved in HTA.

s influenza\$ or flu or grippe
 s zanamivir\$ or relenza\$
 s oseltamivir\$ or tamiflu\$
 s (neuraminidase or sialidase)(w2)(inhibit\$ or antagonist\$) or NA(w2)(inhibitor\$ or antagonist\$)
 s amantadin\$ or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin or aman or amanta\$ or amixx or cerebramed or endantadine or infecto(w)flu or infectoflu or infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor
 s s1 and (s2 or s3 or s4 or s5)
 s 2001/xyr or 2002/xyr or 2003/xyr or 2004/xyr or 2005/xyr or 2006/xyr or 2007/xyr

s s6 and s7

LILACS (Birme Virtual Health Library). 2001-2007/Oct. 23rd November 2007.

0 records were retrieved.

(clinical\$ trial\$) or (controlled trial\$) or (controlled stud\$) or random OR randomisation OR randomization OR randomized or randomised or (singl\$ blind\$) or (singl\$ mask\$) or (doubl\$ blind\$) or (doubl\$ mask\$) or (tripl\$ blind\$) or (tripl\$ mask\$) or (trebl\$ blind\$) or (trebl\$ mask\$) or placebo\$ or crossover or evaluation or (prospective stud\$) or (comparative stud\$) or (phase 4) or (phase four) or (phase IV) or (post market\$ surveillance)[words]

AND

Influenza\$ or flu or grippe [words]

AND

zanamivir\$ or relenza\$ or oseltamivir\$ or tamiflu\$ or (neuraminidase inhibit\$) or (sialidase inhibit\$) or (neuraminidase antagonist\$) or (sialidase antagonist\$) or amantadin\$ or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin or aman or amanta or amixx or cerebramed or endantadine or (gen amantadine) or genamantadine or (pms amantadine) or pmsamantadine or (infecto flu) or infectoflu or infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor [words]

BIOSIS (Dialog). 2001-2007/Nov week 4. 29th November 2007.

89 records were retrieved.

s clinical(2w)trial?

s controlled(2w)(trial? or stud?)

s random or randomi?ation or randomi?ed

s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)

s placebo?

s (prospective(2w)stud?) or (comparative(2w)stud?)

s phase(w)4 or phase(w)four or phase(w)IV

s post(w)market?(w)surveillance

s s1:s8

s influenza? or flu or grippe

s zanamivir? or relenza?

s oseltamivir? or tamiflu?

s (neuraminidase or sialidase or NA)(2n)(inhibit? or antagonist?)

s amantadin? or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin or aman or amanta or amixx or cerebramed or endantadine or gen(w)amantadine or genamantadine or pms(w)amantadine or pmsamantadine or infecto(w)flu or infectoflu or infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor

s s11:s14

s s9 and s10 and s15

s s16/2001-2007

Pascal (Dialog). 2001-2007/Nov week 2. 29th November 2007.

33 records were retrieved.

s clinical(2w)trial?

s controlled(2w)(trial? or stud?)

s random or randomi?ation or randomi?ed

s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)

s placebo?

s (prospective(2w)stud?) or (comparative(2w)stud?)

s phase(w)4 or phase(w)four or phase(w)IV

s post(w)market?(w)surveillance

s s1:s8
s influenza? or flu or grippe
s zanamivir? or relenza?
s oseltamivir? or tamiflu?
s (neuraminidase or sialidase or NA)(2n)(inhibit? or antagonist?)
s amantadin? or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or
adekin or aman or amanta or amixx or cerebramed or endantadine or gen(w)amantadine or
genamantadine or pms(w)amantadine or pmsamantadine or infecto(w)flu or infectoflu or
infex or mantadix or midantan or symadine or viregyt or wiregyt or virofral or tregor
s s11:s14
s s9 and s10 and s15
s s16/2001-2007

Dissertation Abstracts (Dialog). 2001-2007/August. 29th November 2007.

0 records were retrieved.

s clinical(2w)trial?
s controlled(2w)(trial? or stud?)
s random or randomi?ation or randomi?ed
s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
s placebo?
s (prospective(2w)stud?) or (comparative(2w)stud?)
s phase(w)4 or phase(w)four or phase(w)IV
s post(w)market?(w)surveillance
s s1:s8
s influenza? or flu or grippe
s zanamivir? or relenza?
s oseltamivir? or tamiflu?
s (neuraminidase or sialidase or NA)(2n)(inhibit? or antagonist?)
s amantadin? or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or
adekin or aman or amanta or amixx or cerebramed or endantadine or gen(w)amantadine or
genamantadine or pms(w)amantadine or pmsamantadine or infecto(w)flu or infectoflu or
infex or mantadix or midantan or symadine or viregyt or wiregyt or virofral or tregor
s s11:s14
s s9 and s10 and s15
s s16/2001-2007

Inside Conferences (Dialog). 2001-2007/Nov 28th. 29th November 2007.

1 record was retrieved.

s clinical(2w)trial?
s controlled(2w)(trial? or stud?)
s random or randomi?ation or randomi?ed
s (singl? or doubl? or tripl? or trebl?)(2w)(mask? or blind?)
s placebo?
s (prospective(2w)stud?) or (comparative(2w)stud?)
s phase(w)4 or phase(w)four or phase(w)IV
s post(w)market?(w)surveillance
s s1:s8
s influenza? or flu or grippe
s zanamivir? or relenza?
s oseltamivir? or tamiflu?
s (neuraminidase or sialidase or NA)(2n)(inhibit? or antagonist?)
s amantadin? or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or
adekin or aman or amanta or amixx or cerebramed or endantadine or gen(w)amantadine or

genamantadine or pms(w)amantadine or pmsamantadine or infecto(w)flu or infectoflu or infex or mantadix or midantan or symadine or viregyt or wiregyt or virofral or tregor
s s11:s14
s s9 and s10 and s15
s s16/2001-2007

TOXLINE. (TOXNET – US National Library of Medicine). 2001-2007/Nov 30th. 30th November 2007.

202 records were retrieved.

- # 1 influenza
- # 2 zanamivir
- # 3 relenza
- # 4 oseltamivir
- # 5 tamiflu
- # 6 neuraminidase
- # 7 amantadine
- # 8 symmetrel
- # 9 aminoadamantane aminoadamantanes
- # 10 aman
- # 11 mantadix
- # 12 midantan
- # 13 symadine
- # 14 viregyt
- # 15 139110-80-8 [rn]
- # 16 768-94-5 [rn]
- # 17 (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16)
- # 18 (#1 AND #17)
- # 19 AND 2001:2007 [yr]
- # 20 (#18 AND #19)

National Research Register. (Update Software). 2001-2007/Issue 4. 29th November 2007.

12 records were retrieved.

- #1. INFLUENZA HUMAN explode all trees (MeSH)
- #2. (influenza* or flu or grippe)
- #3. (#1 or #2)
- #4. (zanamivir* or relenza*)
- #5. (gg167 or gg-167 or gr121167 or gr-121167 or (gr next 121167x) or gr121167x)
- #6. (139110-80-8 or 139110808)
- #7. (oseltamivir* or tamiflu*)
- #8. (gs4104 or gs-4104)
- #9. (gs4171 or gs-4171)
- #10. (ro-0796 or ro0796 or ro64-0796 or (ro next 64-0796) or ro64-0802 or ro640802)
- #11. NEURAMINIDASE single term (MeSH)
- #12. ((neuraminidase near inhibit*) or (neuraminidase near antagonist*))
- #13. ((sialidase near inhibit*) or (sialidase near antagonist*))
- #14. ((na near inhibit*) or (na near antagonist*))
- #15. AMANTADINE explode tree 1 (MeSH)
- #16. (amantadin* or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin)
- #17. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu or amixx or cerebramed or endantadine)

#18. (gen-amantadine or pms-amantadine or genamantadine or pmsamantadine or infecto-flu or infectoflu or infex or mantadix or midantan or symadine or viregyt or wiregyt or virofral or tregor)

#19. (768-94-5 or 768945)

#20. (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19)

#21. (#3 and #20)

ClinicalTrials.gov. (US National Library of Medicine). 2007/Nov. 30th November 2007.
16 records were retrieved.

Each line searched separately

(zanamivir OR relenza) AND influenza

(oseltamivir OR tamiflu) AND influenza

(neuraminidase OR sialidase) AND influenza

(amantadine OR symmetrel OR symetrel OR lysovir OR aminoadamantane OR adamantylamine OR adekin OR aman OR amanta) AND influenza

(amixx OR cerebramed OR endantadine OR infecto-flu OR infex OR mantadix OR midantan OR symadine OR viregyt OR wiregyt OR virofral OR tregor) AND influenza

Current Controlled Trials (MetaRegister of Current Controlled Trials - mRCT).
2007/Nov. 30th November 2007.

21 records were retrieved.

Each line searched separately

(zanamivir OR relenza) AND influenza

(oseltamivir OR tamiflu) AND influenza

(neuraminidase OR sialidase) AND influenza

(amantadine OR symmetrel OR symetrel OR lysovir OR aminoadamantane OR adamantylamine OR adekin OR aman OR amanta) AND influenza

(amixx OR cerebramed OR endantadine OR “infecto-flu” OR infex OR mantadix OR midantan OR symadine OR viregyt OR wiregyt OR virofral OR tregor) AND influenza

ClinicalStudyResults.org (ClinicalStudyResults website). 2007/Nov. 30th November 2007.

5 records were retrieved.

Each line searched separately

zanamivir

relenza

oseltamivir

tamiflu

(neuraminidase OR sialidase) AND influenza

amantadine

ClinicalTrialResults.org (Clinical Trial Results website). 2007/Nov. 30th November 2007.

0 records were retrieved.

Each line searched separately

zanamivir

relenza

oseltamivir

tamiflu

(neuraminidase OR sialidase) AND influenza
amantadine

International Clinical Trials Registry Platform (ICTRP). 2007/Nov. 30th November 2007.

12 records were retrieved.

Each line searched separately
zanamivir influenza [All words match]
relenza influenza [All words match]
oseltamivir influenza [All words match]
tamiflu [All words match]
neuraminidase influenza [All words match]
sialidase influenza [All words match]

GlaxoSmithKline Clinical Trial Register. 2007/Nov. 30th November 2007.

23 records were retrieved.

Zanamivir studies

Roche Clinical Trial Protocol Registry and Results Database. 2007/Nov. 30th November 2007.

4 protocol and 5 trial records were retrieved.

oseltamivir [Tamiflu]
Tamiflu [oseltamivir]

Supplementary search: influenza season 2007-2008 drug resistance

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OvidSP). 2007-2008/May week 4. 6th June 2008.

54 records were retrieved in MEDLINE and 41 in MEDLINE In-Process & Other Non-Indexed Citations.

1. Influenza, Human/
2. influenza\$.ti,ab.
3. flu.ti,ab.
4. grippe.ti,ab.
5. or/1-4
6. Zanamivir/
7. zanamivir\$.ti,ab.
8. relenza\$.ti,ab.
9. (gg167 or gg 167).mp.
10. (gr121167 or gr 121167 or gr 121167x or gr121167x).mp.
11. 139110-80-8.rn.
12. or/6-11
13. oseltamivir\$.ti,ab,rn.
14. tamiflu\$.ti,ab.
15. (gs4104 or gs 4104).mp.
16. (gs4171 or gs 4171 or gs4071 or gs 4071).mp.
17. (ro-0796 or ro0796 or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802).mp.
18. or/13-17

19. Neuraminidase/
20. ((neuraminidase or sialidase) adj2 (inhibit\$ or antagonist\$)).ti,ab.
21. (NA adj2 (inhibit\$ or antagonist\$)).ti,ab.
22. or/19-21
23. Amantadine/
24. amantadin\$.ti,ab.
25. (symmetrel or symetrel).ti,ab.
26. lysovir.ti,ab.
27. aminoadamantane.ti,ab.
28. adamantylamine.ti,ab.
29. adekin.ti,ab.
30. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu).ti,ab.
31. amixx.ti,ab.
32. cerebramed.ti,ab.
33. endantadine.ti,ab.
34. (gen-amantadine or genamantadine or pms-amantadine or pmsamantadine).ti,ab.
35. (infecto-flu or infectoflu).ti,ab.
36. infex.ti,ab.
37. (mantadix or midantan).ti,ab.
38. symadine.ti,ab.
39. (viregyt or wiregyt).ti,ab.
40. virofral.ti,ab.
41. tregor.ti,ab.
42. 768-94-5.rn.
43. or/23-42
44. 5 and (12 or 18 or 22 or 43)
45. Animals/
46. Humans/
47. 45 not (45 and 46)
48. 44 not 47
49. exp Drug Resistance, Viral/
50. (resist or resists or resistance or resistances or resistant or resisted).mp.
51. 49 or 50
52. 48 and 51
53. (200709\$ or 200710\$ or 200711\$ or 200712\$ or 2008\$).ed.
54. 52 and 53

EMBASE (OvidSP). 2007-2008/week 22. 6th June 2008.

61 records were retrieved.

1. exp Influenza/
2. influenza\$.ti,ab.
3. flu.ti,ab.
4. grippe.ti,ab.
5. or/1-4
6. Zanamivir/
7. zanamivir\$.ti,ab.
8. relenza\$.ti,ab.
9. (gg167 or gg 167).mp.
10. (gr121167 or gr 121167 or gr 121167x or gr121167x).mp.
11. 139110 80 8.rn.
12. or/6-11
13. Oseltamivir/
14. oseltamivir\$.ti,ab.
15. tamiflu\$.ti,ab.

16. (gs4104 or gs 4104).mp.
17. (gs4171 or gs 4171 or gs4071 or gs 4071).mp.
18. (ro-0796 or ro0796 or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802).mp.
19. or/13-18
20. Sialidase Inhibitor/
21. ((neuraminidase or sialidase) adj2 (inhibit\$ or antagonist\$)).ti,ab.
22. (NA adj2 (inhibit\$ or antagonist\$)).ti,ab.
23. or/20-22
24. Amantadine/
25. amantadin\$.ti,ab.
26. (symmetrel or symetrel).ti,ab.
27. lysovir.ti,ab.
28. aminoadamantane.ti,ab.
29. adamantylamine.ti,ab.
30. adekin.ti,ab.
31. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu).ti,ab.
32. amixx.ti,ab.
33. cerebramed.ti,ab.
34. endantadine.ti,ab.
35. (gen-amantadine or genamantadine or pms-amantadine or pmsamantadine).ti,ab.
36. (infecto-flu or infectoflu).ti,ab.
37. infex.ti,ab.
38. (mantadix or midantan).ti,ab.
39. symadine.ti,ab.
40. (viregyt or wiregyt).ti,ab.
41. virofral.ti,ab.
42. tregor.ti,ab.
43. 768 94 5.rn.
44. or/24-43
45. 5 and (12 or 19 or 23 or 44)
46. exp drug resistance/
47. (resist or resists or resistance or resistances or resistant or resisted).mp.
48. 46 or 47
49. 45 and 48
50. Animal/ or Animal Experiment/ or Nonhuman/
51. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
52. 50 or 51
53. exp Human/ or Human Experiment/
54. 52 not (52 and 53)
55. 49 not 54
56. ("200736" or "200737" or "200738" or "200739" or "200740" or "200741" or "200742" or "200743" or "200744" or "200745" or "200746" or "200747" or "200748" or "200749" or "200750" or "200751" or "200752").em.
57. 2008\$.em.
58. 56 or 57
59. 55 and 58

10.1.2 Cost-effectiveness

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OVID gateway). 2001/Oct-2007/Nov week 2. 5th December 2007.

103 records were retrieved in MEDLINE and 3 in MEDLINE In-Process & Other Non-Indexed Citations.

1. economics/
2. exp "costs and cost analysis"/
3. economics, dental/
4. exp "economics, hospital"/
5. economics, medical/
6. economics, nursing/
7. economics, pharmaceutical/
8. (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic\$).tw.
9. (expenditure\$ not energy).tw.
10. (value adj1 money).tw.
11. budget\$.tw.
12. or/1-11
13. ((energy or oxygen) adj cost).ti,ab.
14. (metabolic adj cost).ti,ab.
15. ((energy or oxygen) adj expenditure).ti,ab.
16. or/13-15
17. 12 not 16
18. Influenza, Human/
19. influenza\$.ti,ab.
20. flu.ti,ab.
21. grippe.ti,ab.
22. or/18-21
23. Zanamivir/
24. zanamivir\$.ti,ab.
25. relenza\$.ti,ab.
26. (gg167 or gg 167).mp.
27. (gr121167 or gr 121167 or gr 121167x or gr121167x).mp.
28. 139110-80-8.rm.
29. or/23-28
30. oseltamivir\$.ti,ab,rn.
31. tamiflu\$.ti,ab.
32. (gs4104 or gs 4104).mp.
33. (gs4171 or gs 4171 or gs4071 or gs 4071).mp.
34. (ro-0796 or ro0796 or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802).mp.
35. or/30-34
36. Neuraminidase/
37. ((neuraminidase or sialidase) adj2 (inhibit\$ or antagonist\$)).ti,ab.
38. (NA adj2 (inhibit\$ or antagonist\$)).ti,ab.
39. or/36-38
40. Amantadine/
41. amantadin\$.ti,ab.
42. (symmetrel or symetrel).ti,ab.
43. lysovir.ti,ab.
44. aminoadamantane.ti,ab.
45. adamantylamine.ti,ab.
46. adekin.ti,ab.

47. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu).ti,ab.
48. amixx.ti,ab.
49. cerebramed.ti,ab.
50. endantadine.ti,ab.
51. (gen-amantadine or genamantadine or pms-amantadine or pmsamantadine).ti,ab.
52. (infecto-flu or infectoflu).ti,ab.
53. infex.ti,ab.
54. (mantadix or midantan).ti,ab.
55. symadine.ti,ab.
56. (viregyt or wiregyt).ti,ab.
57. virofral.ti,ab.
58. tregor.ti,ab.
59. 768-94-5.rn.
60. or/40-59
61. 17 and 22 and (29 or 35 or 39 or 60)
62. Animals/
63. Humans/
64. 62 not (62 and 63)
65. 61 not 64
66. (200110\$ or 200111\$ or 200112\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).ed
67. 65 and 66

EMBASE (OVID gateway). 2001-2007/week 48. 5th December 2007.

276 records were retrieved.

1. Health Economics/
2. exp Economic Evaluation/
3. exp Health Care Cost/
4. exp PHARMACOECONOMICS/
5. or/1-4
6. (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic\$).ti,ab.
7. (expenditure\$ not energy).ti,ab.
8. (value adj2 money).ti,ab.
9. budget\$.ti,ab.
10. or/6-9
11. 5 or 10
12. (metabolic adj cost).ti,ab.
13. ((energy or oxygen) adj cost).ti,ab.
14. ((energy or oxygen) adj expenditure).ti,ab.
15. or/12-14
16. 11 not 15
17. editorial.pt.
18. note.pt.
19. letter.pt.
20. or/17-19
21. 16 not 20
22. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh.
23. exp animal/
24. Nonhuman/
25. or/22-24
26. exp human/
27. exp human experiment/

28. 26 or 27
29. 25 not (25 and 28)
30. 21 not 29
31. exp Influenza/
32. influenza\$.ti,ab.
33. flu.ti,ab.
34. grippe.ti,ab.
35. or/31-34
36. Zanamivir/
37. zanamivir\$.ti,ab.
38. relenza\$.ti,ab.
39. (gg167 or gg 167).mp.
40. (gr121167 or gr 121167 or gr 121167x or gr121167x).mp.
41. 139110 80 8.rm.
42. or/36-41
43. Oseltamivir/
44. oseltamivir\$.ti,ab.
45. tamiflu\$.ti,ab.
46. (gs4104 or gs 4104).mp.
47. (gs4171 or gs 4171 or gs4071 or gs 4071).mp.
48. (ro-0796 or ro0796 or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802).mp.
49. or/43-48
50. Sialidase Inhibitor/
51. ((neuraminidase or sialidase) adj2 (inhibit\$ or antagonist\$)).ti,ab.
52. (NA adj2 (inhibit\$ or antagonist\$)).ti,ab.
53. or/50-52
54. Amantadine/
55. amantadin\$.ti,ab.
56. (symmetrel or symetrel).ti,ab.
57. lysovir.ti,ab.
58. aminoadamantane.ti,ab.
59. adamantylamine.ti,ab.
60. adekin.ti,ab.
61. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu).ti,ab.
62. amixx.ti,ab.
63. cerebramed.ti,ab.
64. endantadine.ti,ab.
65. (gen-amantadine or genamantadine or pms-amantadine or pmsamantadine).ti,ab.
66. (infecto-flu or infectoflu).ti,ab.
67. infex.ti,ab.
68. (mantadix or midantan).ti,ab.
69. symadine.ti,ab.
70. (viregyt or wiregyt).ti,ab.
71. virofral.ti,ab.
72. tregor.ti,ab.
73. 768 94 5.rm.
74. or/54-73
75. 30 and 35 and (42 or 49 or 53 or 74)
76. (2001\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).em
77. 75 and 76

CINAHL (OVID gateway). 2001/Oct-2007/Nov week 5. 6th December 2007.

22 records were retrieved.

1. exp "costs and cost analysis"/ or "economic aspects of illness"/ or "economic value of life"/ or economics, pharmaceutical/
2. ((cost or costs or costed or costly or costing) adj (utilit\$ or benefit\$ or effective\$ or stud\$ or minimi\$ or analys\$)).ti,ab.
3. (economic\$ or pharmacoeconomic\$ or price\$ or pricing).ti,ab.
4. (expenditure\$ not energy).ti,ab.
5. (value adj1 money).ti,ab.
6. budget\$.ti,ab.
7. or/1-6
8. Influenza/
9. influenza\$.ti,ab.
10. flu.ti,ab.
11. grippe.ti,ab.
12. or/8-11
13. zanamivir\$.ti,ab.
14. relenza\$.ti,ab.
15. (gg167 or gg 167).mp.
16. (gr121167 or gr 121167 or gr 121167x or gr121167x).mp.
17. 139110-80-8.mp.
18. or/13-17
19. oseltamivir\$.ti,ab.
20. tamiflu\$.ti,ab.
21. (gs4104 or gs 4104).mp.
22. (gs4171 or gs 4171 or gs4071 or gs 4071).mp.
23. (ro-0796 or ro0796 or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802).mp.
24. or/19-23
25. ((neuraminidase or sialidase) adj2 (inhibit\$ or antagonist\$)).ti,ab.
26. (NA adj2 (inhibit\$ or antagonist\$)).ti,ab.
27. 25 or 26
28. Amantadine/
29. amantadin\$.ti,ab.
30. (symmetrel or symetrel).ti,ab.
31. lysovir.ti,ab.
32. aminoadamantane.ti,ab.
33. adamantylamine.ti,ab.
34. adamantylamine.ti,ab.
35. adekin.ti,ab.
36. (aman or amanta or amanta-hci-azu or amanta-sulfate-azu).ti,ab.
37. amixx.ti,ab.
38. cerebramed.ti,ab.
39. endantadine.ti,ab.
40. (gen-amantadine or genamantadine or pms-amantadine or pmsamantadine).ti,ab.
41. (infecto-flu or infectoflu).ti,ab.
42. infex.ti,ab.
43. (mantadix or midantan).ti,ab.
44. symadine.ti,ab.
45. (viregyt or wiregyt).ti,ab.
46. virofral.ti,ab.
47. tregor.ti,ab.
48. 768-94-5.mp.
49. or/28-48
50. 7 and 12 and (18 or 24 or 27 or 49)
51. (200110\$ or 200111\$ or 200112\$ or 2002\$ or 2003\$ or 2004\$ or 2005\$ or 2006\$ or 2007\$).ew.
52. 50 and 51

Science Citation Index (Web of Science). 2001-2007/Dec 6th. 6th December 2007.

94 records were retrieved.

#1 TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
#2 TS=(value SAME money)
#3 TS=budget*
#4 TS=(expenditure* NOT energy)
#5 #1 OR #2 OR #3 OR #4
#6 TS=(influenza* or flu or grippe)
#7 TS=(zanamivir* or relenza*)
#8 TS=(oseltamivir* or tamiflu*)
#9 TS=(neuraminidase or sialidase or NA) SAME TS=(inhibit* or antagonist*)
#10 TS=(neuraminidase or sialidase) SAME TS=(inhibitor* or antagonist*)
#11 TS=(amantadin* or symmetrel or symetrel or lysovir)
#12 TS=(aminoadamantane or adamantylamine or adekin or aman or amanta*)
#13 TS=(amixx or cerebramed or endantadine or infecto-flu or infectoflu or infex or mantadix or midantan or symadine or viregyt or wiregyt or virofral or tregor)
#14 #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 #5 and #6 and #14
Timespan=2001-2007

NHS EED (CRD Internal Databases). 2001-2007/11. 6th December 2007

25 records were retrieved.

s influenza\$ or flu or grippe
s zanamivir\$ or relenza\$
s oseltamivir\$ or tamiflu\$
s (neuraminidase or sialidase)(w2)(inhibit\$ or antagonist\$) or NA(w2)(inhibitor\$ or antagonist\$)
s amantadin\$ or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin or aman or amanta\$ or amixx or cerebramed or endantadine or infecto(w)flu or infectoflu or infex or mantadix or midantan or symadine or viregyt or wiregyt or virofral or tregor
s s1 and (s2 or s3 or s4 or s5)
s 2001/xyr or 2002/xyr or 2003/xyr or 2004/xyr or 2005/xyr or 2006/xyr or 2007/xyr
s s6 and s7

HEED (Wiley Online). 2001-2007/11. 6th December 2007

38 records were retrieved.

AX=influenza or flu or grippe
AX=zanamivir or relenza or gg167 or (gg 167) or gr121167 or (gr 121167) or (gr 121167x) or (139110-80-8)
AX=oseltamivir or tamiflu or gs4104 or (gs 4104) or gs4171 or (gs 4171) or (ro-0796) or ro0796 or (ro 0796) or (ro64-0796) or (ro 64-0796)
AX=(neuraminidase inhibitor) or (neuraminidase inhibitors) or (sialidase inhibitor) or (sialidase inhibitors) or (NA inhibitor) or (NA inhibitors)
AX=(neuraminidase antagonist) or (neuraminidase antagonists) or (sialidase antagonist) or (sialidase antagonists) or (NA antagonist) or (NA antagonists)
AX=amantadine or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin or aman or amanta or amixx or cerebramed or endantadine or (infecto-flu) or infectoflu or infex or mantadix or midantan or symadine or viregyt or wiregyt or virofral or tregor or (768-94-5)

CS=1 and (2 or 3 or 4 or 5 or 6)
JD>=2001
CS=7 and 8

CDSR and CENTRAL (Cochrane Library). 2001-2007:Issue 4. 6th December 2007.

12 reviews were retrieved in CDSR and 3 records in CENTRAL.

- #1 MeSH descriptor Influenza, Human explode all trees
- #2 (influenza* or flu or grippe)
- #3 (#1 OR #2)
- #4 MeSH descriptor Zanamivir explode all trees
- #5 (zanamivir* or relenza*)
- #6 (gg167 or "gg 167" or gg-167 or gr121167 or "gr 121167" or gr-121167 or gr121167x or gr121167x)
- #7 (139110-80-8 or 139110808 or "139110 80 8")
- #8 (#4 OR #5 OR #6 OR #7)
- #9 (oseltamivir* or tamiflu*)
- #10 (gs4104 or "gs 4104" or gs-4104)
- #11 (gs4171 or "gs 4171" or gs-4171)
- #12 (ro-0796 or ro0796 or "ro 0796" or ro64-0796 or ro 64-0796 or ro64-0802 or ro640802)
- #13 (#9 OR #10 OR #11 OR #12)
- #14 MeSH descriptor Neuraminidase explode all trees
- #15 (neuraminidase or sialidase) NEAR/2 (inhibit* or antagonist*)
- #16 NA NEAR/2 (inhibit* or antagonist*)
- #17 (#14 OR #15 OR #16)
- #18 MeSH descriptor Amantadine explode all trees
- #19 (amantadin* or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin)
- #20 (aman or amanta or amanta-hci-azu or amanta-sulfate-azu or amixx or cerebramed or endantadine)
- #21 (gen-amantadine or pms-amantadine or genamantadine or pmsamantadine or infectoflu or infectoflu or infex or mantadix or midantan or symadine or vieregylt or wiregylt or virofral or tregor)
- #22 (768-94-5 or 768945 or "768 94 5")
- #23 (#18 OR #19 OR #20 OR #21 OR #22)
- #24 (#3 AND (#8 OR #13 OR #17 OR #23)), from 2001 to 2007
- #25 MeSH descriptor Economics, this term only
- #26 MeSH descriptor Costs and Cost Analysis explode all trees
- #27 MeSH descriptor Economics, Dental explode all trees
- #28 MeSH descriptor Economics, Hospital explode all trees
- #29 MeSH descriptor Economics, Medical explode all trees
- #30 MeSH descriptor Economics, Nursing explode all trees
- #31 MeSH descriptor Economics, Pharmaceutical explode all trees
- #32 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic*)
- #33 (expenditure* not energy)
- #34 (value NEAR/3 money)
- #35 (budget*)
- #36 (#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #33 OR #34 OR #35)
- #37 (#24 AND #36)

LILACS (Birme Virtual Health Library). 2001-2007/Nov. 6th December 2007.

1 record was retrieved.

economic\$ or cost or costs or costly or costing or price or prices or pricing or
pharmacoeconomic\$ or budget\$ [words]

AND

Influenza\$ or flu or grippe [words]

AND

zanamivir\$ or relenza\$ or oseltamivir\$ or tamiflu\$ or (neuraminidase inhibit\$) or (sialidase
inhibit\$) or (neuraminidase antagonist\$) or (sialidase antagonist\$) or amantadin\$ or
symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or adekin or aman
or amanta or amixx or cerebramed or endantadine or (gen amantadine) or genamantadine or
(pms amantadine) or pmsamantadine or (infecto flu) or infectoflu or infex or mantadix or
midantan or symadine or viiregyt or wiregyt or virofral or tregor
[words]

BIOSIS (Dialog). 2001-2007/Dec week 1. 6th December 2007.

47 records were retrieved.

s economic? or cost or costs or costly or costing or price or prices or pricing or
pharmacoeconomic?

s expenditure? not energy

s value(2w)money

s budget?

s s1:s4

s influenza? or flu or grippe

s zanamivir? or relenza?

s oseltamivir? or tamiflu?

s (neuraminidase or sialidase or NA)(2n)(inhibit? or antagonist?)

s amantadin? or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or
adekin or aman or amanta or amixx or cerebramed or endantadine or gen(w)amantadine or
genamantadine or pms(w)amantadine or pmsamantadine or infecto(w)flu or infectoflu or
infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor

s s7:s10

s s5 and s6 and s11

s s12/2001-2007

Pascal (Dialog). 2001-2007/Nov week 3. 6th December 2007.

16 records were retrieved.

s economic? or cost or costs or costly or costing or price or prices or pricing or
pharmacoeconomic?

s expenditure? not energy

s value(2w)money

s budget?

s s1:s4

s influenza? or flu or grippe

s zanamivir? or relenza?

s oseltamivir? or tamiflu?

s (neuraminidase or sialidase or NA)(2n)(inhibit? or antagonist?)

s amantadin? or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or
adekin or aman or amanta or amixx or cerebramed or endantadine or gen(w)amantadine or
genamantadine or pms(w)amantadine or pmsamantadine or infecto(w)flu or infectoflu or
infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor

s s7:s10

s s5 and s6 and s11

s s12/2001-2007

Dissertation Abstracts (Dialog). 2001-2007/August. 6th December 2007.

1 record was retrieved.

s economic? or cost or costs or costly or costing or price or prices or pricing or
pharmacoeconomic?
s expenditure? not energy
s value(2w)money
s budget?
s s1:s4
s influenza? or flu or grippe
s zanamivir? or relenza?
s oseltamivir? or tamiflu?
s (neuraminidase or sialidase or NA)(2n)(inhibit? or antagonist?)
s amantadin? or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or
adekin or aman or amanta or amixx or cerebramed or endantadine or gen(w)amantadine or
genamantadine or pms(w)amantadine or pmsamantadine or infecto(w)flu or infectoflu or
infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor
s s7:s10
s s5 and s6 and s11
s s12/2001-2007

Inside Conferences (Dialog). 2001-2007/Dec 6th. 6th December 2007.

2 records were retrieved.

s economic? or cost or costs or costly or costing or price or prices or pricing or
pharmacoeconomic?
s expenditure? not energy
s value(2w)money
s budget?
s s1:s4
s influenza? or flu or grippe
s zanamivir? or relenza?
s oseltamivir? or tamiflu?
s (neuraminidase or sialidase or NA)(2n)(inhibit? or antagonist?)
s amantadin? or symmetrel or symetrel or lysovir or aminoadamantane or adamantylamine or
adekin or aman or amanta or amixx or cerebramed or endantadine or gen(w)amantadine or
genamantadine or pms(w)amantadine or pmsamantadine or infecto(w)flu or infectoflu or
infex or mantadix or midantan or symadine or viiregyt or wiregyt or virofral or tregor
s s7:s10
s s5 and s6 and s11
s s12/2001-2007

IDEAS (RePeC). 2001-2007/Nov. 6th December 2007.

0 records were retrieved.

Each line searched separately

zanamivir
relenza
oseltamivir
tamiflu
neuraminidase
sialidase
amantadine
symmetrel

symetrel

10.1.3 Health related quality of life

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OVID gateway). 1950-2008/Jan week 4. 31st January 2008.

87 records were retrieved in MEDLINE and 2 in MEDLINE In-Process & Other Non-Indexed Citations.

1. Influenza, Human/
2. influenza\$.ti,ab.
3. flu.ti,ab.
4. grippe.ti,ab.
5. or/1-4
6. "Quality of Life"/
7. qol.ti,ab.
8. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
9. (multiattribute\$ health or multi attribute\$ health).ti,ab.
10. (health utilit\$ index or health utilit\$ indices).ti,ab.
11. (multiattribute\$ theor\$ or multi attribute\$ theor\$ or multiattribute\$ analys\$ or multi attribute\$ analys\$).ti,ab.
12. (health utilit\$ scale\$ or classification of illness state\$).ti,ab.
13. health state\$ utilit\$.ti,ab.
14. (multiattribute\$ utilit\$ or multi attribute\$ utilit\$).ti,ab.
15. health utilit\$ scale\$.ti,ab.
16. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
17. (sf36 or sf 36).ti,ab.
18. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
19. (sf12 or sf 12).ti,ab.
20. (short form 12 or shortform 12 or sf twelve or short form twelve).ti,ab.
21. (qlq-c30 or fact-c or facit or qli-cp).ti,ab.
22. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$ or shortform six\$ or short form six\$).ti,ab.
23. hrqol.ti,ab.
24. hrql.ti,ab.
25. (health related quality adj2 life\$).ti,ab.
26. cost utilit\$.ti,ab.
27. (proms or Patient Reported Outcome Measure\$).ti,ab.
28. (IIWS or Influenza Impact Wellbeing Scale).ti,ab.
29. (ISS or Influenza Symptom Severity scale).ti,ab.
30. or/6-29
31. 5 and 30
32. Animals/
33. Humans/
34. 32 not (32 and 33)
35. 31 not 34

EMBASE (OVID gateway). 1980-2008/week 4. 31st January 2008.

267 records were retrieved.

1. exp Influenza/
2. influenza\$.ti,ab.
3. flu.ti,ab.

4. grippe.ti,ab.
5. or/1-4
6. "Quality of Life"/
7. qol.ti,ab.
8. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
9. (multiattribute\$ health or multi attribute\$ health).ti,ab.
10. (health utilit\$ index or health utilit\$ indices).ti,ab.
11. (multiattribute\$ theor\$ or multi attribute\$ theor\$ or multiattribute\$ analys\$ or multi attribute\$ analys\$).ti,ab.
12. (health utilit\$ scale\$ or classification of illness state\$).ti,ab.
13. health state\$ utilit\$.ti,ab.
14. (multiattribute\$ utilit\$ or multi attribute\$ utilit\$).ti,ab.
15. health utilit\$ scale\$.ti,ab.
16. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
17. (sf36 or sf 36).ti,ab.
18. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
19. (sf12 or sf 12).ti,ab.
20. (short form 12 or shortform 12 or sf twelve or short form twelve).ti,ab.
21. (qlq-c30 or fact-c or facit or qli-cp).ti,ab.
22. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$ or shortform six\$ or short form six\$).ti,ab.
23. hrqol.ti,ab.
24. hrql.ti,ab.
25. (health related quality adj2 life\$).ti,ab.
26. cost utilit\$.ti,ab.
27. (proms or Patient Reported Outcome Measure\$).ti,ab.
28. (IIWS or Influenza Impact Wellbeing Scale).ti,ab.
29. (ISS or Influenza Symptom Severity scale).ti,ab.
30. or/6-29
31. 5 and 30
32. Animal/ or Animal Experiment/ or Nonhuman/
33. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh.
34. 32 or 33
35. exp Human/ or Human Experiment/
36. 34 not (34 and 35)
37. 31 not 36

CINAHL (OVID gateway). 1982-2007/Dec week 1. 31st January 2008.

21 records were retrieved.

1. Influenza/
2. influenza\$.ti,ab.
3. flu.ti,ab.
4. grippe.ti,ab.
5. or/1-4
6. exp "Quality of Life"/
7. qol.ti,ab.
8. (index of wellbeing or quality of wellbeing or qwb).ti,ab.
9. (multiattribute\$ health or multi attribute\$ health).ti,ab.
10. (health utilit\$ index or health utilit\$ indices).ti,ab.
11. (multiattribute\$ theor\$ or multi attribute\$ theor\$ or multiattribute\$ analys\$ or multi attribute\$ analys\$).ti,ab.

12. (health utilit\$ scale\$ or classification of illness state\$).ti,ab.
13. health state\$ utilit\$.ti,ab.
14. (multiattribute\$ utilit\$ or multi attribute\$ utilit\$).ti,ab.
15. health utilit\$ scale\$.ti,ab.
16. (euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab.
17. (sf36 or sf 36).ti,ab.
18. (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.
19. (sf12 or sf 12).ti,ab.
20. (short form 12 or shortform 12 or sf twelve or short form twelve).ti,ab.
21. (qlq-c30 or fact-c or facit or qli-cp).ti,ab.
22. (sf 6d or sf6d or short form 6d or shortform 6d or sf six\$ or shortform six\$ or short form six\$).ti,ab.
23. hrqol.ti,ab.
24. hrql.ti,ab.
25. (health related quality adj2 life\$).ti,ab.
26. cost utilit\$.ti,ab.
27. (proms or Patient Reported Outcome Measure\$).ti,ab.
28. (IIWS or Influenza Impact Wellbeing Scale).ti,ab.
29. (ISS or Influenza Symptom Severity scale).ti,ab.
30. or/6-29
31. 5 and 30

Science Citation Index (Web of Science). 1900-2008/Jan 26th. 31st January 2008.

255 records were retrieved.

TS=(influenza* or flu or grippe)

TS=(quality of life or qol or index of wellbeing or quality of wellbeing or qwb)

TS=(multiattribute* health or multi attribute* health or health utilit* index or health utilit* indices or multiattribute* theor* or multi attribute* theor* or multiattribute* analys* or multi attribute* analys*)

TS=(health utilit* scale* or classification of illness state* or health state* utilit* or multiattribute* utilit* or multi attribute* utilit* or health utilit* scale*)

TS=(euro qual or euro qol or eq-5d or eq5d or eq 5d or euroqual or euroqol)

TS=(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six or sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or short form twelve)

TS=(qlq-c30 or fact-c or facit or qli-cp or sf 6d or sf6d or short form 6d or shortform 6d or sf six* or shortform six* or short form six*)

TS=(hrqol or hrql)

TS=(health related quality) SAME TS=(life*)

TS=(cost utilit*)

TS=(proms or Patient Reported Outcome Measure*)

TS=(IIWS or Influenza Impact Wellbeing Scale)

TS=(ISS or Influenza Symptom Severity scale)

#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13

#1 and #14

NHS EED, DARE and HTA (CRD Internal Databases). 1994-2007/12. 31st January 2008.

32 records were retrieved in NHS EED, 3 in DARE, and 3 in HTA.

s influenza\$ or flu or grippe

s quality(w)of(w)life or qol

s index(w)of(w)wellbeing or quality(w)of(w)wellbeing or qwb

s multiattribute\$(w)health or multi(w)attribute\$(w)health or health(w)utilit\$(w)index or health utilit\$(w)indices
 s multiattribute\$(w)theor\$ or multi(w)attribute\$(w)theor\$ or multiattribute\$(w)analys\$ or multi(w)attribute\$(w)analys\$
 s health(w)utilit\$(w)scale\$ or classification(w)of(w)illness(w)state\$ or health(w)state\$(w)utilit\$ or multiattribute\$(w)utilit\$ or multi(w)attribute\$(w)utilit\$
 s health(w)utilit\$(w)scale\$
 s euro(w)qual or euro(w)qol or eq(w)5d or eq5d or euroqual or euroqol
 s sf36 or sf(w)36 or short(w)form(w)36 or shortform(w)36 or sf(w)thirtysix or sf(w)thirty(w)six or shortform(w)thirtysix or shortform(w)thirty(w)six or short(w)form(w)thirtysix or short(w)form(w)thirty(w)six
 s sf12 or sf(w)12 or short(w)form(w)12 or shortform(w)12 or sf(w)twelve or short(w)form(w)twelve
 s qlq(w)c30 or fact(w)c or facit or qli(w)cp
 s sf(w)6d or sf6d or short(w)form(w)6d or shortform(w)6d or sf(w)six\$ or shortform(w)six\$ or short(w)form(w)six\$
 s hrqol or hrql or health(w)related(w)quality(w2)life\$
 s cost(w)utilit\$
 s proms or Patient(w)Reported(w)Outcome(w)Measure\$
 s IIWS or Influenza(w)Impact(w)Wellbeing(w)Scale
 s ISS or Influenza(w)Symptom(w)Severity(w)scale
 s s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14 or s15 or s16 or s17
 s s1 and s18

HEED (Wiley Online). 1990-2008/01. 31st January 2008.

13 records were retrieved.

AX=influenza or flu or grippe
 AX=(index of wellbeing) OR (quality wellbeing) OR (qwb)
 AX=(multiattribute health) OR (multi attribute health)
 AX=(health utility index) OR (health utility indices)
 AX=(multiattribute theory) OR (multi attribute theory) OR (multiattribute analysis) OR (multi attribute analysis)
 AX=(health utility scale) OR (classification illness state)
 AX=(health state utility)
 AX=(multiattribute utility) OR (multi attribute utility)
 AX=(euro qual) OR (eruo qol) OR (eq-5d) OR (eq5d) OR (euroqual) OR (euroqol)
 AX=(sf36) OR (sf 36)
 AX=(short form 36) OR (shortform 36) OR (sf thirtysix) OR (sf thirty six) OR (shortform thirtysix) OR (shortform thirty six) OR (short form thirtysix) OR (short form thirty six)
 AX=(sf 6d) OR (sf6d) OR (short form 6d) OR (shortform 6d) OR (sf six) OR (shortform six) OR (short form six)
 AX=hrqol
 AX=hrql
 AX=(health related quality of life)
 AX=(quality of life)
 AX=qol
 AX=(IIWS) OR (Influenza Impact Wellbeing Scale)
 AX=(ISS) OR (Influenza Symptom Severity scale)
 CS=2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
 CS=1 and 20

CEA Registry. (Tufts – New England Medical Center website). 2007/November. 31st January 2008.

19 records were retrieved.

Each line searched separately
influenza
influenzae

Internet sites searched

Websites were browsed (publications, guidelines and research) and searched using a variety of combinations of the following terms: zanamivir, relenza, oseltamivir, tamiflu, neuraminidase, sialidase, amantadine, influenza.

MedlinePlus: <http://www.nlm.nih.gov/medlineplus/medlineplus.html>

Intute: <http://www.intute.ac.uk/>

National Library for Health (NLH): <http://www.library.nhs.uk/>

National electronic Library of Infection (NeLI): <http://www.neli.org.uk/>

Department of Health: <http://www.dh.gov.uk/en/Home>

Health Protection Agency: <http://www.hpa.org.uk/>

British Infection Society: <http://www.britishinfectionsociety.org/>

British Lung Foundation: <http://www.lunguk.org/>

British Thoracic Society: <http://www.brit-thoracic.org.uk/>

Association of Public Health Observatories (APHO): <http://www.apho.org.uk/apho/index.htm>

European Centre for Disease Prevention and Control (ECDC): <http://www.ecdc.eu.int/>

European Scientific Working group on Influenza (ESWI): <http://www.eswi.org/>

US National Institute of Allergy and Infectious Diseases (NIAID): <http://www3.niaid.nih.gov/>

US Center for Disease Control and Prevention (CDC): <http://www.cdc.gov/>

American Lung Association: <http://www.lungusa.org/>

Medicines and Healthcare products Regulatory Agency (MHRA): <http://www.mhra.gov.uk/>

European Agency for Evaluation of Medicinal Products (EMA):
<http://www.emea.europa.eu/>

US Food and Drug Administration (FDA): <http://www.fda.gov/>

10.2 Details of included studies

10.2.1 Clinical effectiveness

Study ID	Study details	Population details	Intervention/ Comparator details
<p>Aoki(2000)⁷⁴</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 1995 - 1996</p> <p>Regions UK, Western Europe, USA/Canada</p> <p>Number of centres recruiting Not reported</p> <p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI Feverish with any other two symptoms</p> <p>Delay to start of treatment 48 hours Mean 30 hours (SD 11 hours) for zanamivir; 29 hours (SD 11 hours) for placebo</p> <p>Use of antipyretics Not reported</p> <p>Length of follow-up 21 days</p>	<p>Number recruited Overall: 1256</p> <p>Number influenza positive Overall: 722 Intervention: 241 Comparator: 240</p> <p>Groups/subgroups for which data are presented Mixed population</p> <p>Proportion male Overall: 92/441 (21%) Intervention: 46/241 (19%) Comparator: 46/240 (19%)</p> <p>Number of withdrawals Not reported</p> <p>Proportion vaccinated within last year Intervention: 1% Comparator: 3%</p> <p>Age range Minimum: 13</p>	<p>Intervention Zanamivir 10 mg inhalation plus nasal spray twice daily</p> <p>Comparator Placebo</p>
<p>Boivin (2000)⁹²⁻⁹⁴</p> <p>Data source Full published paper Company website trials data</p> <p>Language English</p>	<p>Influenza season 1997 - 1998</p> <p>Region USA/Canada</p> <p>Number of centres recruiting 84</p> <p>Was influenza reported as circulating in the community? Yes</p>	<p>Number recruited Overall: 777 Intervention: 412 Comparator: 365</p> <p>Number influenza positive Overall: 569 Intervention: 312 Comparator: 257</p> <p>Groups/subgroups for which data are presented</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
	<p>Definition of ILI T>37.8C with any two symptoms T≥ 37.2 for subjects ≥ 65 years</p> <p>Delay to start of treatment 48 hours</p> <p>Use of antipyretics Relief medication was used but it is unclear whether it was unrestricted.</p> <p>Length of follow-up 14 days</p>	<p>Mixed population At risk</p> <p>Proportion male Overall: 374/ 777 (48%) Intervention: 205/ 412 (50%) Comparator: 169/ 365 (46%)</p> <p>Number of withdrawals Overall: 33/ 777 (4%) Intervention: 17/ 412 (4%) Comparator: 16/ 365 (4%)</p> <p>Proportion vaccinated within last year Overall: 108/ 777 (14%) Intervention: 55/ 412 (13%) Comparator: 53/ 365 (15%)</p> <p>Age range Minimum: 12</p>	
<p>Deng (2004)⁶⁶</p> <p>Data source Full published paper</p> <p>Language Chinese</p>	<p>Influenza season Dates not reported</p> <p>Region Asia</p> <p>Number of centres recruiting Unclear</p> <p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI Not reported</p> <p>Delay to start of treatment 48 hours</p> <p>Use of antipyretics Not reported</p> <p>Length of follow-up Unclear (9 days plus additional follow-up until symptoms relieved)</p>	<p>Number recruited Overall: 1176 Intervention: 599 Comparator: 577</p> <p>Number influenza positive Not reported</p> <p>Groups/subgroups for which data are presented Healthy adults</p> <p>Proportion male Overall: 0.52 Intervention: 0.52 Comparator: 0.52</p> <p>Number of withdrawals Not reported</p> <p>Proportion vaccinated within last year Not reported</p> <p>Age range</p>	<p>Intervention Oseltamivir 75 mg bd</p> <p>Comparator Symptomatic relief Ephedrine</p>

Study ID	Study details	Population details	Intervention/ Comparator details
GlaxoSmithKline NAI30012 (2005) ^{104, 105} Data source Company website trials data Company submission Language English	Influenza season 1999 - 2001 Regions UK, Western and Eastern Europe, USA/Canada and other America, Australia/NZ, Russia, South Africa, Israel Number of centres recruiting 119 Was influenza reported as circulating in the community? Yes Definition of ILI T>37.8C with any two symptoms Delay to start of treatment Maximum 48 hours Use of antipyretics Unrestricted Length of follow-up Visit at 29 days with further telephone call at 56 days	Mean: 32±16 years Number recruited Overall: 358 Intervention: 191 Comparator: 167 Number influenza positive Overall: 234 Intervention: 120 Comparator: 114 Groups/subgroups for which data are presented Elderly Proportion male Overall: ITTI 102/234=44%; ITT 41% Intervention: ITTI 52/120=43%; ITT 39% Comparator: ITTI 50/114=44%; ITT 44% Number of withdrawals Overall: 17 (5%) Intervention: 10 (5%) Comparator: 7 (4%) Proportion vaccinated within last year Overall: ITTI 40%; ITT 46% Intervention: ITTI 50/120=42%; ITT 47% Comparator: ITTI 44/114=39%; ITT 44% Age range Minimum: 65	Intervention Zanamivir 10 mg inhalation twice daily Comparator Placebo
GlaxoSmithKline NAI30020 (2006) ⁹⁸ Data source Company website trials data Language English	Influenza season 1999 - 2001 Region Western Europe Number of centres recruiting 94 Was influenza reported as circulating in the community? No	Number recruited Overall: 331 Intervention: 224 Comparator: 107 Number influenza positive Not reported Groups/subgroups for which data are presented At risk Proportion male	Intervention Zanamivir 10 mg inhalation twice daily Comparator Placebo

Study ID	Study details	Population details	Intervention/ Comparator details
	<p>Definition of ILI T>37.8C with any two symptoms</p> <p>Delay to start of treatment Maximum 48 hours</p> <p>Length of follow-up 5 days</p>	<p>Overall: 141/286 (49%) Intervention: 97/189 (51%) Comparator: 44/97 (45%)</p> <p>Number of withdrawals Overall: 6 (2%) Intervention: 4 (2%) Comparator: 2 (2%)</p> <p>Proportion vaccinated within last year Not reported</p> <p>Age range Minimum: 18</p>	
<p>GlaxoSmithKline NAI30028 (2006)^{102, 103}</p> <p>Data source Company website trials data Company submission</p> <p>Language English</p>	<p>Influenza season 2000 - 2001</p> <p>Region Western Europe</p> <p>Number of centres recruiting 45</p> <p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI T≥37.8C with no evidence of bacteria infection</p> <p>Delay to start of treatment Maximum 48 hours</p> <p>Use of antipyretics Unrestricted</p> <p>Length of follow-up 6 days for main outcomes 14 days for adverse events.</p>	<p>Number recruited Overall: 266 Intervention: 176 Comparator: 90</p> <p>Number influenza positive Not reported</p> <p>Groups/subgroups for which data are presented Children</p> <p>Proportion male Overall: 61% Intervention: 63% Comparator: 59%</p> <p>Number of withdrawals Overall: 6 (2%) Intervention: 5 (3%) Comparator: 1 (1%)</p> <p>Proportion vaccinated within last year Not reported</p> <p>Age range 5 to 12 years (oldest child recruited was 14 years)</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p> <p>Comparator Placebo</p>
<p>GlaxoSmithKline NAI30011⁸⁶</p>	<p>Influenza season 1999 - 2000</p>	<p>Number recruited Overall: 466 Intervention: 229</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p>

Study ID	Study details	Population details	Intervention/ Comparator details
<p>Data source Company submission</p> <p>Language English</p>	<p>Region USA/Canada</p> <p>Number of centres recruiting 53</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI T>37.8C with any two symptoms (T>37.2C for the elderly)</p> <p>Delay to start of treatment Maximum 48 hours Mean 28.1 hours for zanamivir; 28.7 hours for placebo Range 3-64 hours for zanamivir; 4-48 hours for placebo</p> <p>Use of antipyretics Restricted</p> <p>Length of follow-up 21 days</p>	<p>Comparator: 237</p> <p>Number influenza positive Overall: 211 Intervention: 104 Comparator: 107</p> <p>Groups/subgroups for which data are presented Healthy adults (Included elderly without comorbidity)</p> <p>Proportion male Overall: 202/466 (43%) Intervention: 91/229 (40%) Comparator: 111/237 (47%)</p> <p>Number of withdrawals Overall: 31/466 (7%) Intervention: 16/229 (7%) Comparator: 15/237 (6%)</p> <p>Proportion vaccinated within last year Overall: 42/466 (9%) Intervention: 21/229 (9%) Comparator: 21/237 (9%)</p> <p>Age range 18 – 99 years (maximum age for ITTI, 61; 5 patients over 65 years (1 zanamivir; 4 placebo))</p>	<p>Comparator Placebo</p>
<p>Hayden (1997)⁷⁶</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 1994 - 1995</p> <p>Regions UK, Western Europe, USA/Canada</p> <p>Number of centres recruiting 70</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI Feverish with any other two symptoms</p>	<p>Number recruited Overall: 417 Intervention: 132 Comparator: 144</p> <p>Number influenza positive Overall: 262 Intervention: 85 Comparator: 89</p> <p>Groups/subgroups for which data are presented Healthy adults</p> <p>Proportion male Overall: 56% (ITTI)</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
	<p>Delay to start of treatment Maximum 48 hours Mean 31 hours (SD 12 hours) for zanamivir; 30 hours (SD 12 hours) for placebo</p> <p>Use of antipyretics Unrestricted</p> <p>Length of follow-up 21 to 28 days</p>	<p>Intervention: 59% (ITTI) Comparator: 54% (ITTI)</p> <p>Number of withdrawals Overall Prior to treatment: 1 On treatment: 28 (7%) Intervention: 10 (8%) Comparator: 8 (6%)</p> <p>Proportion vaccinated within last year Vaccinated individuals were excluded from the trial</p> <p>Age range Minimum: 18 years (Europe), 13 years (U.S.)</p>	
<p>Hedrick (2000)⁹⁹⁻¹⁰¹</p> <p>Data source Full published paper Company website trials data Company submission</p>	<p>Influenza season 1999 - 1999</p> <p>Regions UK, Western Europe, USA/Canada, Israel, Russia</p> <p>Number of centres recruiting 67</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI T>37.8 °C and no clinical evidence of bacterial infection</p> <p>Delay to start of treatment Maximum 36 hours Mean (ITT population) 20.3 hours (SD 9.4 hours) for zanamivir; 20.0 hours (SD 8.8 hours) for placebo Mean (ITTI population) 21.6 hours (SD 9.3 hours) for zanamivir; 20.1 hours (SD 9.0 hours) for placebo</p> <p>Use of antipyretics Restricted</p> <p>Length of follow-up 28 days</p>	<p>Number recruited Overall: 471 Intervention: 224 Comparator: 247</p> <p>Number influenza positive Overall: 346 Intervention: 164 Comparator: 182</p> <p>Groups/subgroups for which data are presented Children</p> <p>Proportion male Overall: 0.55 Intervention: 0.57 Comparator: 0.53</p> <p>Number of withdrawals Overall: 16 (3%) Intervention: 5 (2%) Comparator: 11 (4%)</p> <p>Proportion vaccinated within last year Overall: 0.02 Intervention: 0.03 Comparator: 0.02</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
		Age range 5 – 12 years	
Kashiwagi (2000) ⁶⁸ Data source Full published paper Language Japanese	Influenza season 1998 - 2000 Region Asia Number of centres recruiting 79 Was influenza reported as circulating in the community? No Definition of ILI T>38C with any two symptoms Delay to start of treatment Maximum 36 hours Mean 24.5 hours (SD 7.7 hours) for oseltamivir; 22.5 hours (SD8.4 hours) for placebo Range 4.9-38.5 hours for oseltamivir; 4.7-43.0 hours for placebo Use of antipyretics Unrestricted Length of follow-up 21 days	Number recruited Overall: 316 Intervention: 154 Comparator: 162 Number influenza positive Overall: 252 Intervention: 122 Comparator: 130 Groups/subgroups for which data are presented Healthy adults Proportion male Overall: 116/252 (46%) Intervention: 47/122 (39%) Comparator: 69/130 (53%) Number of withdrawals Overall: 14 (4%) Intervention: 3 (2%) Comparator: 11 (7%) Proportion vaccinated within last year Vaccinated individuals were excluded from the trial Age range 16 – 80 years	Intervention Oseltamivir 75 mg bd Comparator Placebo
Li (2004) ^{69, 70} Data source Full published paper Language English	Influenza season 2001 - 2001 Region Asia Number of centres recruiting 7 Was influenza reported as circulating in the community? Yes Definition of ILI	Number recruited Overall: 478 Intervention: 216 Comparator: 235 Number influenza positive Overall: 273 Intervention: 134 Comparator: 139 Groups/subgroups for which data are presented Healthy adults	Intervention Oseltamivir 75 mg bd Comparator Placebo

Study ID	Study details	Population details	Intervention/ Comparator details
	<p>T>37.8C with any two symptoms</p> <p>Delay to start of treatment Maximum 36 hours Mean 23.09 hours (SD 8.51 hours) for oseltamivir; 22.29 hours (SD 7.96 hours) for placebo</p> <p>Use of antipyretics Unrestricted</p> <p>Length of follow-up 21 days</p>	<p>Proportion male Overall: 136/273 (50%) Intervention: 63/134 (47%) Comparator: 73/139 (53%)</p> <p>Number of withdrawals Overall: 16 (3%)</p> <p>Proportion vaccinated within last year Not reported</p> <p>Age range 18 – 65 years</p>	
<p>Lin (2006)^{71, 72, #128}</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 2002 - 2003</p> <p>Region Asia</p> <p>Number of centres recruiting 9</p> <p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI T>37.8C with any two symptoms</p> <p>Delay to start of treatment Maximum 48 hours Mean 25 hours (SD 10 hours) for oseltamivir; 26 hours (SD 12 hours) for symptomatic relief</p> <p>Use of antipyretics Unrestricted for the first 8 days</p> <p>Length of follow-up 21 days</p>	<p>Number recruited Overall: 118 Intervention: 58 Comparator: 60</p> <p>Number influenza positive Overall: 56 Intervention: 27 Comparator: 29</p> <p>Groups/subgroups for which data are presented At risk: general respiratory and cardiac co-morbidities</p> <p>Proportion male Overall: 33/56 (59%) Intervention: 17/27 (63%) Comparator: 16/29 (55%)</p> <p>Number of withdrawals None</p> <p>Proportion vaccinated within last year Vaccinated individuals were excluded from the trial</p> <p>Age range Not reported</p>	<p>Intervention Oseltamivir 75 mg bd</p> <p>Comparator Symptomatic relief</p>
<p>Mäkelä (2000)⁹⁵</p> <p>Data source</p>	<p>Influenza season 1997 - 1998</p> <p>Region</p>	<p>Number recruited Overall: 356 Intervention: 174 Comparator: 182</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p>

Study ID	Study details	Population details	Intervention/ Comparator details
<p>Full published paper</p> <p>Language English</p>	<p>Western Europe</p> <p>Number of centres recruiting 42</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI T>37.8C with any two symptoms T≥37.2°C for patients ≥65 years of age</p> <p>Delay to start of treatment Maximum 48 hours</p> <p>Use of antipyretics Restricted</p> <p>Length of follow-up 28 days</p>	<p>Number influenza positive Overall: 277 Intervention: 136 Comparator: 141</p> <p>Groups/subgroups for which data are presented Mixed population At risk</p> <p>Proportion male Overall: 165/ 356 (46%) Intervention: 84/ 174 (48%) Comparator: 81/ 182 (45%)</p> <p>Number of withdrawals Overall: 7 (2%) Intervention: 4 (2%) Comparator: 3 (2%)</p> <p>Proportion vaccinated within last year Overall: 14/ 356 (4%)</p> <p>Age range Minimum: 12</p>	<p>Comparator Placebo</p>
<p>Markovski (2002)⁵⁷</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 2001 - 2002</p> <p>Region Macedonia</p> <p>Number of centres recruiting 1</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI T>37.5C, chills and the presence of any two other symptoms</p> <p>Delay to start of treatment Maximum 48 hours</p>	<p>Number recruited Overall: 50 Intervention: 20 Comparator: 30</p> <p>Number influenza positive Overall: 41 Intervention: 17 Comparator: 24</p> <p>Groups/subgroups for which data are presented Mixed population</p> <p>Proportion male Not reported</p> <p>Number of withdrawals Not reported</p>	<p>Intervention Oseltamivir 75 mg twice daily</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
	<p>Use of antipyretics Unrestricted</p> <p>Length of follow-up 10 days</p>	<p>Proportion vaccinated within last year Not reported</p> <p>Age range Minimum: 18</p>	
<p>Martin (2001)^{46, 73, 108}</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season Dates not reported</p> <p>Region Not reported</p> <p>Number of centres recruiting Not reported</p> <p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI T>38C with one systemic and one respiratory symptom T≥37.5°C for elderly patients</p> <p>Delay to start of treatment Maximum 36 hours</p> <p>Use of antipyretics Not reported</p> <p>Length of follow-up 21 days</p>	<p>Number recruited Overall: 1138 Intervention: 559 Comparator: 579</p> <p>Groups/subgroups for which data are presented Elderly At risk: general respiratory and cardiac co-morbidities</p> <p>Proportion male Overall: 177/402 (44%) at risk; 316/736 (43%) elderly Intervention: 86/199 (43%) at risk; 150/360 (42%) elderly Comparator: 91/203 (45%) at risk; 166/376 (44%) elderly</p> <p>Proportion vaccinated within last year Overall: 111/402 (28%) at risk; 15/736 (43%) elderly Intervention: 56/199 (28%) at risk; 143/360 (40%) elderly Comparator: 55/203 (27%) at risk; 172/376 (46%) elderly</p> <p>Number of withdrawals Not reported</p> <p>Age range 13 – 88 years</p>	<p>Intervention Oseltamivir 75 mg bd</p> <p>Comparator Placebo</p>
<p>Matsumoto (1999)⁸⁵</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 1995 - 1995</p> <p>Region Asia</p> <p>Number of centres recruiting 28</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI</p>	<p>Number recruited Overall: 116 (third arm not considered in current review) Intervention: 37 Comparator: 39</p> <p>Number influenza positive Overall: 51/76 (67%) Intervention: 22 (59%) Comparator: 29 (74%)</p> <p>Groups/subgroups for which data are presented Healthy adults</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
	<p>Axillary T\geq37.5C and any two symptoms</p> <p>Delay to start of treatment Maximum 36 hours Mean 25.4 hours (SD 15.0 hours) for zanamivir; 24.6 hours (SD 14.9) for placebo</p> <p>Use of antipyretics Restricted</p> <p>Length of follow-up 28 days</p>	<p>Proportion male Overall: 48/76 (63%) Intervention: 13/37 (35%) Comparator: 15/39 (38%)</p> <p>Number of withdrawals Not reported</p> <p>Proportion vaccinated within last year None</p> <p>Age range 16 – 65 years</p>	
<p>MIST (1998)^{90, 91}</p> <p>Data source Full published paper Company website trials data</p> <p>Language English</p>	<p>Influenza season 1997 - 1997</p> <p>Regions Australia/NZ, South Africa</p> <p>Number of centres recruiting 13</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI T$>$37.8C or feverishness with any two symptoms</p> <p>Delay to start of treatment Maximum 36 hours Mean 24.8 hours (SD 7.4 hours) for zanamivir; 25 hours (SD 7.4 hours) for placebo</p> <p>Use of antipyretics Restricted</p> <p>Length of follow-up 28 days</p>	<p>Number recruited Overall: 455 Intervention: 227 Comparator: 228</p> <p>Number influenza positive Overall: 321 Intervention: 161 Comparator: 160</p> <p>Groups/subgroups for which data are presented Mixed population</p> <p>Proportion male Overall: 241/455 (53%) Intervention: 135/227 (59%) Comparator: 106/228 (46%)</p> <p>Number of withdrawals Overall: 31 (7%) Intervention: 13 (6%) Comparator: 18 (8%)</p> <p>Proportion vaccinated within last year Overall: 26/455 (6%) Intervention: 14/227 (6%) Comparator: 12/228 (5%)</p> <p>Age range Minimum: 12</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
<p>Monto (1999)⁷⁵</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 1995 - 1996</p> <p>Regions UK, Western Europe, USA/Canada</p> <p>Number of centres recruiting Not reported</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI Feverish with any other two symptoms</p> <p>Delay to start of treatment Maximum 48 hours Mean 29 hours (SD 11 hours) for both zanamivir and placebo</p> <p>Use of antipyretics Restricted</p> <p>Length of follow-up 21 days</p>	<p>Number recruited Overall: 1256 (including 3rd arm) Intervention: 419 Comparator: 422</p> <p>Number influenza positive Overall: 481 (57%) Intervention: 241 (58%) Comparator: 240 (57%)</p> <p>Groups/subgroups for which data are presented Mixed population At risk</p> <p>Proportion male Overall: 368/841 (44%) Intervention: 181/419 (43%) Comparator: 187/422 (44%)</p> <p>Number of withdrawals Overall: 48 (6%) Intervention: 24 (6%) Comparator: 24 (6%)</p> <p>Proportion vaccinated within last year Overall: 11/841 (1%) Intervention: 3/419 (1%) Comparator: 8/422 (2%)</p> <p>Age range Minimum: 13</p>	<p>Intervention Zanamivir 10 mg inhalation plus nasal spray twice daily</p> <p>Comparator Placebo</p>
<p>Murphy (2000)^{97, 114, 115}</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 1998 - 2000</p> <p>Regions UK, Western Europe, Eastern Europe, USA/Canada, Other America, Australia/NZ, South Africa, Israel</p> <p>Number of centres recruiting 159</p> <p>Was influenza reported as circulating in the community? Yes</p>	<p>Number recruited Overall: 525 Intervention: 262 Comparator: 263</p> <p>Number influenza positive Overall: 312 Intervention: 160 Comparator: 152</p> <p>Groups/subgroups for which data are presented COAD/asthma</p>	<p>Intervention Zanamivir 10 mg inhalation twice daily</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
	<p>Definition of ILI T>37.8C with any two symptoms</p> <p>Delay to start of treatment Maximum 36 hours Mean 22.5h for zanamivir; 22.7h for placebo</p> <p>Use of antipyretics Restricted</p> <p>Length of follow-up 28 days</p>	<p>Proportion male Overall: 223/525 (42%) Intervention: 109/262 (42%) Comparator: 114/263 (43%)</p> <p>Number of withdrawals Overall: 37 (7%) Intervention: 16 (6%) Comparator: 21 (8%)</p> <p>Proportion vaccinated within last year Overall: 122/525 (23%) Intervention: 65/262 (25%) Comparator: 57/263 (22%)</p> <p>Age range Minimum: 12</p>	
<p>Nicholson (2000)¹⁰⁶</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 1998 - 1998</p> <p>Regions UK, Western Europe, USA/Canada, Asia</p> <p>Number of centres recruiting 63</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI T>38C with one respiratory symptom and one systemic</p> <p>Delay to start of treatment Maximum 36 hours Median 24 hours for oseltamivir (4-60 hours); 23 hours for placebo (0-59 hours)</p> <p>Use of antipyretics Unrestricted</p> <p>Length of follow-up 21 days</p>	<p>Number recruited Overall: 726 Intervention: 243 Comparator: 239</p> <p>Number influenza positive Overall: 475 Intervention: 158 Comparator: 161</p> <p>Groups/subgroups for which data are presented Healthy adults</p> <p>Proportion male Intervention: 50% Comparator: 50%</p> <p>Number of withdrawals Overall: 38 (5%) Intervention: 8 (3%) Comparator: 15 (6%)</p> <p>Proportion vaccinated within last year Vaccinated individuals were excluded from the trial</p>	<p>Intervention Oseltamivir 75 mg bd</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
		Age range 18 – 65 years	
Puhakka (2003) ⁸⁷⁻⁸⁹ Data sources Full published paper Company website trials data Company submission Language English	Influenza season 1999 - 2001 Region Western Europe Number of centres recruiting 5 residential units of the Finish Defence Forces Was influenza reported as circulating in the community? Yes Definition of ILI T>37.8C with any two symptoms Delay to start of treatment Maximum 48 hours Mean: 23.6 (SD 11.4) for zanamivir; 24.5 (SD 11.4) for placebo Use of antipyretics Restricted Length of follow-up 28 days	Number recruited Overall: 588 Intervention: 293 Comparator: 295 Number influenza positive Overall: 435 Intervention: 222 Comparator: 213 Groups/subgroups for which data are presented Healthy adults Proportion male Overall: 99% Intervention: 99% Comparator: 100% Number of withdrawals Overall: 14 (2%) Intervention: 5 (2%) Comparator: 9 (3%) Proportion vaccinated within last year Overall: <0.01 Intervention: <0.01 Comparator: < 0.01 Age range 17 – 29 years	Intervention Zanamivir 10 mg inhalation twice daily Comparator Placebo
Roche (1999) WV15730 ^{82, 83} Data source Company submission Abstract Language English	Influenza season 1998 - 1998 Region Australia/NZ, South Africa Number of centres recruiting 12 Was influenza reported as circulating in the community? Yes	Number recruited Overall: 60 Intervention: 31 Comparator: 27 Number influenza positive Overall: 38 Intervention: 19 Comparator: 19 Groups/subgroups for which data are presented	Intervention Oseltamivir 75 mg twice daily Comparator Placebo

Study ID	Study details	Population details		Intervention/ Comparator details
	<p>Definition of ILI T>38C with one respiratory and one systemic symptom</p> <p>Delay to start of treatment Maximum 36 hours Mean 25.6 (SD 7.7) hours for oseltamivir; 24.2 (SD 9) hours for placebo Range 8.9-35.5 hours for oseltamivir; 5.8-36 hours for placebo</p> <p>Use of antipyretics Unrestricted</p> <p>Length of follow-up 21 days</p>	<p>Healthy adults</p> <p>Proportion male Overall: 30/58 (52%) Intervention: 16/31 (52%) Comparator: 14/27 (52%)</p> <p>Number of withdrawals Before treatment: 2/60 (3%) Overall on treatment: 4/58 (7%) Intervention: 1/31 (7%) Comparator: 3/27 (6%)</p> <p>Proportion vaccinated within last year Overall: 42/466 (9%) Intervention: 21/229 (9%) Comparator: 21/237 (9%)</p> <p>Age range 18 – 65 years</p>		
<p>Roche (2004)[#59; #302]</p> <p>Data source Full paper Company website trials data</p> <p>Language English</p>	<p>Influenza season 1998 - 1999</p> <p>Region Not reported</p> <p>Number of centres recruiting Not reported</p> <p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI T>37.8C with one respiratory symptom</p> <p>Delay to start of treatment Maximum 48 hours Mean 27.5 hours (SD 12.1 hours) for oseltamivir; 26.9 hours (SD 12.1 hours) for placebo</p> <p>Use of antipyretics Unrestricted</p>	<p>Children and/or adolescents with asthma</p> <p>Johnston (2005)⁷⁸</p> <p>Number recruited Overall: 335 Intervention: 170 Comparator: 164</p> <p>Number influenza positive Overall: 179 Intervention: 84 Comparator: 95</p> <p>Proportion male Overall: 212/334 (63%) Intervention: 111/170 (65%) Comparator: 101/164 (62%)</p> <p>Proportion vaccinated within last year Overall: 65/334 (19%) Intervention: 31/170=18%</p>	<p>Roche web site⁷⁷</p> <p>Number recruited Overall: 329</p> <p>Number influenza positive Overall: 94 Intervention: 43 Comparator: 51</p> <p>Age range 6 - 17</p>	<p>Intervention Johnston (2005)⁷⁸ Oseltamivir 2 mg/kg</p> <p>Company web site⁷⁷ 45, 60 or 75 mg oseltamivir depending on weight</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details		Intervention/ Comparator details
	Length of follow-up 28 days	Comparator: 34/164 (21%) Number of withdrawals (ITT) Overall: 17 (9%) Intervention: 11 (13%) Comparator: 6 (6%) Age range 5 – 12 years		
Sato (2005) ¹¹⁰ Data source Full published paper Language English	Influenza season 2002 - 2003 Region Asia Number of centres recruiting 1 Was influenza reported as circulating in the community? Yes Definition of ILI All diagnosed with influenza using a rapid diagnosis kit. Delay to start of treatment Maximum 48 hours Use of antipyretics Not reported Length of follow-up 21 days	Number recruited Overall: 63 Intervention: 21 Comparator: 22 Number influenza positive Overall: 59 Intervention: 20 Comparator: 20 Groups/subgroups for which data are presented Children: hospitalised for dehydration or respiratory complication. Proportion male Not reported Number of withdrawals Not reported Proportion vaccinated within last year Not reported Age range 5 months - 12 years		Intervention Oseltamivir 2 mg/kg Comparator Zanamivir 10 mg inhalation twice daily
Tan (2002) ⁶⁷ Data source Full published paper Language Chinese	Influenza season Unclear Region Asia Number of centres recruiting Unclear	Number recruited Overall: 80 Intervention 34 completed Comparator 39 completed Number influenza positive Overall: 47 Intervention: 22		Intervention Oseltamivir 75 mg bd Comparator Placebo

Study ID	Study details	Population details	Intervention/ Comparator details
	<p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI Unclear</p> <p>Delay to start of treatment Not reported</p> <p>Use of antipyretics Unclear</p> <p>Length of follow-up 21 days</p>	<p>Comparator: 25</p> <p>Groups/subgroups for which data are presented Healthy adults</p> <p>Number of withdrawals Overall: 7 (9%)</p> <p>Age range 18 - 65 years</p>	
<p>Treanor (2000)⁶⁵</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 1998 - 1998</p> <p>Region USA/Canada</p> <p>Number of centres recruiting 60</p> <p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI T>38C with one systemic and one respiratory symptom</p> <p>Delay to start of treatment Maximum 36 hours Median 24 hours for oseltamivir (0-41 hours); 26 hours for placebo (2-39 hours)</p> <p>Use of antipyretics Unrestricted</p> <p>Length of follow-up 21 days</p>	<p>Number recruited Overall: 629 (including 3rd arm) Intervention: 211 Comparator: 209</p> <p>Number influenza positive Overall: 253/419 (60%) Intervention: 124/210 (59%) Comparator: 129/209 (62%)</p> <p>Groups/subgroups for which data are presented Healthy adults</p> <p>Proportion male Overall: 195/419 (47%) Intervention: 98/210 (47%) Comparator: 97/209 (46%)</p> <p>Number of withdrawals Overall: 27 (4%) Intervention: 16 (8%) Comparator: 11 (4%)</p> <p>Proportion vaccinated within last year Vaccinated individuals were excluded from the trial</p> <p>Age range 18 – 65 years</p>	<p>Intervention Oseltamivir 75 mg bd</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
<p>Treanor (2000b)⁸¹</p> <p>Data source Abstract</p> <p>Language English</p>	<p>Influenza season Dates not specified</p> <p>Region USA/Canada</p> <p>Number of centres recruiting 164</p> <p>Was influenza reported as circulating in the community? No</p> <p>Definition of ILI T>37.8C with one respiratory symptom and one systemic</p> <p>Delay to start of treatment Not reported</p> <p>Use of antipyretics Not reported</p> <p>Length of follow-up Unclear</p>	<p>Number recruited Overall: 1459</p> <p>Number influenza positive Overall: 1063</p> <p>Groups/subgroups for which data are presented Mixed population</p> <p>Proportion male Not reported</p> <p>Number of withdrawals Not reported</p> <p>Proportion vaccinated within last year Overall: 16%</p> <p>Age range 13 – 80 years</p>	<p>Intervention Oseltamivir 75 mg bd</p> <p>Comparator Placebo</p>
<p>Whitley (2001)¹⁰⁹</p> <p>Data source Full published paper</p> <p>Language English</p>	<p>Influenza season 1998 - 1999</p> <p>Region USA/Canada</p> <p>Number of centres recruiting 80</p> <p>Was influenza reported as circulating in the community? Yes</p> <p>Definition of ILI T>37.8C with one respiratory symptom</p> <p>Delay to start of treatment Maximum 48 hours; some patients included after 48 hours Median (ITT) 26.7 hours for oseltamivir; 28.0 hours for placebo</p> <p>Use of antipyretics</p>	<p>Number recruited Overall: 698 enrolled, 3 withdrew prior to medication Intervention: 344 Comparator: 351</p> <p>Number influenza positive Overall: 452 Intervention: 217 Comparator: 235</p> <p>Groups/subgroups for which data are presented Children</p> <p>Proportion male Overall: 50% Intervention: 50% Comparator: 51%</p> <p>Number of withdrawals Overall: Prior to treatment: 3; On treatment: 18 (3%)</p>	<p>Intervention Oseltamivir 2 mg/kg</p> <p>Comparator Placebo</p>

Study ID	Study details	Population details	Intervention/ Comparator details
	Unrestricted Length of follow-up 28 days	Intervention: 10 (3%) Comparator: 8 (2%) Proportion vaccinated within last year Overall: 3% (ITT) Intervention: 3% (ITT) Comparator: 2% (ITT) Age range 1 year - 12 years	

10.2.2 Cost-effectiveness

Study details	<i>Armstrong et al. (2000)</i>	<i>Brady et al. (2001)</i>	<i>Burls et al. (2002)</i>
Economic evaluation type	Cost-effectiveness analysis	Cost-effectiveness and cost-utility analysis	Cost-effectiveness and cost-utility analysis
Currency (year)	USD (2000)	CAD (2000)	GBP (2000)
Study design	Decision tree	Decision tree	Decision tree
Perspective	Managed care organisation	Govt payer, society	NHS
Setting	USA	Canada	UK
Patient population	Otherwise healthy (aged 12-65yrs) and 'at risk' patients presenting within either 36hrs or 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy (aged 12-65yrs) and 'at risk' patients presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy (aged 12-65yrs) and 'at risk' patients presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.
Time horizon	1997/98 flu season	Flu season. Extrapolated to up to 10yrs in sensitivity analysis of mortality.	1997/98 flu season
Comparators	1. Oseltamivir 5 days 75mg bid 2. Zanamivir 5 days 10mg inhaled bid 3. Placebo	1. Zanamivir 5 days 10mg inhaled bid 2. Symptomatic relief	1. Zanamivir 5 days 10mg inhaled bid 2. Symptomatic relief
Resources used and costs	NIs and antibiotic use, follow-up physician visits, hospitalisations. Direct costs were included.	Follow-up physician visits, NI and antibacterial use, hospitalisations and length of stay. OTC medication use, productivity losses (societal persp. only). Direct and indirect (societal persp. only) costs were included.	NI and antibacterial use, GP visits (all patients). Hospitalisations and length of stay ('at risk' subgroup only). Direct costs were included.
Source of resources used	NIs and antibiotic use were both estimated from trial data. Follow-up visits were taken from zanamivir trials, and then applied to oseltamivir trials. Hospitalisations were estimated for no treatment from 2 national surveys, and then adjusted for NI treatment with corresponding LRTIs reduction rate estimated from trials.	Follow-up physician visits were taken from a national study. Antibacterial use was estimated from a national study for otherwise healthy patients, and taken from the UK NICE HTA for 'at risk' patients. Hospitalisations were estimated from US (national) national data-bases for otherwise healthy ('at risk') patients. Length of stay was taken from a national data-base for otherwise healthy patients, and assumed fixed for 'at risk' patients. OTC medications were estimated from a national survey. Productivity losses were assumed fixed across subgroups.	Antibacterial use was taken from 2 meta-analysis of different RCTs for all and 'at risk' patients. GP visit and hospitalisation rates were obtained from a UK population study and applied across treatment strategies. Length of hospital stay was derived from the literature.
Source of costs	NI costs were average wholesale prices. Antibiotics and follow-up visits were costed from a published economic study. Hospital costs were derived from a retrospective data-base study.	Cost of zanamivir was based on average wholesale price. Physician visits were costed at the average provincial fee. Antibacterial cost was based on average formulary price. Hospitalisation costs were estimated from 3 provincial cost lists. OTC medication costs were based on average symptomatic relief costs. Productivity losses were valued via a human capital-cost	Cost of zanamivir was taken from the BNF. Antibacterial cost was obtained from an international study. Costs of GP visits and hospital days were derived from a published UK source.

Study details	<i>Armstrong et al. (2000)</i>	<i>Brady et al. (2001)</i>	<i>Burls et al. (2002)</i>
		approach.	
Clinical outcomes	Number of symptom-free days, complications.	Symptom-free days, complications, mortality ('at risk' subgroup only).	Time to alleviation of major symptoms, complications, hospitalisation and mortality ('at risk' subgroup only).
Source of clinical outcomes	Oseltamivir data were compiled from 2 published RCTs. Zanamivir data were compiled from a published RCT, a RCT available in abstract form and data on file (GlaxoWellcome).	Symptom-free days were estimated from a meta-analysis of flu-positive patients from RCTs. Complications were taken from a GlaxoWellcome meta-analysis of RCTs for otherwise healthy patients, and from the UK NICE HTA for 'at risk' patients. Assumptions on mortality originated from national studies.	Efficacy data were taken from a meta-analysis of 11 international RCTs for flu-positive patients. Baseline mortality for 'at risk' patients was taken from a US retrospective study. Zanamivir was assumed to impact on hospitalisations and mortality at its antibiotic reduction rate (6%).
HRQoL	Not included	QALY	QALY
Source of HRQoL	Not applicable	Elicited from 11 adults via the HUI-3 instrument due to lack of data.	Flu was assumed to score 2 on each dimension of the EQ-5D instrument due to lack of data (utility = 0.516). A UK survey informed a score of 0.8 for the non-flu health state.
Adverse events	Not included in base-case analysis. Bronchospasm included in sensitivity analysis.	Not included in base-case analysis. A 1 per 1,000-10,000 incidence in patients on zanamivir, entailing 4 days of hospital stay, was tested in a sensitivity analysis.	Not included since no excess of adverse events between treatment strategies was observed in the trials.
Subgroup analysis	Incremental costs were computed for zanamivir on 'at risk' (aged 65+yrs, with chronic cardiovascular, respiratory or metabolic disorder, immunocompromised) patients. Not performed for oseltamivir due to lack of data.	Separate results were reported for 'at risk' (aged 65+yrs, with chronic cardiovascular, respiratory or metabolic disorder, diabetic, immunocompromised) patients.	Separate results were reported for 'at risk' (aged 65+yrs, with chronic cardiovascular or respiratory disorder, diabetic, immunocompromised) patients.
Diagnostic accuracy (ITT/ITTI)	Efficacy measures were informed on an ITTI basis, due to between-study heterogeneity in diagnostic accuracy; no specific use of ITT data was made explicit. Diagnostic accuracy was not accounted for in base-case.	Efficacy measures were informed on an ITTI basis; no specific use of ITT data was made explicit. Base-case diagnostic accuracies of 14% (A) and 35% (B) were chosen for the flu season and viral activity period respectively, based on UK NICE HTA, observational studies and expert opinion.	Efficacy measures were derived from ITTI patients. Base-case flu prevalences during the influenza season and epidemic periods were estimated at 14% and 34% respectively from national PHLS (now HPA) surveillance data and a UK GlaxoWellcome study. ITT data informed a sensitivity analysis of flu prevalence.
Discounting	Not applied	Not applied in base-case. 5% used on life-years gained in sensitivity analysis of mortality.	Not applied
CEA results	1. Incremental cost per successfully treated patient w.r.t. no treatment: \$358 (zanamivir); \$677 (oseltamivir) 2. Incremental cost per complication averted: same as 1. in base-case 3. Incremental cost per symptom-free day: \$16 (zanamivir); \$39 (oseltamivir)	1. Incremental cost per symptom-free day: otherwise healthy \$194 (A), \$77 (B); 'at risk' \$234 (A), \$93 (B) 2. Incremental cost per QALY gained: otherwise healthy \$235,000 (A), \$94,600 (B); 'at risk' \$195,000 (A), \$77,500 (B) Results were reported for increasing diagnostic accuracy.	1. Incremental cost per symptom-free day: £50 (otherwise healthy), £42 ('at risk') 2. Incremental cost per QALY gained: £65,000 (otherwise healthy), £54,000 ('at risk')
Quadrant on CE plane	NE	NE	NE
Sensitivity analysis	1-way analysis of adverse events rate, hospitalisation rate and cost, probability of antibiotic	1- and multi-way analysis of symptom-free days, utilities, diagnostic accuracy, zanamivir	1-way analysis of antibiotic use, hospitalisation rates, follow-up GP visits, flu prevalence,

Study details	<i>Armstrong et al. (2000)</i>	<i>Brady et al. (2001)</i>	<i>Burls et al. (2002)</i>
	prescription, probability of follow-up visit, cost of NIs and diagnostic accuracy.	and antibacterial use and costs, follow-up visits, hospitalisation rate, mortality (in 'at risk' subgroup), compliance, adverse events, new and late presentation, indirect costs.	symptom-free days, utilities, diagnostic accuracy and cost and availability of zanamivir.
Conclusions	Zanamivir was more CE than oseltamivir w.r.t. standard care across all outcome measures and scenarios. Zanamivir dominates standard care in the 'at risk' patient subgroup.	From a govt payer perspective, zanamivir was not cost-effective for the treatment of flu in individuals not 'at risk'. Its CE profile for 'at risk' patients was unclear but unlikely cost-saving, so its inclusion in a drug plan would have required additional budgetary resources.	Zanamivir was unlikely to be CE in the treatment of flu in all patients under any scenario considered. Results in 'at risk' patients (£15,000-£117,000 cost/QALY) suggested a potential CE profile for zanamivir under optimistic assumptions.
Key CE drivers	Cost of NIs, probability of hospitalisation, 'at risk' status	Symptom-free days, utilities, diagnostic accuracy, zanamivir cost (all patients); hospitalisation rate, mortality, compliance, new and late presentation ('at risk' subgroup).	Utilities, prevalence, cost and availability of zanamivir, symptom-free days.
Conflicts of interest	Authors employed by GlaxoWellcome	None	None

Study details	<i>Griffin et al. (2001)</i>	<i>Husereau et al. (2001)</i>	<i>Inoue et al. (2005)</i>
Economic evaluation type	Cost-effectiveness and cost-utility analysis	Cost-effectiveness and cost-utility analysis	Cost-utility analysis
Currency (year)	GBP (1999)	CAD (2001)	USD (2002)
Study design	IPD bootstrap analysis of 6 pooled multinational RCTs	Decision tree	Decision tree
Perspective	Govt payer	Govt payer, society	Health-care payer
Setting	UK	Canada	Japan
Patient population	'at risk' patients aged 12+yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy (aged 12+yrs) and 'at risk' patients presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy (aged 12-65yrs) and 'at risk' patients presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.
Time horizon	Flu season. Censored efficacy measures were extrapolated to 28 days.	Flu season	2 weeks (based on duration of flu infection)
Comparators	1. Zanamivir 5 days 10mg inhaled bid 2. Placebo	1. Oseltamivir 5 days 75mg bid 2. No treatment	1. Oseltamivir 5 days 75mg bid 2. Zanamivir 5 days 10mg inhaled bid 3. Symptomatic relief (e.g. antibacterials)
Resources used and costs	NI and antibacterial use, GP/nurse consultations, hospitalisations, OTC medication use. Direct costs were included.	NI and antibacterial use, physician visits, hospitalisations and length of stay. Direct and indirect (societal persp. only) costs were included.	Hospitalisations, NI and antibiotic use, physician visits. Direct costs were included (also for diagnostic tests).
Source of resources used	Resource use data were collected alongside the RCTs as part of the Case Report Form (CRF). Hospitalisation data were derived retrospectively from Serious Adverse Events (SAEs) forms.	Hospitalisations (otherwise healthy patients) were taken from a national economic evaluation. Hospitalisations ('at risk' subgroup) and antibacterial use were derived from flu-positive patients on placebo in the RCTs. Physician visits were derived by 'at risk' status from CCOHTA's zanamivir report. Length of hospital stay was obtained by 'at risk' status from a national data-base. Work-days lost were estimated from otherwise healthy flu-positive patients enrolled in 2 RCTs.	Hospitalisation rates were derived from a national observational study (the national health ministry) for otherwise healthy ('at risk') patients on no treatment, and adjusted by 'at risk' status with the pneumonia rates taken from the UK NICE HTA for each NI strategy. Hospital length of stay was assumed the same across treatment strategies. Baseline antibiotic use was derived for otherwise healthy patients from the UK NICE HTA due to lack of data, and adjusted for each NI by 'at risk' status with complication rates estimated from the trials' corresponding arms. Physician visits were estimated from a national (international) study for patients on no treatment (NIs).
Source of costs	GP/nurse consultations and hospitalisations were valued at standard UK unit costs. Antibacterial cost was derived from the UK Medical Data Index and BNF. OTC medication use was costed from a GlaxoWellcome market research.	Cost of oseltamivir was based on average wholesale price. Physician visits were costed at the average provincial fee. Antibacterial cost was based on a provincial formulary price. Hospitalisation costs were estimated from a provincial cost list. Productivity losses were valued as in the CCOHTA zanamivir report (i.e. via a human cost-capital approach).	Physician visits, antibiotic use and hospitalisations were costed using a national survey. Diagnostic tests were priced through medical fee tables. NIs costs were taken from the national Health Insurance Price List.
Clinical outcomes	Time to return to normal activity, time to alleviation of symptoms, treatment effect on	Time to alleviation of symptoms, time to return to normal activity, treatment effect on antibacterial	Time to alleviation of symptoms.

Study details	<i>Griffin et al. (2001)</i>	<i>Husereau et al. (2001)</i>	<i>Inoue et al. (2005)</i>
	complications and hospitalisations.	use and hospitalisations ('at risk' subgroup only).	
Source of clinical outcomes	Time to return to normal activity and to alleviation of symptoms and information on complications were part of the CRFs compiled alongside (after) the RCTs. Treatment impact on hospitalisation was derived from serious adverse events forms compiled after the trials.	Treatment effects on hospitalisation, on duration of symptoms and on time to return to normal activity were estimated from a pooled analysis of flu-positive patients from RCTs. Due to lack of data oseltamivir was assumed not to impact on hospitalisations (otherwise healthy patients only) and physician visits.	Time to alleviation of symptoms was taken by 'at risk' status and treatment strategy from the UK NICE HTA due to lack of data.
HRQoL	QALY	QALY	QALY
Source of HRQoL	Estimated from EQ-5D questionnaires retrospectively completed by patients from a UK GP data-base and double-checked with an EQ-5D questionnaire from a UK GP panel for a hypothetical 'at risk' patient.	Due to lack of data utilities were taken for the flu – outpatient state (0.636) from CCOHTA's zanamivir report (i.e. from 11 adults via the HUI-3 instrument), while for the flu – inpatient state were assumed fixed (0.35).	Utility was measured on the EQ-5D instrument from a national study as the difference between QoL without and with flu (0.883).
Adverse events	Hospitalisations resulting from SAEs were included in base-case analysis.	Not included as those observed from the trials were not significant.	Not included.
Subgroup analysis	Results presented for 'at risk' (aged 65+yrs, with chronic cardiovascular or respiratory disorder, diabetic, immunocompromised) patients only.	Separate results were reported for 'at risk' (aged 65+yrs, with chronic cardiovascular, respiratory or metabolic disorder, diabetic, immunocompromised) patients.	Separate results were reported for 'at risk' (aged 65+yrs, with chronic cardiovascular or respiratory disorder, diabetic, immunocompromised) patients.
Diagnostic accuracy (ITT/ITTI)	Evaluation conducted on an ITT basis; no specific use of ITTI data was made explicit. Flu prevalence was estimated at 71% from 'at risk' patients in the trials.	ITTI data were utilised to estimate productivity losses (societal persp. only) and reduced symptom days. No specific use of ITT data was made explicit. 4 diagnostic accuracies (A = 14%, B = 35%, C = 50%, D = 68%) reflecting flu season/viral activity period were used in base-case and sensitivity analysis, based on the UK NICE HTA, ITTI data from the pooled trials, international studies and expert opinion.	Efficacy was evaluated on an ITTI basis; no specific use of ITT data was made explicit. Flu prevalence was estimated at 66.4% from national RCTs.
Discounting	Not applied	Not applied	Not applied
CEA results	1. ICER for time to return to normal activity: £18.14 2. ICER for time to alleviation of symptoms: £22.08 3. ICER for incidence of complications: £501 4. Incremental cost per QALY gained: £7,490	1. Incremental cost per symptom-free day: otherwise healthy \$299 (A), \$119 (B), \$83 (C) and \$61 (D); at risk \$478 (A), \$180 (B), \$120 (C) and \$83 (D) 2. Incremental cost per QALY gained: otherwise healthy \$299,500 (A), \$119,500 (B), \$83,500 (C) and \$61,300 (D); 'at risk' \$454,800 (A), \$170,700 (B), \$113,900 (C) and \$78,800 (D) Results were reported for increasing diagnostic accuracy.	Incremental cost per QALY gained w.r.t. no treatment: oseltamivir dominant (otherwise healthy), \$2138.77 ('at risk'); zanamivir \$107.34 (otherwise healthy), dominant ('at risk')
Quadrant on CE plane	NE	NE	NE/SE (depending on 'at risk' status)
Sensitivity analysis	Two scenario analyses excluding either hospitalisations	1- and multi-way analysis of diagnostic accuracy, symptom-	1-way analysis of hospitalisation costs, 2-way analysis of

Study details	<i>Griffin et al. (2001)</i>	<i>Husereau et al. (2001)</i>	<i>Inoue et al. (2005)</i>
	or one patient hospitalised with pneumonia.	free days, utilities, physician visits, antibacterial use, hospitalisation, late presentation, compliance, early return to normal activity (societal perspective).	probability of hospitalisation by treatment strategy, PSA of direct costs.
Conclusions	Zanamivir was a CE strategy for the treatment of flu in 'at risk' patients.	From a govt payer perspective, oseltamivir was unlikely cost-effective for the treatment of flu in either otherwise healthy and 'at risk' patients, unless very favourable assumptions applied.	Treatment of flu with NIs led to higher clinical efficacy and cost savings compared to symptomatic care. Oseltamivir was not recommended for treating flu in otherwise healthy patients, and was less CE than zanamivir in 'at risk' patients.
Key CE drivers	Zanamivir cost, hospitalisation costs, outlying patient (i.e. one hospitalisation with pneumonia).	Symptom-free days, QALY, diagnostic accuracy, compliance, late presentation, hospitalisation ('at risk' subgroup).	Cost and probability of hospitalisation, direct costs.
Conflicts of interest	Authors employed by GlaxoWellcome	None	None

Study details	<i>Järvinen et al. (2007)</i>	<i>Lee et al. (2002)</i>	<i>Mauskopf et al. (2000)</i>
Economic evaluation type	Cost-utility analysis	Cost-effectiveness analysis	Cost-effectiveness and cost-utility analysis
Currency (year)	EUR (2005)	USD (2001)	AUD (1998)
Study design	Decision tree	Decision tree	Decision tree populated with the double-blind multinational MIST RCT
Perspective	Health-care payer, society	Society	Health-care payer
Setting	Finland	USA	Australia
Patient population	Separate assessment of (i) otherwise healthy adults (aged 13-64yrs), (ii) 'at risk' (aged 65+yrs, with co-morbidities) patients and (iii) children (aged 1-12yrs) presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy patients aged 18-50yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	'at risk' (aged 65+yrs, with co-morbidities) patients presenting within 36hrs of ILI symptom onset with either confirmed and unconfirmed flu.
Time horizon	Lifetime (to account for life-years lost to mortality)	Single flu season	4 weeks (single flu season)
Comparators	1. Oseltamivir 5 days 75mg bid 2. Symptomatic relief (OTC medication)	1. Vaccination + rimantadine 2. Vaccination + zanamivir 3. Vaccination + oseltamivir 4. Vaccination + no treatment 5. No vaccination + rimantadine 6. No vaccination + zanamivir 7. No vaccination + oseltamivir 8. No vaccination + no treatment Treatments administered as per licensed indications	1. Zanamivir 5 days 10mg inhaled bid 2. Standard care
Resources used and costs	GP/specialist visits, hospitalisations, NI, antibiotic and OTC medication use. Direct and indirect (societal persp. only) costs were included.	Vaccine, antiviral and antibiotic use, physician visits, work-days lost. Direct and indirect costs were included.	Hospitalisations and length of stay, physician visits, NI and antibacterial use. Direct costs were included.
Source of resources used	Resource use data were taken from published RCTs or the literature.	Vaccine, antiviral and antibiotic use were taken from trial data. A physician visit was assumed upon infection onset. Work-days lost were derived from various trial-based and observational studies.	Hospitalisations were estimated with data from the national health institute. Length of hospital stay was assumed equal to the national average for a DRG. Physician visits were taken from the national RCGP and health insurance data. Antibacterial use was estimated from the MIST trial.
Source of costs	Oseltamivir, antibiotics and OTC medication were costed from national price guidelines. GP/specialist visits were costed from both national official health-care costs and a US survey. Hospitalisation costs were taken from national official health-care costs. Productivity losses were valued at the national average gross income using the human-capital approach.	Antibiotic use was costed from an International Classifications of Disease code. Vaccination costs were informed by data from a previous trial. NIs were valued at average retail prices, whereas rimantadine was costed from a national health-care cost data-base Work-days lost were valued at the average national gross wage.	Zanamivir cost was its dispensed price. Antibacterial costs were taken from 2 national price lists. Physician visits were costed from the national Medicare Benefits Schedule.
Clinical outcomes	Time to return to normal activity, complications, hospitalisation and mortality rates.	Illness duration, time to return to normal activity	Time to alleviation of major symptoms, complications.
Source of	Time to return to normal activity	Health outcomes were	Time to alleviation of major

Study details	<i>Järvinen et al. (2007)</i>	<i>Lee et al. (2002)</i>	<i>Mauskopf et al. (2000)</i>
clinical outcomes	<p>was derived from 2 clinical studies and an international RCT. Complication and corresponding hospitalisation rates were taken from a UK population study, a meta-analysis of international RCTs and an epidemiological study.</p> <p>Mortality rates by causing complication were obtained from various clinical and observational studies and from assumptions.</p>	<p>estimated from published evaluations of various RCTs.</p>	<p>symptoms was derived for all treatment strategies from the MIST trial in the outpatient setting, and assumed equal to length of hospital stay + 7 days in the inpatient setting.</p> <p>Treatment was assumed not to impact on the course of complications. Probabilities of complications were estimated by treatment strategy from the MIST trial.</p>

Study details	<i>Järvinen et al. (2007)</i>	<i>Lee et al. (2002)</i>	<i>Mauskopf et al. (2000)</i>
HRQoL	QALY	Willingness to pay for a symptom-free and side effects day averted	QALY
Source of HRQoL	Utilities on ILI, bronchitis, pneumonia, otitis media and sinusitis were taken from 2 international studies through the EQ-5D instrument recalibrated onto VAS and TTO scores.	Utilities were obtained through a conjoint analysis of a national primary care survey of 210 patients.	Measured from the MIST trial through the QWB instrument.
Adverse events	Not included.	Side effects were assumed not to attract additional physician visits. Side effect rates for rimantadine (nervous = 2%, gastro-intestinal = 1%) and oseltamivir (gastro-intestinal = 9%) were informed by 2 national reviews and a clinical study respectively. Zanamivir and prophylaxis were assumed not to cause side effects, in line with trial evidence.	Not included.
Subgroup analysis	Not implemented	Not implemented	Not implemented
Diagnostic accuracy (ITT/ITTI)	Baseline complication rates were computed from the ITTI population; no specific use of ITT data was made explicit. Base-case assumed 70% patients were flu-positive based on oseltamivir RCTs.	The evaluation was conducted on an ITTI basis; no specific use of ITT data was made explicit. Seasonal flu prevalence was estimated at 15% from various published sources. Type A flu prevalence was estimated at 83.7% from unpublished national average rates over a 10yrs period.	Clinical effectiveness was measured on an ITTI basis. Hospitalisations and length of stay were assumed the same across ITT/ITTI populations irrespective of treatment. Base-case flu prevalence was estimated at 70% from the MIST RCT.
Discounting	Health outcomes discounted at 5%	Not applied	Not applied
CEA results	Incremental cost per QALY gained: otherwise healthy €13,405 (health-care payer persp.); dominant (societal persp.); 'at risk' €754 (health-care payer persp.); children €15,404 (health-care payer persp.), €5,745 (societal persp.)	Incremental net benefit w.r.t. no treatment/vaccination: \$30.97 (vaccination + rimantadine), \$30.13 (vaccination + zanamivir), \$29.50 (vaccination + no treatment), \$29.39 (vaccination + oseltamivir), \$4.61 (no vaccination + rimantadine), \$1.97 (no vaccination + zanamivir), -\$0.032 (no vaccination + oseltamivir)	1. Incremental cost per symptom-free day: \$14.20 2. Incremental cost per QALY gained: \$11,715
Quadrant on CE plane	NE/SE (depending on health-care perspective and population)	NE/SE (depending on comparison)	NE
Sensitivity analysis	1-way analysis of probability of ILI being flu, late presentation, NI efficacy, discount rate and productivity loss. PSA of time to return to normal activity, length of hospital stay and probabilities of complications, hospitalisation and death.	1-way analysis and PSA of all inputs.	1-way analysis of flu prevalence, hospitalisation rate and length of stay, utility, NI efficacy, diagnostic accuracy.
Conclusions	Oseltamivir was found to be equally CE for treating flu in otherwise healthy adults and children, and also very CE in 'at risk' individuals, both from a	Vaccination was found to be CE for otherwise healthy working adults in a wide variety of settings. Its combining antiviral choice mostly depended on	Zanamivir was a CE treatment for flu in 'at risk' patients under a wide variety of assumptions.

Study details	<i>Järvinen et al. (2007)</i>	<i>Lee et al. (2002)</i>	<i>Mauskopf et al. (2000)</i>
	health-care payer and societal perspective.	drug cost and circulating viral strain.	
Key CE drivers	Diagnostic accuracy, late presentation	Flu prevalence (overall and by type), antiviral efficacy, work-days lost.	Hospitalisation rate, NI efficacy, diagnostic accuracy
Conflicts of interest	2 authors employed by Roche	None	2 authors employed by GlaxoWellcome

Study details	<i>O'Brien et al. (2003)</i>	<i>Postma et al. (2007)</i>	<i>Reisinger et al. (2004)</i>
Economic evaluation type	Cost-effectiveness and cost-utility analysis	Cost-effectiveness analysis	Cost-effectiveness and cost-utility analysis
Currency (year)	CAD (1999)	EUR (2003)	GBP (2002)
Study design	Decision tree populated with IPD analysis of 4 pooled international RCTs	Decision tree	Decision tree
Perspective	Health-care payer	Health-care payer, society	Health-care payer
Setting	Canada	The Netherlands	UK
Patient population	Otherwise healthy, unvaccinated patients aged 16-64yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Separate assessment of (i) otherwise healthy and (ii) 'at risk' (with co-morbidities) elderly (aged 65+yrs) and (iii) 'at risk' adults (aged 12+yrs with co-morbidities) presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy patients aged 1-12yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.
Time horizon	1 week	Unspecified	Flu season (extrapolated to account for life-years lost due to mortality)
Comparators	1. Oseltamivir 5 days 75mg bid 2. No treatment	1. Oseltamivir 5 days 75mg bid 2. Symptomatic relief (OTC medication)	1. Oseltamivir 5 days 2mg/kg bid 2. Symptomatic relief (OTC medication)
Resources used and costs	Hospitalisations, NI and antibiotic use, physician visits. Direct costs were included.	NI and antibacterial use, hospitalisations and length of stay, initial GP visit with OTC medication prescription, work-days lost (non-elderly, societal persp. only). Direct and indirect (societal persp. only) costs were included.	GP/specialist visits, tests for complications, NI and antibiotic use, hospitalisations. Direct costs were included.
Source of resources used	Hospitalisations were derived from a US observational study. Antibiotic use and physician visits were taken from a US health insurance data-base. Base-case assumed no late presentation to a physician, in line with market research data.	Antibacterial use was informed by expert opinion. Hospitalisations and length of stay were separately estimated for pneumonia and other complications from a national health-care data-base. Base-case assumed no follow-up GP visits. Days lost were assumed to average 1.5 based on various economic studies.	Resource use data by complication (bronchitis, pneumonia, otitis media) were taken from a US health-care data-base due to lack of national detailed sources. Base-case assumed no late presentation.
Source of costs	Oseltamivir was costed at its dispensing price. Antibiotics were costed from the national formulary. Hospitalisation costs were taken from a regional hospital. Physician visits were costed from a regional health-care fees list.	Oseltamivir was costed at a national average dispensing cost. A fixed cost was assumed for an initial GP visit including OTC medication course. Work-days lost were valued via a friction-costing approach.	Physician visits, tests and hospitalisations were costed from a UK health-care data-base. The cost of antibiotics was taken from the UK BNF. Oseltamivir was costed at its average wholesale price.
Clinical outcomes	Time to symptoms resolution, complications.	Antibacterial use, complication, hospitalisation and mortality reduction rates.	Time to return to normal activity, complication, hospitalisation and mortality reduction rates.
Source of clinical outcomes	Time to symptoms resolution was estimated from 4 pooled and separate RCTs. Complications (including pneumonia) were recorded from the RCTs.	Health outcomes were derived for oseltamivir across assessed populations from a meta-analysis of 11 international RCTs, and for no treatment for each population from 3 national observational studies adjusted with vaccination coverage and efficacy rates informed by national studies.	Time to return to normal activity and complication reduction rates were derived from a multinational RCT data and a UK population study. Hospitalisation and mortality rates by causing complication were estimated for each treatment strategy from observational studies, a meta-analysis of 11 international RCTs

Study details	<i>O'Brien et al. (2003)</i>	<i>Postma et al. (2007)</i>	<i>Reisinger et al. (2004)</i>
			and assumptions.
HRQoL	QALY	Not included	QALY
Source of HRQoL	Reported daily for a week by enrolled patients through VAS instrument.	Not applicable	Unspecified utilities for each health state were recorded from the efficacy trials during the first week of illness. Same QoL improvement was assumed in the trials for otherwise healthy children and adults due to lack of data.
Adverse events	Implicitly accounted for by VAS evaluations.	Not included	Not included.
Subgroup analysis	Not implemented	Not implemented	Separate results were reported for children aged 1-5yrs.
Diagnostic accuracy (ITT/ITTI)	Clinical efficacy was obtained on an ITTI basis; no specific use of ITT data was made explicit. Flu prevalence was estimated at 69% from available RCTs.	Efficacy was measured on an ITT basis; no specific use of ITTI data was made explicit. A flu prevalence rate of 65% was assumed based on a meta-analysis of 11 international RCTs.	Efficacy outcomes were informed by flu-positive patients only. No specific use of ITT data was made explicit. Diagnostic accuracy was estimated at 60% from the trials.
Discounting	Not applied	4% used on life-years lost	1.5% used on life-years lost
CEA results	1. Incremental cost per flu day averted: \$48.52 (CI = \$30.72 – \$107.32) 2. Incremental cost per QALY gained: \$57,863 (CI = \$48,919 – \$70,149)	ICER: €1,759 (otherwise healthy elderly), dominant ('at risk' elderly), dominant ('at risk' adults including indirect costs), €429 ('at risk' adults excluding indirect costs)	1. Incremental cost per illness day averted: 1-12yrs £9.52 (CI = £6.88 – £13.61); 1-5yrs dominant (CI = dominant – £9.06) 2. Incremental cost per QALY gained: 1-12yrs £11,173 (CI = £18,10 – dominated); 1-5yrs dominant (CI = dominant – dominated)
Quadrant on CE plane	NE	NE/SE (depending on subgroup and inclusion of indirect costs)	NE/SE (depending on age group)
Sensitivity analysis	2-way analysis of flu prevalence and late presentation. PSA on complications, pneumonia hospitalisation, antibiotic use and flu prevalence.	1-way analysis of 1-day ICU stay, 1 extra-GP visit for 50% patients with ILI, treatment effectiveness, discount rate, late presentation. PSA of antibacterial prescription rate, days lost, productivity loss (adults).	1-way analysis of diagnostic accuracy, late presentation, flu hospitalisation rate, treatment efficacy. PSA of complications, hospitalisations, mortality, treatment efficacy and costs.
Conclusions	Oseltamivir was potentially a CE strategy for flu treatment in otherwise healthy adults depending on flu prevalence and treatment compliance.	Oseltamivir was likely a cost-saving, where not CE, treatment for flu in 'at risk' elderly and adults (provided productivity losses incurred by the latter were included) under various scenarios.	Oseltamivir treatment of flu in children was found to be CE even under conservative assumptions with most ICERs per QALY gained under £30,000.
Key CE drivers	Flu prevalence, late presentation	Indirect costs, discount rate, 1 extra-GP visit for 50% patients with ILI, productivity loss, late presentation.	Diagnostic accuracy, late presentation, flu hospitalisation rate, treatment efficacy.
Conflicts of interest	Study funded by Hoffman-La Roche	2 authors supported by Roche	Study funded by Hoffman-La Roche

Study details	<i>Roche submission to NICE (2008)</i>	<i>Rothberg et al. (2003a)</i>	<i>Rothberg et al. (2003b)</i>
Economic evaluation type	Cost-utility analysis	Cost-utility analysis	Cost-utility analysis
Currency (year)	GBP (2007)	USD (2001)	USD (2001)
Study design	Decision tree	Decision tree	Decision tree
Perspective	NHS	Society	Society
Setting	UK	USA	USA
Patient population	Otherwise healthy and 'at risk' patients aged 1-64yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy patients aged 65+yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy, unvaccinated patients aged 20-50yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.
Time horizon	Lifetime (to account for life-years lost due to mortality)	Lifetime	Single flu season
Comparators	1. Oseltamivir 5 days 75mg bid 2. Zanamivir 5 days 10mg inhaled bid (not administered to children aged 1-5yrs due to license restrictions) 3. Standard care (OTC medication)	1. No treatment 2-5. Amantadine, rimantadine, oseltamivir or zanamivir treatment as per licensed indications 6-9. QuickVue test + antiviral treatment	1. No treatment 2-5. Amantadine, rimantadine, oseltamivir or zanamivir treatment as per licensed indications 6-9. Non-discriminating flu test + antiviral treatment 10-13. Discriminating flu test (Directigen AB) + antiviral treatment
Resources used and costs	GP visits, NI and antibiotic use, OTC medication, hospitalisations. Direct costs were included.	Hospitalisations and length of stay, physician visits, flu test, antibiotic and antiviral use. Due to the average patients' age, only direct costs were included.	Hospitalisations, rapid tests, physician visits, antibiotic and antiviral use, work-days lost. Direct and indirect costs were included.
Source of resources used	Resource use data were taken and reviewed from the UK NICE TA58, which referred to a US health-care data-base. Antibiotic use was informed by expert opinion.	Hospitalisations were taken for patients by low, intermediate and high risk (depending on co-morbidities) from a national study. Physician visits and antibiotic use were derived from a US health-care data-base.	Hospitalisations were derived from 3 national studies. Physician visits and antibiotic use were derived from trials on treatment efficacy. Work-days lost were derived from 3 international studies.
Source of costs	GP fees were taken from a national health-care cost table. NIs were valued at average wholesale prices. Antibiotics and hospitalisations were respectively costed according to assumptions and national HRG figures.	Hospitalisation costs were based on data from a national hospital network. Flu tests were costed at average retail prices; antivirals and antibiotics were costed at average wholesale prices. Physician visits were valued from a national study.	Hospitalisation costs were based on data from a network of national hospitals. Flu tests were costed at average retail prices; antivirals and antibiotics were costed at average wholesale prices. Physician visits were valued from a national study. Work-days lost were valued at the national average employee wage.
Clinical outcomes	Time to return to normal activity, complication, hospitalisation and mortality reduction rates.	Length of influenza illness, hospitalisation and length of stay, antibiotic reduction rate, treatment impact on complications requiring antibiotics, vaccine efficacy, mortality	Length of influenza illness, length of hospital stay, treatment impact on complications requiring antibiotics, mortality
Source of clinical outcomes	NIs were assumed equally effective and not to alter the course of complications. Time to return to normal activity was collected through self-reported VAS instruments in the oseltamivir trials. Subgroup-adjusted baseline complications were observed from a national	Length of influenza illness was estimated from 2 RCTs. Based on published trial results, antivirals were assumed to equally impact on influenza duration. Amantanes were assumed not to impact on complications, hospitalisation or mortality due to lack of data.	Length of influenza illness was derived from an economic evaluation (adamantines) and trial data (NIs). Antivirals were assumed to equally impact on influenza duration. Length of hospital stay was derived from a national observational study. Due to lack of evidence,

Study details	<i>Roche submission to NICE (2008)</i>	<i>Rothberg et al. (2003a)</i>	<i>Rothberg et al. (2003b)</i>
	population study (pneumonia, bronchitis) and the placebo arms of the oseltamivir RCTs (otitis media), and were adjusted with NI reduction rates from various published and unpublished oseltamivir trials. Hospitalisation reduction rates by causing complications were obtained from both trial-based and observational studies and assumptions. Subgroup-specific mortality rates were taken from a national population study and adjusted across treatments with the hospitalisations reduction rate.	Treatment impact on antibiotic use, complications requiring antibiotics and hospitalisation was estimated for each NI from various RCTs. Vaccine efficacies by disease state were derived from published trial and observational data. Mortality was extrapolated from the hospitalisation rate, in line with an observational study.	adamantanes were assumed not to impact on complications and no drug was assumed to impact on hospitalisation or mortality. Treatment impact on antibiotic use, complications requiring antibiotics and hospitalisation was estimated for each NI from various RCTs. Mortality was extrapolated from the hospitalisation rate, in line with an observational study.
HRQoL	QALY	QALY	QALY
Source of HRQoL	Health-state utilities (ILI usual care = 0.811, ILI oseltamivir = 0.904, bronchitis = 0.913, pneumonia = 0.9, otitis media = 0.91) were collected from patients in oseltamivir trials for 21 days through a 3 11-point VAS instrument and transformed into TTO scores.	Utility values (flu = -0.883, hospitalisation = -0.983, side effects = -0.23) were assessed from elderly trial patients via the EQ-5D instrument.	Utility values (flu = 0.25, hospitalisation = 0.2, side effects = 0.88) were retrospectively collected from a sample of 15 otherwise healthy adults via the HUI-3 instrument.
Adverse events	Not included	Side effects were estimated for each treatment from studies of nursing home prophylaxis and were assumed to last 2 days.	Side effects were estimated for each treatment from the trials on efficacy and were assumed to last 2 days.
Subgroup analysis	Separate results were reported for (i) otherwise healthy and (ii) 'at risk' (with co-morbidities) adults (aged 13-64yrs) and children (aged 1-12yrs and 1-5yrs).	Not implemented	Not implemented
Diagnostic accuracy (ITT/ITTI)	No specific use of ITT/ITTI data was made explicit. Flu prevalence was fixed at 31% from the UK NICE TA58 (alternative case). Type A flu prevalence was estimated at 76% from RCTs on both NIs.	Efficacy was evaluated on an ITTI basis; no specific use of ITT data was made explicit. Base-case flu prevalence was estimated at 35% to reflect flu seasonal activity, based on a primary care study. Lower and higher rates for flu prevalence as tested in sensitivity analysis were informed by various published sources and assumptions. Flu prevalence by type A was estimated at 89% from national flu surveillance reports.	Efficacy was evaluated on an ITTI basis; no specific use of ITT data was made explicit. Base-case flu prevalence was estimated at 77% from a pooled analysis of national RCTs. Lower and higher rates for flu prevalence as tested in sensitivity analysis were informed by various published sources and assumptions. Flu prevalence by type A was estimated at 89% from national flu surveillance reports.
Discounting	3.5% used on life-years lost	Not applied	Not applied
CEA results	Incremental cost per QALY gained: oseltamivir vs. usual care £5,452 (otherwise healthy adults), £652 ('at risk' adults), £5,992 (children 1-12yrs), £4,687 (children 1-5yrs); oseltamivir vs. zanamivir -£0.19 (otherwise healthy and 'at risk' adults), £5.65 (children 1-12yrs)	Incremental cost per QALY gained: \$1,129 (amantadine vs. no treatment), \$5,025 (flu test + oseltamivir vs. amantadine), \$19,296 (oseltamivir vs. flu test + oseltamivir), dominated or extendedly dominated (otherwise) Base-case results referred to an otherwise healthy, unvaccinated patient.	Incremental cost per QALY gained: \$77,000 (amantadine vs. no treatment), \$133,000 (zanamivir vs. amantadine), dominated or extendedly dominated (otherwise)
Quadrant on	NE/SE (depending on	NE/SE	NE/SE

Study details	<i>Roche submission to NICE (2008)</i>	<i>Rothberg et al. (2003a)</i>	<i>Rothberg et al. (2003b)</i>
CE plane	comparison)		
Sensitivity analysis	1-way analysis of diagnostic accuracy, late presentation, GP visits, life-years lost, hospitalisations, critical care cost, resistance, NI cost (children only), utilities. PSA of all inputs.	1- and multi-way analysis of all variables except drug costs, at risk and vaccination status, adamantane efficacy. PSA of length of hospital stay and hospitalisation, complication and mortality rates.	1- and multi-way analysis of flu prevalence (overall and by type), treatment efficacy, side effects, workday value, utilities, flu test.
Conclusions	Oseltamivir exhibited a CE profile compared to standard care under a wide variety of assumptions, yielding an ICER well below £20,000. It also proved a cost-saving option relative to zanamivir across all patients subgroups.	Oseltamivir was CE for the treatment of flu in unvaccinated or high-risk vaccinated patients. Flu test followed by oseltamivir treatment was usually found to be CE in other subgroups.	Depending on the active viral strain, amantadine and zanamivir were found to be CE flu therapies in otherwise healthy adults. Flu testing was generally found to have no role.
Key CE drivers	Diagnostic accuracy, late presentation, NI and critical care costs.	'at risk' and vaccination status, flu prevalence, impact of oseltamivir on hospitalisations, hospitalisation and mortality rates.	Flu prevalence (overall and by type), treatment efficacy, workday value.
Conflicts of interest	NICE submission sponsored by Roche	None	None
Study details	Rothberg et al. (2005)	Sander et al. (2004)	Sander et al. (2005)
Economic evaluation type	Cost-utility analysis	Cost-effectiveness and cost-utility analysis	Cost-effectiveness and cost-utility analysis
Currency (year)	USD (2003)	GBP (2001)	GBP (2001)
Study design	Decision tree	Decision tree	Decision tree
Perspective	Society	Health-care payer	NHS, society
Setting	USA	UK	UK
Patient population	Separate assessment of otherwise healthy children aged (i) 2, (ii) 7 and (iii) 15yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy elderly (aged 65+yrs) and 'at risk' (aged 13-64yrs with co-morbidities) patients presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy patients aged 13-64yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.
Time horizon	2 flu seasons	Single flu season (extrapolated to account for life-years lost due to mortality)	21 days, with censored time to return to normal activity (life years lost) not extrapolated (extrapolated to account for mortality).
Comparators	1. No treatment 2. Amantadine as per licensed indications 3. Oseltamivir 5 days 75mg bid 4-5. QuickVue test + amantadine or oseltamivir treatment 6-7. ZstatFlu test + amantadine or oseltamivir treatment	1. Oseltamivir 5 days 75mg bid 2. Standard care (symptomatic relief with OTC medication)	1. Oseltamivir 5 days 75mg bid 2. Zanamivir 5 days 10mg inhaled bid 3. Standard care (OTC medication)
Resources used and costs	Hospitalisations, physician visits, 2 flu tests, antiviral and antibacterial use, work-days lost. Direct and indirect costs were included.	GP and specialist visits, flu tests, OTC medications, NI use, hospitalisations. Direct costs were included.	GP/specialist visits, tests, antibiotic and NI use, OTC medications, hospitalisations and length of stay, work-days lost (societal persp. only). Direct and indirect (societal persp. only) costs were included.
Source of resources used	Hospitalisations were taken from a national study. Physician	Resource use data were taken from a US health-care	Resource use data were taken from a US health-care

Study details	<i>Roche submission to NICE (2008)</i>	<i>Rothberg et al. (2003a)</i>	<i>Rothberg et al. (2003b)</i>
	visits were extracted from a national observational study. Flu tests were evaluated from a published review. Work-days lost were derived from 3 regional elementary schools.	population survey due to lack of detailed national sources. Hospitalisations by causing complication (ILI, bronchitis, pneumonia) were derived from trial and observational data and from assumptions.	population survey due to lack of detailed national sources. Hospitalisations by causing complication (ILI, bronchitis, pneumonia) were informed by trial and observational data and from assumptions. Work-days lost were taken from the days to return to normal activity estimated from trial and epidemiological sources.
Source of costs	Hospitalisations were costed from a national health-care data-base. Physician fees were based on Medicare relative value units. Flu tests were costed at average retail prices; antivirals and antibacterials were costed at average wholesale prices. Parental work-days lost were valued at the national average employee compensation.	Hospitalisations and GP and specialist visits were costed from a national health-care cost list. Flu tests and antibiotics were costed from a US health-care data-base. OTC medications cost was assumed fixed.	Hospitalisations and length of stay and GP/specialist visits were costed from a national health-care cost list. Tests were costed from a US health-care data-base. Antibiotic costs were taken from the UK BNF. NIs were costed at the average wholesale prices. Cost of OTC medications was assumed fixed. Productivity losses were valued via a human-capital approach based on the national average gross income. Indirect costs of mortality were excluded, since they were already captured by the QALYs.
Clinical outcomes	Hospitalisations and length of stay, complications requiring antibiotics, mortality, time to return to school.	Time to return to normal activity, treatment impact on QoL, complications, hospitalisation and mortality	Time to return to normal activity, complications and flu-related hospitalisation reduction rates, mortality
Source of clinical outcomes	Antivirals were assumed not to impact on hospitalisation or mortality. Length of hospital stay was estimated from a national health-care data-base. Complications requiring antibiotics (otitis media) were observed from placebo arms of 3 RCTs. Mortality was estimated from a national health-care data-base. Time to return to school for the oseltamivir strategy was taken from the UK NICE HTA, and was applied to amantadine due to lack of data.	Time to return to normal activity was estimated from a pooled analysis of 6 multicentre RCTs. Treatment impact on QoL was taken from the UK NICE HTA. Treatment impact on complications (bronchitis, pneumonia) and hospitalisations was derived from a meta-analysis of 11 international RCTs. Baseline mortality was estimated by causing complication (ILI, pneumonia, bronchitis) from 2 national studies, and extrapolated to oseltamivir using overall reduction in hospitalisations from the trials.	Time to return to normal activity was recorded on diary cards alongside RCTs. Flu-related hospitalisation reduction rates were derived from published trial data and assumed the same for the two NIs. Baseline complications were estimated from a national population study, and adjusted by treatment strategy with reduction rates derived from published trial data. Mortality by causing complication (ILI, pneumonia, bronchitis) was derived from trial and observational data and assumptions. Treatments were assumed not to impact on mortality.
HRQoL	QALY	QALY	QALY
Source of HRQoL	Measured on the EQ-5D instrument from unpublished data from zanamivir trials of children combined with carers' opinion.	Utilities (ILI = 0.89, bronchitis = 0.99, pneumonia = 0.9) were assessed from flu-positive patients in the trials on 3 11-point VAS and projected onto TTO scores.	The incremental utility for oseltamivir relative to standard care for ILI (0.94) was taken from diary records relative to the first 9 days of patients in oseltamivir trials on Likert scores re-calibrated into VAS and projected onto a TTO scale. Same QoL improvement was assumed for patients on zanamivir due to lack of data. Generic utility weights from an international study were applied to bronchitis (0.99) and pneumonia (0.9).
Adverse events	Side effects were estimated for each treatment from various	Not included	Not included

Study details	<i>Roche submission to NICE (2008)</i>	<i>Rothberg et al. (2003a)</i>	<i>Rothberg et al. (2003b)</i>
	RCTs and were assumed to start on day 2 of treatment and last for 4 days.		
Subgroup analysis	Not reported	Not implemented	Not implemented
Diagnostic accuracy (ITT/ITTI)	No specific use of ITTI data was made explicit. Flu prevalence during the activity period was estimated at 68% from 2 published RCTs. Flu type A prevalence was estimated for dominant (99%) and mixed (55%) seasons from national surveillance reports.	Clinical efficacy was assessed on an ITTI basis; no specific use of ITT data was made explicit. Base-case flu prevalence was estimated at 70% based on the oseltamivir trials; the UK NICE HTA informed a low diagnostic accuracy of 34% for sensitivity analysis purposes.	Baseline inputs were informed on an ITT basis. Base-case diagnostic accuracy was fixed at 70% based on European oseltamivir trials; the UK NICE HTA informed a low diagnostic accuracy of 34% which was used in sensitivity analysis. No specific use of ITTI data was made explicit.
Discounting	Not applied	1.5% used on life-years lost	1.5% used on life-years lost
CEA results	Incremental cost per QALY gained: type A dominant seasons \$1,775 (amantadine vs. no therapy, 15yrs), dominated (otherwise); mixed flu seasons \$7,440 (oseltamivir vs. amantadine, 7yrs), \$4,329 (amantadine vs. no therapy, 15yrs), \$47,153 (oseltamivir vs. amantadine, 15yrs), dominated (otherwise)	1. Incremental cost per illness day averted: £3.16 (range = dominant – £8.63) 2. Incremental cost per QALY gained: £225.48 (range = oseltamivir dominant – dominated)	1. Incremental cost per QALY gained: oseltamivir vs. no treatment £5,600 (range = £1,403 – dominated), zanamivir vs. oseltamivir dominated (range = £3,737 – dominated) 2. Incremental cost per illness day averted: oseltamivir vs. no treatment £14.36 (range = £10.69 – £17.67), zanamivir vs. oseltamivir £112.84 (range = £93.88 – £149.67) Results were also reported from a societal perspective.
Quadrant on CE plane	NE/SE (depending on flu type prevalence and age)	NE significantly	NE/SE (depending on comparisons and health-care perspective)
Sensitivity analysis	1- and multi-way analyses and PSA of all variables except drug cost, flu prevalence (overall and by type).	1- and multi-way analyses of diagnostic accuracy, late presentation, treatment impact on adverse events. PSA of complication, hospitalisation and mortality rates, time to return to normal activity.	1- and multi-way analyses of diagnostic accuracy, late presentation, treatment impact on adverse events, discount rate, productivity loss. PSA of complication, hospitalisation and mortality rates, length of hospital stay, time to return to normal activity.
Conclusions	Antiviral therapy for flu in children generally showed a favourable CE profile. Oseltamivir was preferred (equivalent) to amantadine in cases of significant (insignificant) flu type B prevalence. Flu testing was generally found to have no role.	Oseltamivir showed a CE profile compared to usual care for treating flu in 'at risk' patients even under conservative assumptions (i.e. with ICERs between £225 and £17,900).	Oseltamivir generally exhibited a CE profile compared to usual care and zanamivir for treating flu in otherwise healthy adults from an NHS perspective and it was dominant under a societal perspective.
Key CE drivers	Flu prevalence (overall and by type), cost and specificity of one test, treatment efficacy, flu morbidity, work-day cost, oseltamivir cost.	Complication, hospitalisation and mortality rates, diagnostic accuracy, treatment impact on adverse events.	Diagnostic accuracy, late presentation, treatment impact on adverse events.
Conflicts of interest	None	1 author supported by Hoffman-La Roche	Study funded by Hoffman-La Roche

Study details	<i>Schwarzinger et al. (2003)</i>	<i>Smith and Roberts (2002)</i>	<i>Turner et al. (2003)</i>
Economic evaluation type	Cost-effectiveness analysis	Cost-effectiveness and cost-utility analysis	Cost-effectiveness and cost utility analysis
Currency (year)	USD (1999)	USD (2000)	GBP (2001)
Study design	Decision tree	Decision tree	Decision tree
Perspective	Society	Society, third-party payer	NHS
Setting	USA	USA	UK
Patient population	Otherwise healthy, unvaccinated patients aged 14-64yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy patients aged on average 32yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Otherwise healthy and 'at risk' patients presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.
Time horizon	ILI duration	Single illness episode	Single flu season (extrapolated to account for life-years lost due to mortality)
Comparators	1. Flu test + zanamivir treatment as per licensed indications 2. Zanamivir treatment 3. No test/treatment	1. No test/treatment 2. Any NI treatment as per licensed indications 3-4. Adamantane treatment as per licensed indications 5. Flu test + any NI treatment 6-7. Flu test + adamantane treatment	1. Amantadine 5 days 100mg daily 2. Oseltamivir 5 days 75mg bid 3. Zanamivir 5 days 10mg inhaled bid 4. Standard care (antibiotics or no treatment)
Resources used and costs	Antibacterial and zanamivir use, flu test, OTC medications, follow-up physician visits, work-days lost. Direct and indirect costs were included.	Flu tests, antiviral and antibacterial use, physician visits, hospitalisations, work-hours lost. Direct and indirect (societal persp. only) costs were included.	GP visits, drug and antibiotic use. Hospitalisations and work-days lost (sensitivity analysis only). Direct and indirect (sensitivity analysis only) costs were included.
Source of resources used	Baseline antibacterial use and OTC medications were estimated based on a pooled analysis of placebo arms from RCTs. Test specificity and sensitivity were fixed at 80% and 90% respectively, based on 3 published evaluations. Follow-up physician visits were estimated from a meta-analysis of 11 multinational RCTs. Work-days lost were estimated from a multinational RCT.	Each flu and complications episode was assumed to attract a physician visit and 1hr work lost. Pneumonia episodes were assumed to lead to hospitalisation.	Subgroup-adjusted GP visits were derived from the population size, excess flu consultations and attack rates. Antibiotic use was taken from a national population study. Baseline hospitalisations were obtained from 2 national observational studies. Work-days lost were taken from illness durations estimated from the trials for otherwise healthy adults.
Source of costs	Antibacterial use and OTC medications was costed at an average wholesale price. Zanamivir and flu test were costed from medical studies. Physician fees were taken from the US Medicare data-base. Work-days lost were valued via a human-capital approach based on the national average gross income.	Flu testing was costed from a published study. Antiviral and antibacterial costs were average wholesale prices. Hospitalisations were costed relative to a national Medicare DRG. Work-hours lost were valued at a national average gross wage.	GP visits were costed from a national health-care cost table. Drug (antibiotic) costs were average wholesale (retail) prices. Hospitalisations were costed according to national HRG codes. Work-days lost were valued at the national average gross wage.
Clinical outcomes	Time to alleviation of symptoms, reduction rates for antibacterial and OTC medication use and for follow-up visits	Treated and untreated illness duration, complications and mortality reduction rates.	Illness duration, serious complications rates. Hospitalisation and mortality reduction rates (sensitivity analysis only).
Source of clinical outcomes	Time to alleviation of symptoms was derived from a pooled analysis of a multinational RCT.	Illness durations were estimated from trial data. Antiviral agents were assumed to be equally	Illness duration was estimated by 'at risk' status and age group from placebo (no treatment)

Study details	<i>Schwarzinger et al. (2003)</i>	<i>Smith and Roberts (2002)</i>	<i>Turner et al. (2003)</i>
	Antibacterial and follow-up reductions due to treatment were obtained from a meta-analysis of 11 multinational RCTs. OTC medication reductions were extracted from published trial results.	effective on illness duration in the base-case. Both complications (pneumonia, bronchitis/sinusitis) and pneumonia-related mortality rates were informed by various published RCTs, and were assumed the same regardless of the treatment strategy.	strategy) and treatment (oseltamivir and zanamivir) arms of the reviewed RCTs and from a Cochrane Review (amantadine). Amantadine was assumed not to influence the course of complications due to lack of data. Baseline serious complication rates were obtained from the national Weekly Returns Service, and adjusted for each NI with the antibiotic prescription rate. Baseline hospitalisation rates were adjusted for each NI with the corresponding pneumonia rate, in turn estimated from adult patients enrolled in the placebo arms of NI trials and applied to children due to lack of data. Otitis media rates for children on oseltamivir (other comparators) were derived from the treatment (placebo) arms of the oseltamivir trials. Subgroup-adjusted baseline mortality was extracted from a national population study, and was adjusted for each NI with the corresponding pneumonia rate.
HRQoL	Not included	Not specified	QALY
Source of HRQoL	Not applicable	Utilities were taken from a national health survey (well state adjusted by age group) or from a national study on short-term diseases (non-flu illness = 0.65). Illness (treated = 0.783, untreated = 0.65), pneumonia (0.5) and side effects (0.9) utilities were derived by adjusting well state utilities with corresponding disability weights.	Subgroup-specific utilities were collected for each health state (ILI for each treatment, pneumonia, otitis media, death) from flu-positive patients alongside the oseltamivir trials for 21 days (7 days for sensitivity analysis) through a 10-point Likert scale instrument calibrated to VAS and transformed into TTO scores.
Adverse events	Not included	Side effects were modelled through discontinuances, in turn estimated from trial data for each treatment and assumed to lead to no flu moderation and disutility (assumed the same for all antivirals).	Amantadine-related side effects were incorporated into corresponding utilities in line with trial evidence.
Subgroup analysis	Not implemented	Not implemented	Separate results were reported for (i) otherwise healthy adults (aged 12-65yrs), (ii) 'at risk' (aged 65+yrs and/or with co-morbidities) patients and (iii) children (aged 1-12yrs).
Diagnostic accuracy (ITT/ITTI)	Efficacy was assessed on an ITTI basis; no specific use of ITT data was made explicit. Flu prevalence was estimated at 66% from pooled oseltamivir trial data.	No specific use of ITTI data was made explicit. NI trials informed a 60% base-case flu prevalence. Type A flu prevalence was estimated at 81.5% from national surveillance data.	Efficacy analysis and utility assessment were conducted on an ITTI basis; no specific use of ITT data was made explicit. Flu prevalence was estimated at 46% (47.5% for children) from national RCGP surveillance reports. Subgroup-adjusted type A flu prevalence was obtained from national PHLs (now HPA) data.
Discounting	Not applied	Not applied	1.5% applied in base-case to life-years gained; 0% and 6% applied in sensitivity analysis.

Study details	<i>Schwarzinger et al. (2003)</i>	<i>Smith and Roberts (2002)</i>	<i>Turner et al. (2003)</i>
CEA results	Incremental costs per flu day averted w.r.t. no test/treatment: \$36.79 (zanamivir), \$22.15 (flu test + zanamivir)	1. Incremental cost per illness day averted: \$9.06 (amantadine vs. no test/treatment), \$198 (zanamivir vs. amantadine), dominated or extendedly dominated (otherwise) 2. Incremental cost per flu day averted: \$11.60 (amantadine vs. no test/treatment), \$185 (zanamivir vs. amantadine), dominated or extendedly dominated (otherwise)	1. Incremental cost per QALY gained w.r.t. standard care: healthy adults £6,132 (amantadine), £18,690 (oseltamivir), £30,750 (zanamivir); 'at risk' adults £4,471 (amantadine), £21,441 (oseltamivir), £16,468 (zanamivir); residential care elderly £4,471 (amantadine), £22,350 (oseltamivir), £16,838 (zanamivir); children £5,911 (amantadine), £19,739 (oseltamivir), £31,142 (zanamivir) 2. Incremental cost per illness day averted: healthy adults £5.05 (amantadine), £20.01 (oseltamivir), £33.24 (zanamivir); 'at risk' adults £2.99 (amantadine), £24.25 (oseltamivir), £18.25 (zanamivir); residential care elderly £2.99 (amantadine), £23.49 (oseltamivir), £17.7 (zanamivir); children £5.96 (amantadine), £24.94 (oseltamivir), £38.86 (zanamivir)
Quadrant on CE plane	NE	NE/SE (depending on comparison and outcome)	NE
Sensitivity analysis	1-way analysis of flu prevalence, flu test specificity and sensitivity, baseline antibacterial use, impact of zanamivir on antibacterial and OTC medication use, zanamivir and flu test costs, work-days lost and daily earnings. 2-way analysis of flu prevalence and each remaining input.	1- (multi-) way analysis of all (selected) inputs and late presentation. PSA of treated and untreated flu duration, flu prevalence (overall and by type), flu utility, discontinuance.	1- and 2-way analyses of utilities, flu prevalence (overall and by type), GP visits, late presentation, antibiotic prescription, productivity loss, oseltamivir price, discount rate. PSA of all inputs except drug prices, utilities, pneumonia and adverse events rates.
Conclusions	Zanamivir alone was a dominant strategy compared to no flu treatment for otherwise healthy adults at flu prevalence rates greater than 39%. Flu testing combined with zanamivir was generally CE depending on the test's reliability and cost.	Antiviral treatment without testing was reasonably CE for the treatment of flu in otherwise healthy adults. Testing was found to be CE at low flu prevalence depending on utilities, circulating viral strain and willingness to pay.	The CE profile of the examined flu treatment options was generally unfavourable and markedly variable across patient subgroups, due to uncertainties in the available evidence base.
Key CE drivers	Flu prevalence, flu test specificity and sensitivity, flu test cost, work-days lost and daily earnings.	Flu prevalence (overall and by type), flu utility, untreated flu duration.	GP visits, late presentation, flu prevalence (overall and by type), pneumonia and adverse events rates.
Conflicts of interest	None	None	None

Study details	<i>Vindt Holm et al. (2004)</i>		
Economic evaluation type	Cost-utility analysis	HRQoL	QALY
Currency (year)	EUR (2002)	Source of HRQoL	Utilities (adjusted for the time spent in each health state) were measured for 21 days alongside the RCTs for each treatment strategy with the EQ-5D instrument on the Likert scale calibrated to VAS and transformed into TTO scores.
Study design	Decision tree	Adverse events	Not included
Perspective	Health-care payer, society	Subgroup analysis	Not implemented
Setting	Denmark	Diagnostic accuracy (ITT/ITTI)	Time to return to normal activity was derived on an ITTI basis. Complication, hospitalisation and mortality rates were obtained on a ITT basis. Base-case flu prevalence was fixed at 70% in line with the efficacy trials.
Patient population	Otherwise healthy patients aged 13-64yrs presenting within 48hrs of ILI symptom onset with either confirmed and unconfirmed flu.	Discounting	3% applied to both costs and benefits
Time horizon	Single flu season (extrapolated to account for life-years lost and income loss due to mortality)	CEA results	Incremental cost per QALY gained: oseltamivir dominant (societal perspective), €5,063 (health-care payer perspective)
Comparators	1. Oseltamivir 5 days 75mg bid 2. Standard care (OTC medication)	Quadrant on CE plane	NE/SE
Resources used and costs	GP visits, antibiotic and OTC medication use, oseltamivir use, hospitalisations, work-hours lost (societal persp. only). Direct and indirect (societal persp. only) costs were included.	Sensitivity analysis	Multi-way analysis assuming no complications, hospitalisations or mortality.
Source of resources used	Antibiotic and OTC medication use were estimated by the authors from own data. Baseline hospitalisations were derived from an US observational study. The source for GP visits was left unclear. Work-hours lost were taken from hours to return to normal activity as estimated from the trials.	Conclusions	Oseltamivir was a CE flu treatment strategy for otherwise healthy adolescents and adults even under conservative assumptions, yielding up to a €11,448 cost per QALY gained.
Source of costs	Direct costs were based on national formulary and fee tables. Work-hours lost were valued at a national average wage.	Key CE drivers	Complications, hospitalisations and mortality (health-care payer persp. only), productivity loss (societal persp. only).
Clinical outcomes	Time to return to normal activity, complications, hospitalisations and mortality reduction rates.	Conflicts of interest	One author employed by Hoffman-La Roche
Source of clinical outcomes	Time to return to normal activity and treatment impact on hospitalisation was estimated from Roche RCTs. Complication rates for pneumonia and bronchitis were derived by outcome (outpatient, inpatient, death) from a UK population study, international reviews or assumptions. Treatment impact on mortality was extrapolated using the reduction in hospitalisations.		

10.3 Excluded clinical effectiveness studies with rationale

Full papers retrieved that did not meet the inclusion criteria are listed; the reasons for exclusion were:

- Not RCT ¹
- Review ²
- Experimentally induced influenza ³
- Prophylaxis trial ⁴
- Incorrect intervention ⁵
- Incorrect population ⁶
- Outcomes required not reported ⁷

Anonymous (2001) ^{165 1}	Kawai (2006) ^{186 1}
Anonymous (2001) ^{166 1}	Kawai (2007) ^{187 1}
Anonymous (2001) ^{167 1}	Kawai (2007) ^{117 1}
Barr (2007) ^{168 1}	LaForce (2007) ^{188 4}
Bettis (2006) ^{169 2}	McGeer (2007) ^{189 1}
Blumentals (2007) ^{170 1}	Mitamura (2007) ^{190 2}
Collier (2001) ^{171 1}	Monto (1999) ^{191 2}
Enger (2004) ^{172 1}	Monto (2000) ^{192 2}
Fagan (2004) ^{173 1}	O'Brien (2003) ^{137 2}
Fleming (1999) ^{174 1}	Phillips (2003) ^{193 2}
GlaxoSmithKline: C94-085 (NAIB1002) ^{175 6}	Pitts (2002) ^{194 2}
GlaxoSmithKline: NAI10901 ^{176 6}	Postma (2007) ^{138 1}
GlaxoSmithKline: NAI40012 ^{177 1}	Reina (2006) ^{195 5}
GlaxoSmithKline: NAIA1009 ^{178 5}	Robson (2006) ^{196 4}
Hayden (2000) ^{84 4}	Rothberg (2005) ^{142 1}
Imamura (2003) ^{179 1}	Sander (2002) ^{197 1}
Ison (2003) ^{180, 181 5}	Satoh (2007) ^{198 1}
Iyer (2002) ^{182 3}	Uyeki (2003) ^{199 2}
Kaiser (2000) ^{183 2}	von Bremen (2003) ^{200 7}
Kaiser (2003) ^{153 2}	Williamson (2000) ^{201 1}
Kawai (2004) ^{184 1}	Yamaura (2003) ^{202 1}
Kawai (2005) ^{185 1}	

10.4 Protocol change

The original protocol stated that studies evaluating any treatment dose and duration of regimen would be included in the review, with separate analyses being undertaken for licensed and unlicensed regimens. However, during the course of the review, difficulties obtaining data resulted in time constraints that precluded such a wide-ranging analysis, and the review was restricted to evaluations of the licensed treatment regimens.

10.5 Quality assessment

10.5.1 Clinical effectiveness

Author/ year	Randomisation reported	Randomisation appropriate?	Allocation concealment	Comparability	At least double blind	Patients blinded?	Outcome assessors blinded?	Care givers blinded?	Regions	Participants randomised per centre	Definition of ILI	ILI definition specified a temperature	Power calculation	Selection/eligibility criteria reported	Representative sample recruited?	Losses to follow-up reported/explained?	At least 95% follow-up?
Aoki (2000) ⁷⁴	Y	UC	UC	Y	Y	UC	UC	UC	N	UC	Y	N	N	Y	Y	N	Y
Boivin (2000) ^{79, 92-94}	Y	UC	UC	Y	Y	UC	UC	UC	Y	N	Y	Y	Y	Y	N	Y	Y
Deng (2004) ⁶⁶	Y	UC	UC	Y	N	N	N	N	Y	UC	N	N/A	N	Y	UC	N	UC
GlaxoSmithKline 2001 ⁸⁶	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N
GlaxoSmithKline 2005 ^{104, 105}	Y	UC	UC	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y
GlaxoSmithKline 2006 ^{102, 103}	Y	Y	Y	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y
GlaxoSmithKline 2006 ⁹⁸	Y	UC	UC	UC	Y	UC	UC	UC	Y	N	Y	Y	N	Y	Y	Y	Y
Hayden (1997) ⁷⁶	Y	UC	UC	Y	Y	UC	UC	UC	N	N	Y	N	Y	Y	Y	Y	N
Hedrick (2000) ^{99, 100}	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y
Johnston NV16871 (2005) ⁷⁸	Y	UC	UC	Y	Y	UC	UC	UC	UC	UC	Y	Y	Y	Y	N	Y	N
Kashiwagi (2000) ⁶⁸	Y	UC	UC	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y
Li (2004) ⁶⁹	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Lin (2006) ^{71, 72}	Y	UC	N	Y	N	N	N	N	Y	N	Y	Y	N	Y	N	Y	Y

Author/ year	Randomisation reported	Randomisation appropriate?	Allocation concealment	Comparability	At least double blind	Patients blinded?	Outcome assessors blinded?	Care givers blinded?	Regions	Participants randomised per centre	Definition of ILI	ILI definition specified a temperature	Power calculation	Selection/eligibility criteria reported	Representative sample recruited?	Losses to follow-up reported/explained?	At least 95% follow-up?
Makela (2000) ^{79, 95, 96}	Y	Y	Y	Y	Y	UC	UC	UC	Y	N	Y	Y	Y	Y	Y	Y	Y
Martin (2001) ^{73, 108}	Y	UC	UC	UC	Y	UC	UC	UC	Y	Y	Y	Y	N	Y	UC	N	UC
Martin (2001) ^{73, 108}	Y	UC	UC	Y	Y	UC	UC	UC	UC	UC	Y	Y	N	Y	UC	N	UC
Matsumoto (1999) ⁸⁵	Y	UC	UC	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	N	Y
MIST (1998) ^{79, 90, 91}	Y	Y	UC	Y	Y	UC	UC	UC	N	Y	Y	Y	N	Y	Y	Y	N
Monto (1999) ^{75, 79}	Y	UC	UC	Y	Y	UC	UC	UC	N	UC	Y	N	Y	Y	Y	Y	N
Murphy (2000) ^{97, 114, 115}	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	N
Nicholson (2000) ^{80, 106}	Y	Y	UC	Y	UC	UC	UC	UC	N	N	Y	Y	Y	Y	Y	Y	Y
Puhakka (2003) ^{87, 88}	Y	Y	UC	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Roche WV15730 (1999) ^{46, 83}	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y
Roche NV16871 ⁷⁷	Y	UC	UC	UC	Y	UC	UC	UC	UC	UC	Y	Y	N	Y	N	N	UC
Sato (2005) ¹¹⁰	Y	Y	UC	UC	UC	UC	UC	UC	Y	Y	N	N/A	N	Y	N	N	UC
Tan (2002) ⁶⁷	Y	Y	UC	UC	Y	Y	UC	Y	Y	Y	N	N/A	N	Y	UC	Y	N
Treanor (2000) ⁶⁵	Y	Y	Y	Y	Y	Y	UC	UC	Y	N	Y	Y	Y	Y	Y	Y	N
Treanor (2000b) ⁸¹	Y	UC	UC	UC	Y	UC	UC	UC	Y	N	Y	Y	N	N	UC	N	UC
Whitely (2001) ¹⁰⁹	Y	UC	UC	Y	Y	Y	UC	UC	Y	N	Y	Y	Y	Y	Y	N	Y

Guidelines for completing the quality assessment

1. Was the number of participants randomised stated?
Yes: Number of people randomised to each arm of the trial was reported No: Only the total number of participants was reported or only the number that actually received each treatment was reported
2. Was the method of randomisation appropriate?
Yes: Computer generated random numbers or the use of random number tables No: Any other method of randomisation Unclear: The study stated that randomisation occurred, but did not report the method
3. Was allocation concealment adequate?
Yes: Any robust method that would not allow the patient status to influence the allocation of treatment No: Other methods of allocation concealment Unclear: Either allocation was concealed but the method was not reported, or the concealment of allocation was not reported
4. Were the treatment groups comparable at baseline?
Yes: There were no significant differences between the participants of the treatment arms at baseline No: There were significant differences between the participants of the treatment arms at baseline Unclear: Baseline characteristics were not reported
5. Was the study reported as being at least double blind?
Yes: The study was reported as being double or triple blind No: The study did not report whether it was double blind or not
6. Patients blinded?
Yes: It was explicitly stated that patients were blinded to treatment or methods described that implied patients were blinded No: It was explicitly stated that patients were not blinded to treatment Unclear: There was no specific information regarding the blinding of patients was not reported
7. Outcome assessors blinded?
Yes: It was explicitly stated that outcome assessors were blinded to treatment or methods described that implied outcome assessors were blinded No: It was explicitly stated that outcome assessors were not blinded to treatment Unclear: There was no specific information regarding the blinding of outcome assessors was not reported
8. Care givers blinded?
Yes: It was explicitly stated that care givers were blinded to treatment or methods described that implied care givers were blinded No: It was explicitly stated that care givers were not blinded to treatment Unclear: There was no specific information regarding the blinding of care givers was not reported
9. Did the study run in only one continent?
Yes: The study recruited participants from only one continent No: The study recruited participants from more than one continent Unclear: Location of sites was not adequately reported
10. Was the mean number of participants randomised per centre ≥ 15?
Yes: The mean number of participants randomised per centre was ≥ 15 No: The mean number of participants randomised per centre was not ≥ 15 Unclear: The total number of centres was not stated
11. Definition of influenza like illness (ILI)?
Yes: The authors did define what was meant by ILI No: The authors did not define what was meant by ILI

12. ILI definition specify a temperature?
Yes: The definition of ILI did specify a temperature No: The definition of ILI did not specify a temperature or there was no definition of ILI given
13. Power calculation used?
Yes: Power calculation was used No: Power calculation was not used, or its use was not reported
14. Selection/eligibility criteria reported?
Yes: Selection/eligibility criteria were reported No: Selection/eligibility criteria were not adequately reported
15. Representative sample recruited?
Yes: The study sample was representative of the study population in clinical practice No: The study sample was not truly representative of the study population (e.g. age range for a given group was too narrow) Unclear: Criteria were not adequately reported
16. Losses to follow-up reported/explained?
Yes: Losses to follow-up were reported/explained No: Losses to follow-up were not reported/explained
17. Were at least 95% of those randomised followed-up?
Yes: At least 95% were followed-up at the final time point reported No: <95% were followed-up at the final time point reported Unclear: Loss to follow-up was not reported

10.5.2 Economic evaluation

	Turner et al (2003)	Roche submission
Study question	Grade	Grade
1. Costs and effects examined	✓	✓
2. Alternatives compared	✓	✓
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	✓
Selection of alternatives		
4. All relevant alternatives are compared (including doing nothing if applicable)	✓	✓/X
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	✓
6. The rationale for choosing the alternative programmes or interventions compared is stated	✓	✓
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	X
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	X
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	✓
10. Effectiveness data from RCT or review of RCTs	✓/X	X
11. Potential biases identified (especially if data not from RCTs)	X	X
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	NA
Costs		
13. All the important and relevant resource use included	✓	✓
14. All the important and relevant resource use measured accurately (with methodology)	✓	X
15. Appropriate unit costs estimated (with methodology)	✓	✓
16. Unit costs reported separately from resource use data	X	✓
17. Productivity costs treated separately from other costs	NA	✓
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	✓
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓
20. Methods to value health states and other benefits are stated	X	✓
21. Details of the individuals from whom valuations were obtained are given	NA	NA
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	✓
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	✓	✓
24. All model outputs described adequately.	✓	✓
Discounting		
25. Discount rate used for both costs and benefits	✓	✓
26. Do discount rates accord with NHS guidance?	✓	✓
Allowance for uncertainty		
Stochastic analysis of patient-level data	✓	✓
27. Details of statistical tests and confidence intervals are given for stochastic data	✓	✓
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	✓	✓
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates)	✓	✓

and analytic decisions (e.g. methods to handle missing data).		
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	✓
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	✓
32. Are the probability distributions adequately detailed and appropriate?	✓	✗
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	✓
Deterministic analysis		
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	✓
35. The choice of variables for sensitivity analysis is justified	✓	✓
36. The ranges over which the variables are varied are stated	✓	✓
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	✗	✗
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	✓
39. Applicable to the NHS setting	✓	✓

Modelling checklist for Turner *et al.* (2003)

Quality criterion	Question(s)	Response (✓, x or NA)	Comments
S1	Is there a clear statement of the decision problem?	✓	"To identify the optimal prevention and treatment strategies for influenza and, in particular the role, if any, that neuraminidase inhibitors (NI) have to play" (p.1)
	Is the objective of the evaluation and model specified consistent with the stated decision problem?	✓	"Alternative options for the treatment and prophylaxis of influenza were assessed in terms of cost-effectiveness using decision analytic models for four separate patient groups: healthy adults, high-risk adults, children and residential care elderly" (p.108)
	Is the primary decision-maker specified?	✓/x	Not explicitly, although the report is written for HTA/NICE
S2	Is the perspective of the model stated clearly?	✓	"The analysis is primarily undertaken from the perspective of the NHS" (p.110)
	Are the model inputs consistent with the stated perspective?	✓	NHS/PSS costs and QALYs (pp.119-123)
	Has the scope of the model been stated and justified?	✓	Patient groups and options under evaluation are specified clearly. Each structural assumption is discussed and (in some cases) justified (pp.123-126)
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓	"Main results are reported in terms of incremental cost per QALY gained and we also report the cost per influenza day avoided" (p.108). Length of illness is determined from the control arms of trials or from Cochrane review data
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓	The model structure is consistent with an assumed treatment pathway, although this pathway is not fully justified. The progression of disease is not modelled (not applicable)
	Are the sources of data used to develop the structure of the model specified?	x	No details are given regarding the development of the structure of the model
	Are the causal relationships described by the model structure justified appropriately?	✓/x	Some justification given (pp.123-126)
S4	Are the structural assumptions transparent and justified?	✓	A list of all assumptions is provided along with the likely effect of bias (pp.135-136)
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓	All structural assumptions are justifiable, whether or not explicit justification is given
S5	Is there a clear definition of the options under evaluation?	✓	All options are specified clearly (p.109)
	Have all feasible and practical options been evaluated?	✓	Amantadine treatment considered; rimantadine not considered but in the absence of a UK license this may not necessarily be considered a feasible or practical alternative
	Is there justification for the exclusion of feasible options?	NA	
S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	✓	Tree model represents probabilities of events (probability of flu, presentation to the GP, presentation within 48 hours of onset of symptoms, of drug treatment if presenting before or after 48 hours, probability of severe complications and resultant death). Model examines a single treatment episode;

			repeat treatment over time is not considered, but lack of reliable data on resistance limits the usefulness of such analysis
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	✓	Lifetime time horizon (to capture life years lost due to influenza mortality), although only a single flu season considered. "An 10-point (sic) Likert scale was completed daily over a 21-day period... Patients continued to complete the instrument after 7 days only if they had not recovered" (p.119-121)
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓	Decision tree represents the pathways patients may follow when they have ILI
S9	Is the cycle length defined and justified in terms of the natural history of disease?	NA	
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	✓	Effectiveness data come from full systematic review of the trial evidence and Cochrane reviews. Data for other parameters in the model are based on reviews of the literature and meta-analyses
	Where choices have been made between data sources, are these justified appropriately?	✓	
	Has particular attention been paid to identifying data for the important parameters in the model?	×	Main treatment effects are derived from trial data, whilst probabilities are derived from reviews of evidence. A key uncertainty was found to be the QALY values associated with adverse events: "We estimated the EQ-5D status for persons suffering from these conditions from expert opinion" (p.207); no further research was carried out to reduce the uncertainty around this estimate
	Has the quality of the data been assessed appropriately?	✓	An assessment of quality was undertaken for the systematic review
	Where expert opinion has been used, are the methods described and justified?	×	Expert opinion was used to identify EQ-5D scores for adverse events – no details are given regarding the methods used
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	✓	Random effects meta-analysis used to estimate time to symptoms across all trials of NIs. Meta-regression used to estimate the relationship between time to symptoms alleviated and time to fever in days
D2a	Is the choice of baseline data described and justified?	✓	All data are derived from the control group of trials
	Are transition probabilities calculated appropriately?	NA	
	Has a half-cycle correction been applied to both cost and outcome?	NA	
	If not, has this omission been justified?	NA	
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using	✓	Random effects meta-analysis

	appropriate techniques?		
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	✓	Length of flu illness for amantadine was extrapolated using meta-regression techniques based on the observed relationship between length of fever and length of illness
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	✓	Different time-frames for extrapolation explored (7 days, 21 days)
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	✓	
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	✓	Different time-frames explored (7 days, 21 days)
D2c	Are the costs incorporated into the model justified?	✓	All come from standard sources
	Has the source for all costs been described?	✓	
	Have discount rates been described and justified given the target decision-maker?	✓	1.5% benefits, 6% costs
D2d	Are the utilities incorporated into the model appropriate?	✓/x	Utilities are derived from trial data; quality-adjusted life expectancy calculated from life tables (p.205); no details are given regarding the methods used to identify EQ-5D scores for adverse events
	Is the source for the utility weights referenced?	✓	
	Are the methods of derivation for the utility weights justified?	✓	QALY weights were taken from a Likert scale administered in the trials, which were manipulated to mean visual analogue scale scores from the Measurement and Validation of Health (MVH) study. These were then converted into time trade off estimates (p.119). No data existed for children, therefore adults weights were applied. The effect of using 7 days of data instead of 21 days was examined through sensitivity analysis. Justification given for using expert opinion to derive EQ-5D scores for adverse events (p.207)
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	✓	All sources are referenced
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	✓	US data used to determine attack rates on the basis that over time attack rates in the USA and Europe would be the same
	Is the process of data incorporation transparent?	✓	Data incorporated as distributions and as point estimates
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	✓	All distributions are described for each parameter but not justified. However, the choice does reflect the properties of the parameter
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓	Monte Carlo simulation used to reflect second order uncertainty

D4	Have the four principal types of uncertainty been addressed?	✓	Although this is not explicitly stated.
	If not, has the omission of particular forms of uncertainty been justified?	NA	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✓	Effect of discount rates assessed
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	✓	The effect of structural assumptions is assessed. For example, data used to derive the length of illness varied from using 21 days' worth of data to using just 7 days
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	✓	The model was run for four groups
D4d	Are the methods of assessment of parameter uncertainty appropriate?	✓	Probabilistic sensitivity analysis plus a series of one-way sensitivity analyses
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	✓	Mean value used for deterministic analysis
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	×	
C2	Are any counterintuitive results from the model explained and justified?	NA	The model results do not appear to be counterintuitive
	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	✓	The results are compared with three other models (pp.136-137). The reasons for differences are explained clearly

Modelling checklist for Roche submission (2008)

Quality criterion	Question(s)	Response (✓, × or NA)	Comments
S1	Is there a clear statement of the decision problem?	✓	"The economic case for treating all individuals who present to the GP with influenza like illness (ILI)." (p.47).
	Is the objective of the evaluation and model specified consistent with the stated decision problem?	✓	"The cost effectiveness case... will be presented comparing oseltamivir to usual care and zanamivir, as defined in the final scope" (p.48)
	Is the primary decision-maker specified?	✓	Given in title of the report
S2	Is the perspective of the model stated clearly?	✓	"The economic analysis is performed from the NHS and PSS perspective as per the NICE reference case" (p.51)
	Are the model inputs consistent with the stated perspective?	✓	"The total QALYs and direct NHS costs of each cohort are compared..." (p.50)
	Has the scope of the model been stated and justified?	✓/×	Scope stated (p.48-51). Justification for considering only one complication given later (p.83). Flawed justification given for not addressing the issue of whether the availability of a new technology will increase patient consultation rates (p.49).
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	×	"The duration of ILI is defined as time to return to normal activities" (p.59). Turner <i>et al.</i> (2003) considered time to return to normal activities only as part of the sensitivity analysis in order to value productivity costs, which are not considered relevant under the NICE reference case.
S3	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓/×	The model structure is consistent with an assumed treatment pathway, although this pathway is not fully justified and has some unusual implications regarding hospitalisation and mortality (see critique). The progression of disease is not modelled (not applicable)
	Are the sources of data used to develop the structure of the model specified?	✓	"The economic model... is similar to that previously used in [Roche's submission to] TA58 and also the model developed by the Assessment Groups [for TA58]" (p.48)
	Are the causal relationships described by the model structure justified appropriately?	✓/×	Not explicitly, but some justification is given in Turner <i>et al.</i> 2003 and it is explicitly stated that this model follows a similar structure (p.48)
S4	Are the structural assumptions transparent and justified?	✓/×	A list of all assumptions is provided. Whilst these are not fully justified, some of the limitations of the model are given (pp.83-84)
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓	All structural assumptions are justifiable, whether or not explicit justification is given (not addressing the issue of whether the availability of a new technology will increase patient consultation rates is justifiable given the lack of data, but not for the reason stated)
S5	Is there a clear definition of the options under evaluation?	✓	All options are specified clearly (p.50). Information on doses is given (p.13)
	Have all feasible and practical options been evaluated?	×	Amantadine treatment is not considered; rimantadine not considered either but in the absence of a UK license this may not necessarily be considered a feasible or practical alternative
	Is there justification for the exclusion of feasible options?	✓	Amantadine has been excluded from the final scope

S6	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	✓	Tree model represents probabilities of events (probability of flu, presentation to the GP, presentation within 48 hours of onset of symptoms, of drug treatment if presenting before or after 48 hours, probability of severe complications and resultant death). Model examines a single treatment episode; repeat treatment over time is not considered, but lack of reliable data on resistance limits the usefulness of such analysis
S7	Is the time horizon of the model sufficient to reflect all important differences between options?	✓	“The time horizon employed in the model is a lifetime time horizon... Although all the influenza related events are captured within 1 year, the lifetime horizon is applied in the model in order to capture life years lost due to influenza mortality” (p.51)
	Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	
S8	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓	Decision tree represents the pathways patients may follow when they have ILI
S9	Is the cycle length defined and justified in terms of the natural history of disease?	NA	
D1	Are the data identification methods transparent and appropriate given the objectives of the model?	×	
	Where choices have been made between data sources, are these justified appropriately?	×	See critique. Lack of justification of data sources, particularly around utility values
	Has particular attention been paid to identifying data for the important parameters in the model?	×	
	Has the quality of the data been assessed appropriately?	×	
	Where expert opinion has been used, are the methods described and justified?	×	The estimate of 31% for diagnostic accuracy is arbitrary (originating in the sensitivity analysis conducted by Turner <i>et al.</i> , 2003). The submission states that the estimate was “validated at a 2008 UK Roche advisory board as being an appropriate assumption” (p.53) but no details are given
D2	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	✓	
D2a	Is the choice of baseline data described and justified?	✓/×	In most cases, although choice of baseline utility scores not justified
	Are transition probabilities calculated appropriately?	NA	
	Has a half-cycle correction been applied to both cost and outcome?	NA	
	If not, has this omission been justified?	NA	
D2b	If relative treatment effects have been derived from trial	✓/×	

	data, have they been synthesised using appropriate techniques?		
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	?	
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	N/A	
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	×	The model assumes that, once treatment is complete, patients may have a reduced duration of illness and that each of the days on which patients no longer have ILI should carry a utility weight of 1 – this is undocumented unjustified in the printed submission
	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis?	N/A	
D2c	Are the costs incorporated into the model justified?	✓/×	All cost data are stated and justified, although drug cost for zanamivir (£16.55 per treatment) appears to be incorrect
	Has the source for all costs been described?	✓	
	Have discount rates been described and justified given the target decision-maker?	✓	“All health care costs occur within 1 year and are not discounted. However, life years gained due to avoided premature mortality which occur in the future are discounted at a rate of 3.5%, as per the NICE reference case” (p.51)
D2d	Are the utilities incorporated into the model appropriate?	×	Utilities are derived from trial data and the literature; quality-adjusted life expectancy is calculated from life tables and EuroQoL data (p.66). However, there appears to be considerable bias in the choice of trial data analysed and assumptions made in calculating life years lost
	Is the source for the utility weights referenced?	×	Harvard utility scores not properly referenced
	Are the methods of derivation for the utility weights justified?	×	Utilities for patients receiving usual care were taken from Harvard utility weights and Stouthard (1997). To calculate the relative improvement from antivirals, QALY weights were taken from a Likert scale administered in the trials for oseltamivir, which were manipulated to mean visual analogue scale scores from the Measurement and Validation of Health (MVH) study – these were then converted into time trade off estimates in order to calculate a relative improvement from oseltamivir of 11.52% (pp.64-65). The same relative improvement was assumed for all antivirals in all subgroups (p.64). However, despite stating in the text that VAS scores were completed for 21 days, the 11.52% figure was calculated using just 7 days of data, without explanation (p.65). It was assumed that any utility loss resulting from minor complications would already be incorporated in the VAS scores and so was not considered separately (p.72)
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	×	Harvard utility scores and Cox data not properly referenced
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	✓	
	Is the process of data	✓/×	Data incorporated as distributions and as point

	incorporation transparent?		estimates, but the printed submission does not detail all distributions considered in the model
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	×	Distributions are described for most parameters but not justified. However, whilst in some cases the choice of distribution reflect the properties of the parameter, for a substantial number of parameters a triangular distribution has been chosen without any justification
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	✓	Monte Carlo simulation used to reflect second order uncertainty (5000 simulations)
D4	Have the four principal types of uncertainty been addressed?	✓	Although this is not explicitly stated.
	If not, has the omission of particular forms of uncertainty been justified?	NA	
D4a	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	✓	
D4b	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	✓	The effect of structural assumptions is assessed
D4c	Has heterogeneity been dealt with by running the model separately for different subgroups?	✓	The model was run for four groups
D4d	Are the methods of assessment of parameter uncertainty appropriate?	✓	Probabilistic sensitivity analysis plus a series of one-way sensitivity analyses
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	×	
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	×	
C2	Are any counterintuitive results from the model explained and justified?	NA	The model results do not appear to be counterintuitive
	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	
	Have the results of the model been compared with those of previous models and any differences in results explained?	×	

10.6 Forest plots

Health adults

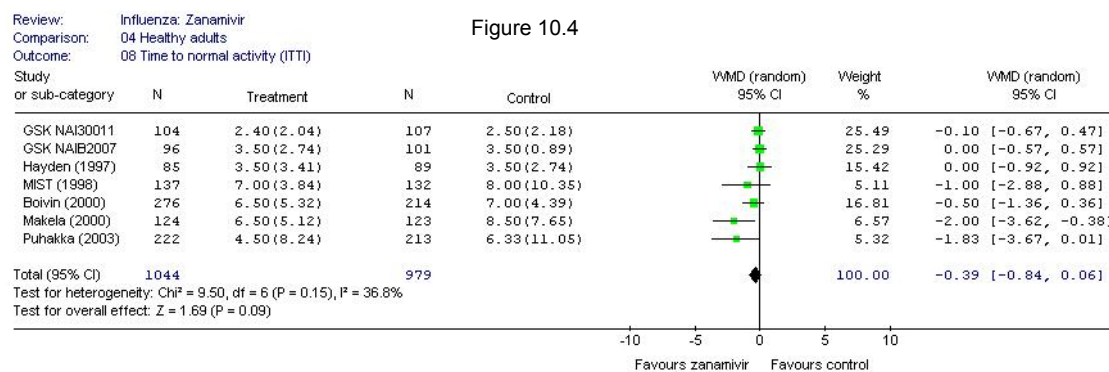
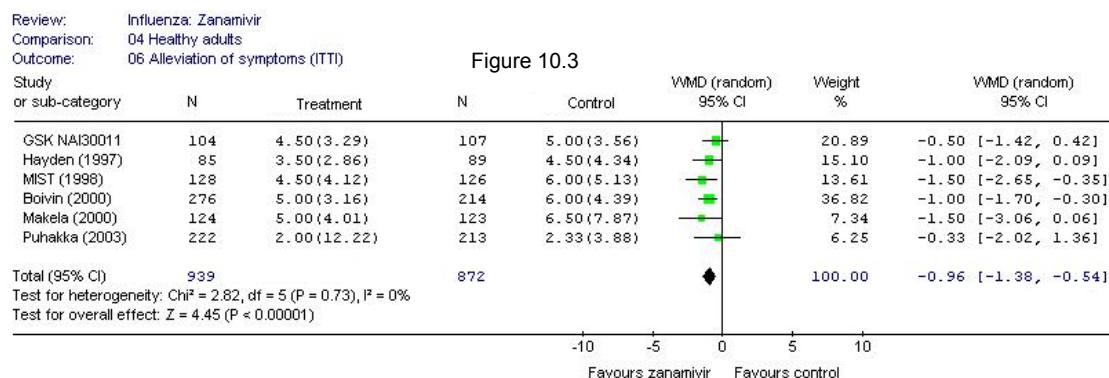
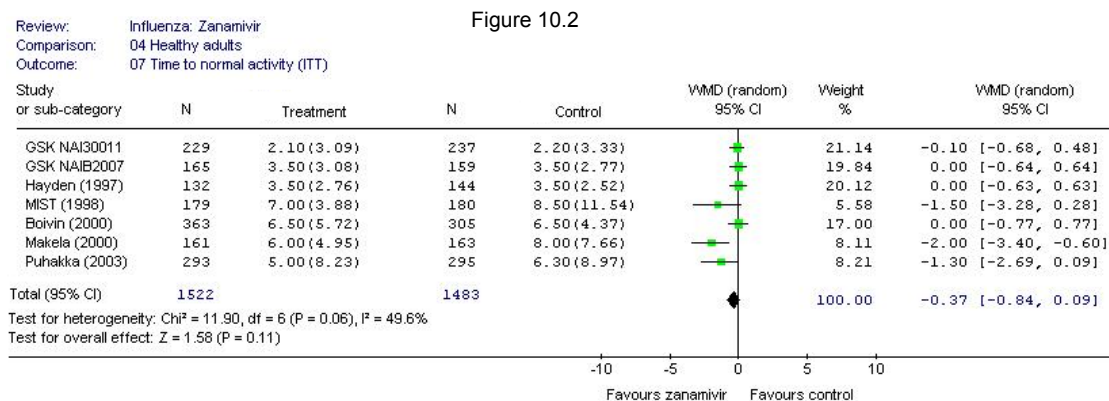
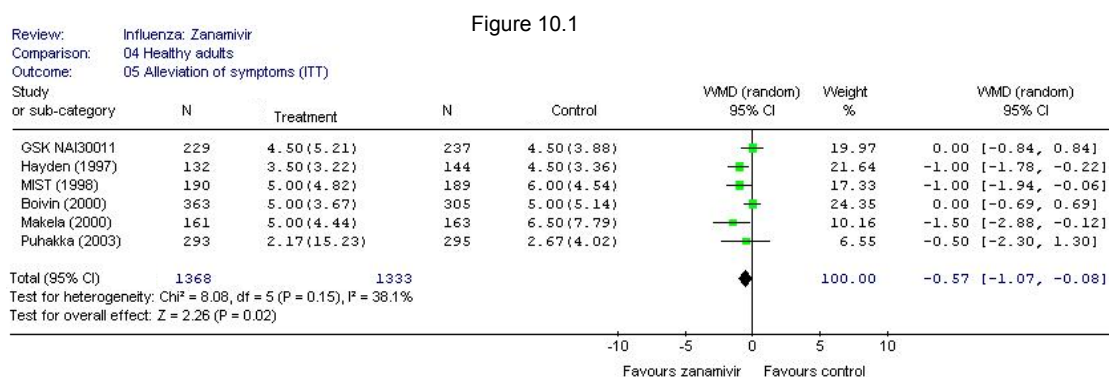


Figure 10.5

Review: Influenza: Zanamivir
 Comparison: 04 Healthy adults
 Outcome: 01 Bronchitis (ITT)

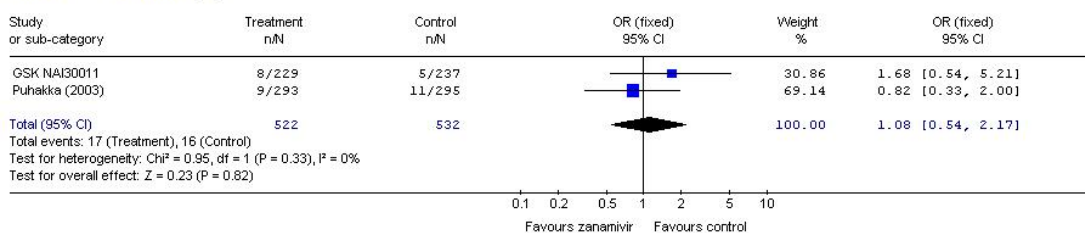


Figure 10.6

Review: Influenza: Zanamivir
 Comparison: 04 Healthy adults
 Outcome: 02 Overall adverse events (ITT)

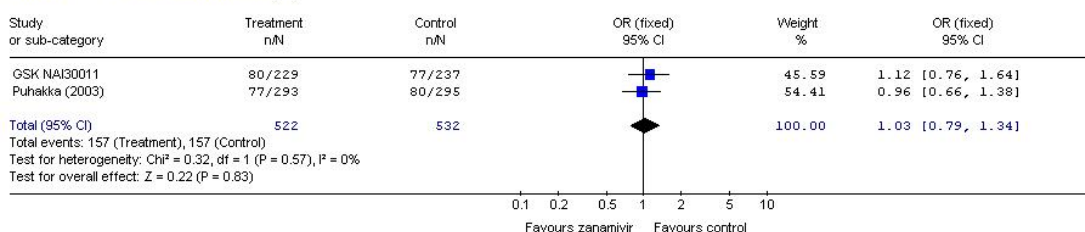


Figure 10.7

Review: Influenza: Zanamivir
 Comparison: 04 Healthy adults
 Outcome: 04 Drug-related adverse events (ITT)

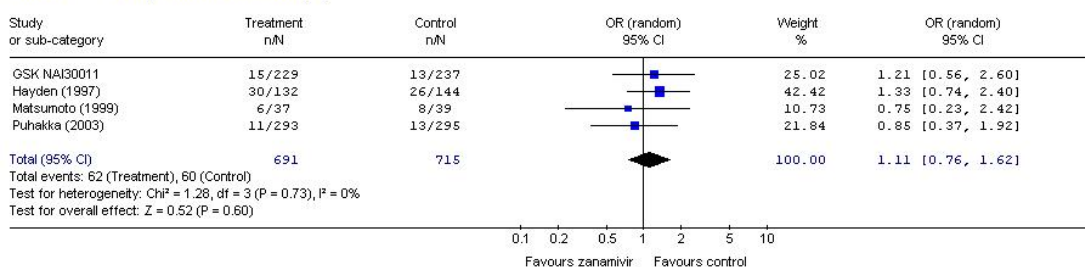


Figure 10.8

Review: Influenza: Zanamivir
 Comparison: 04 Healthy adults
 Outcome: 03 Serious adverse events (ITT)

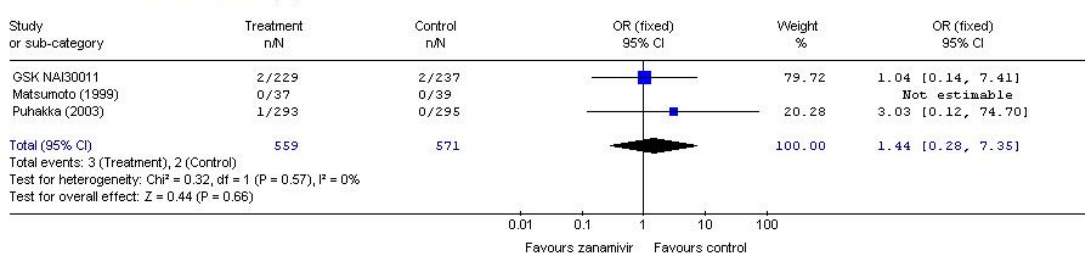
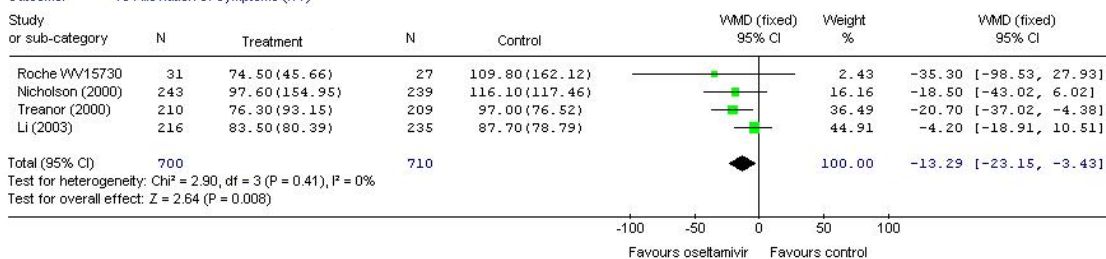


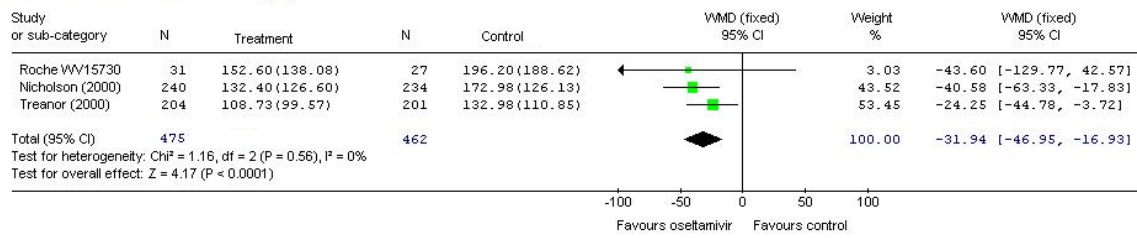
Figure 10.9

Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 10 Alleviation of symptoms (ITT)



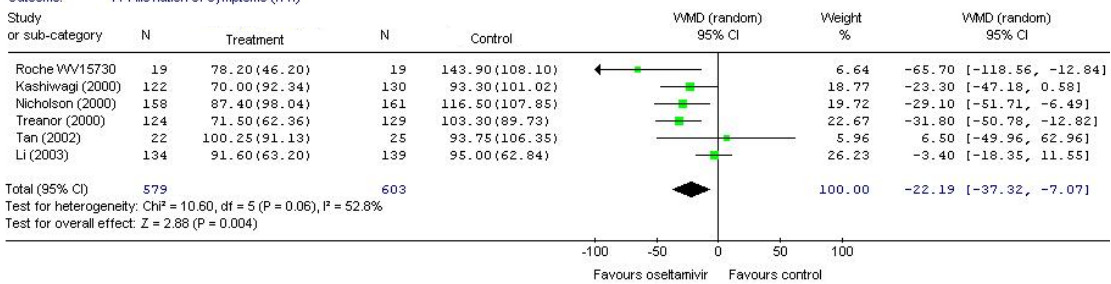
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 14 Time to normal activity (ITT)

Figure 10.10



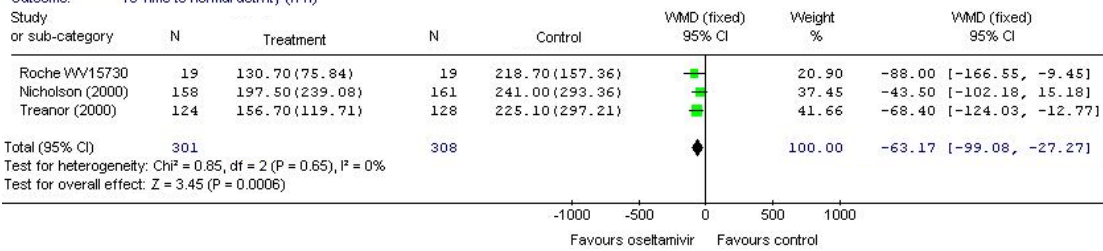
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 11 Alleviation of symptoms (ITTI)

Figure 10.11



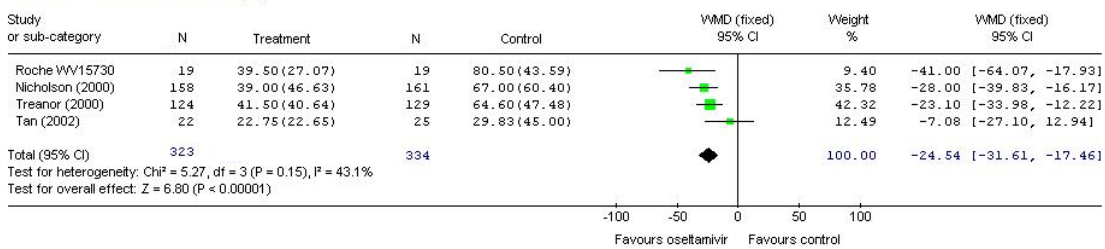
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 15 Time to normal activity (ITTI)

Figure 10.12



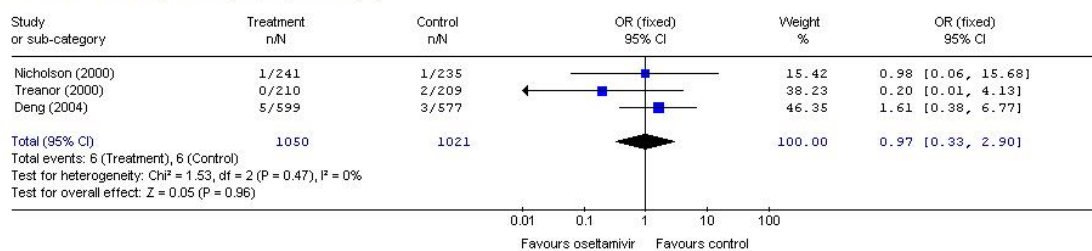
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 13 Alleviation of fever (ITTI)

Figure 10.13



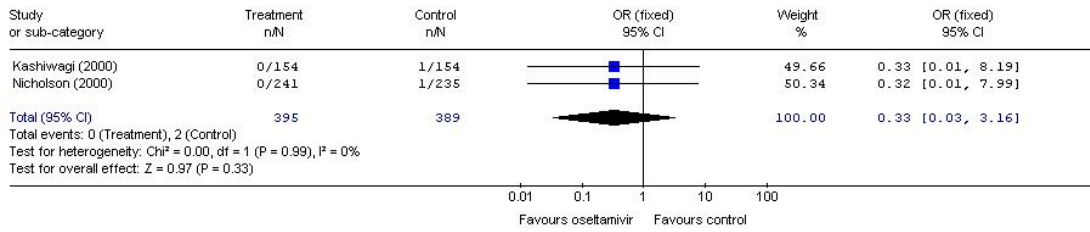
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 16 Complications requiring hospitalisation (ITT)

Figure 10.14



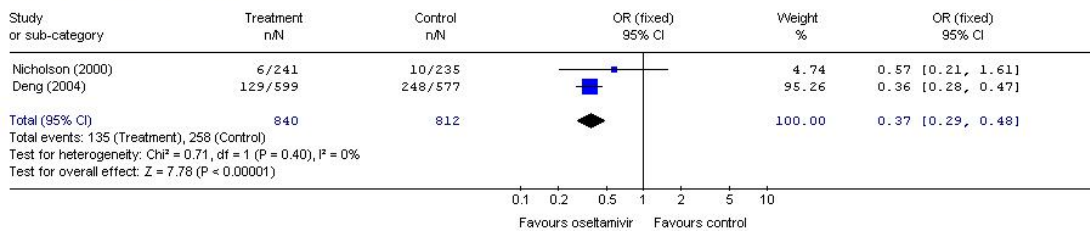
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 01 Pneumonia (ITT)

Figure 10.15



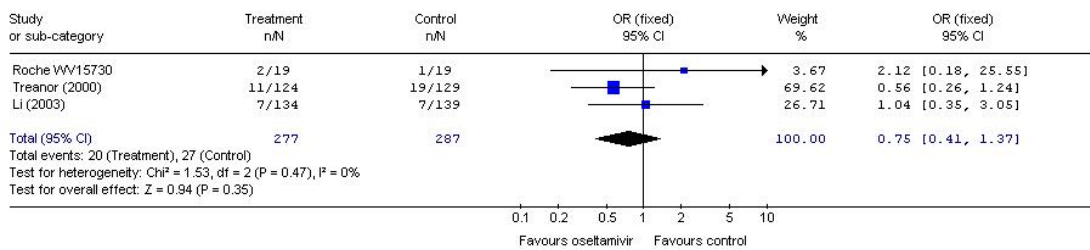
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 03 Antibiotic use (ITT)

Figure 10.16



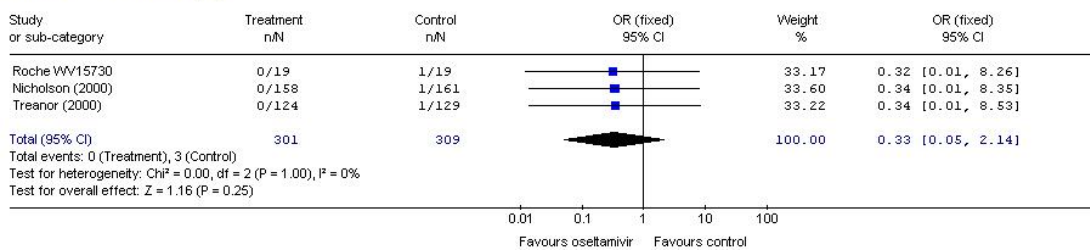
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 04 Overall complications (ITT)

Figure 10.17



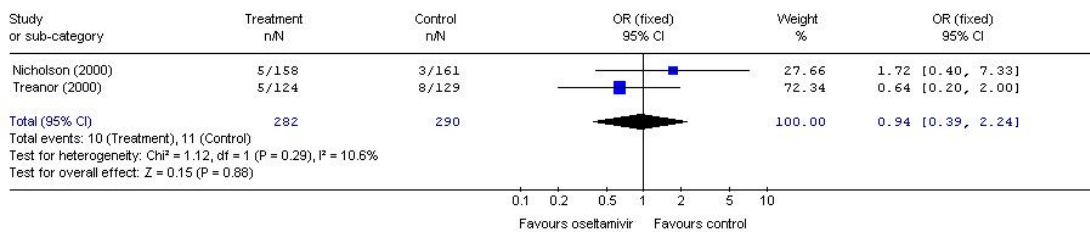
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 05 Pneumonia (ITT)

Figure 10.18



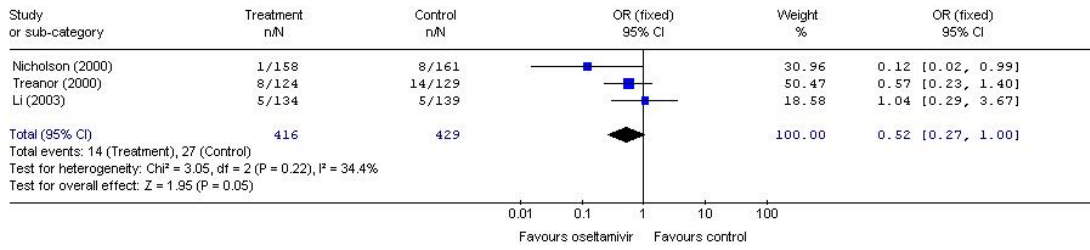
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 06 Bronchitis (ITT)

Figure 10.19



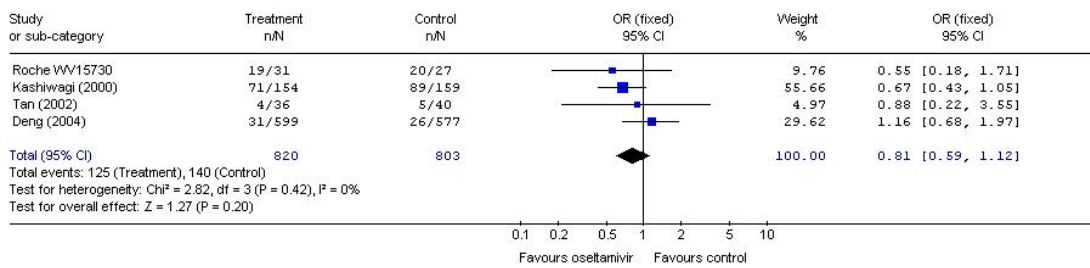
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 07 Antibiotic use (ITT)

Figure 10.20



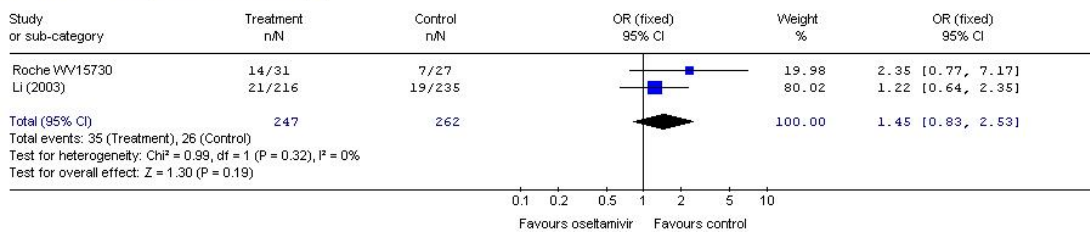
Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 02 Overall adverse events (ITT)

Figure 10.21



Review: Influenza: Oseltamivir
 Comparison: 04 Healthy adults
 Outcome: 09 Drug-related adverse events (ITT)

Figure 10.22



At risk

Figure 10.23

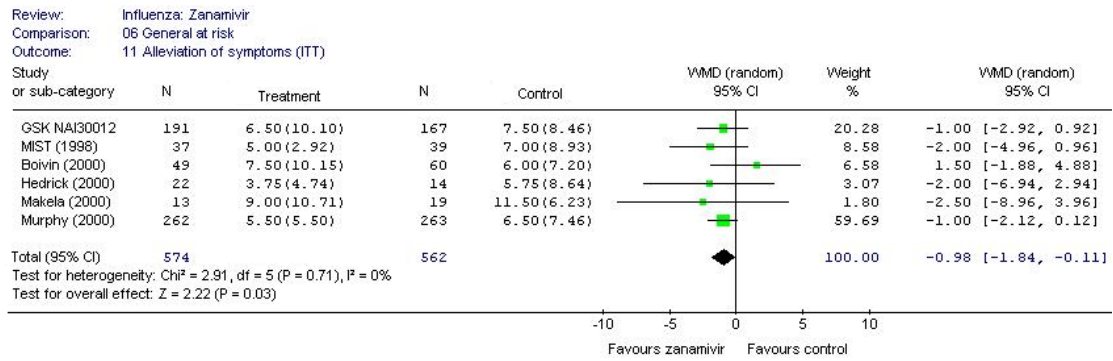


Figure 10.24

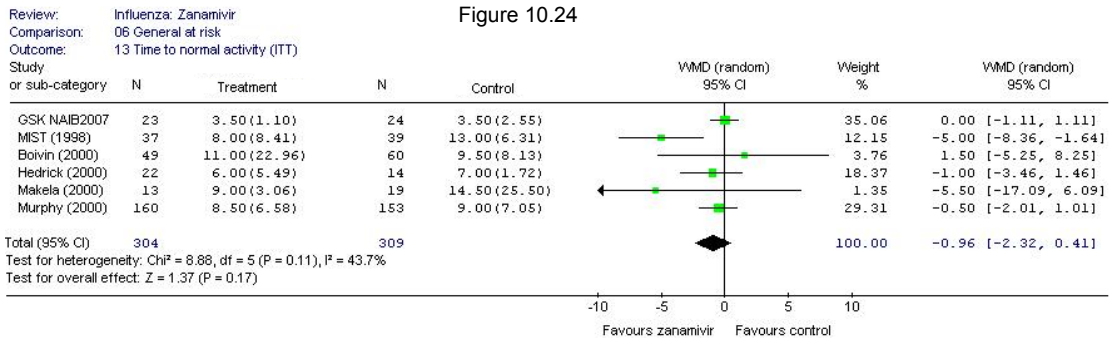


Figure 10.25

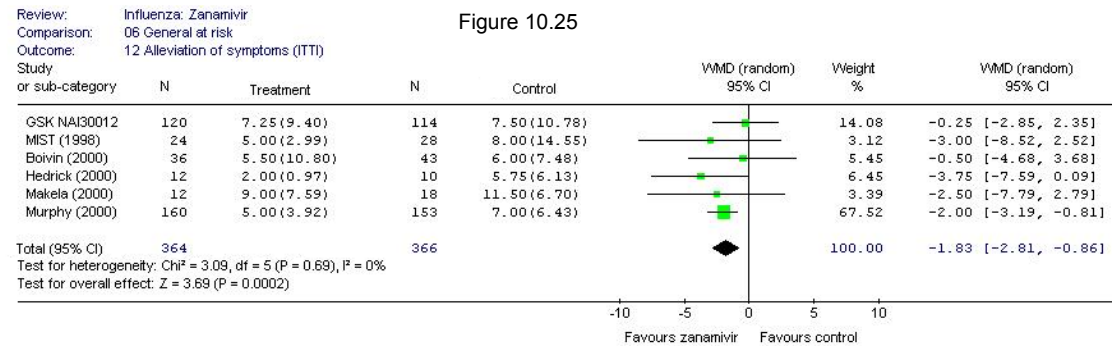
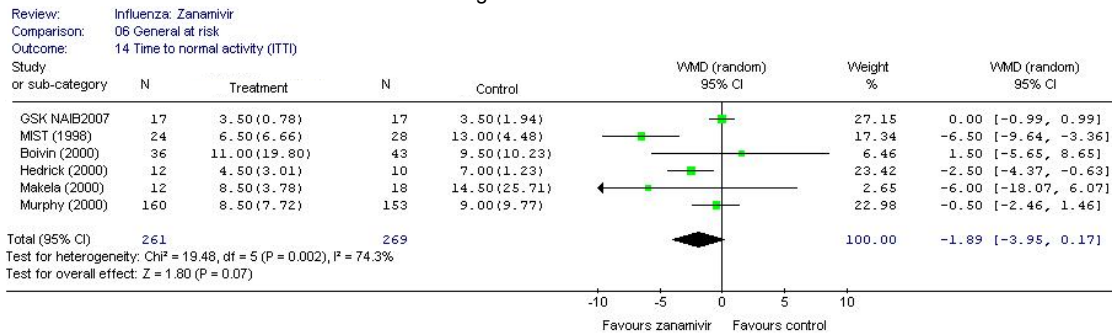
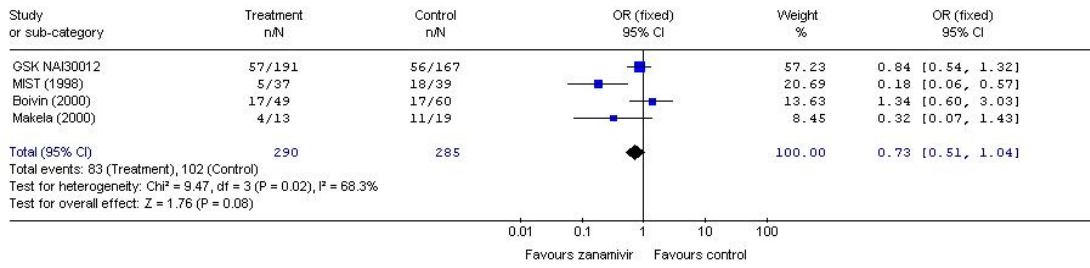


Figure 10.26



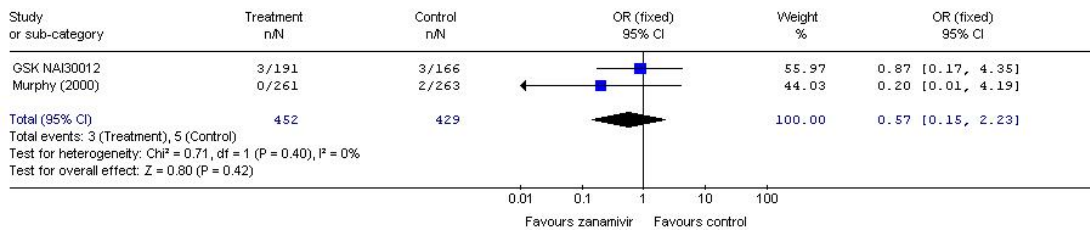
Review: Influenza: Zanamivir
 Comparison: 06 General at risk
 Outcome: 01 Overall complications (ITT)

Figure 10.27



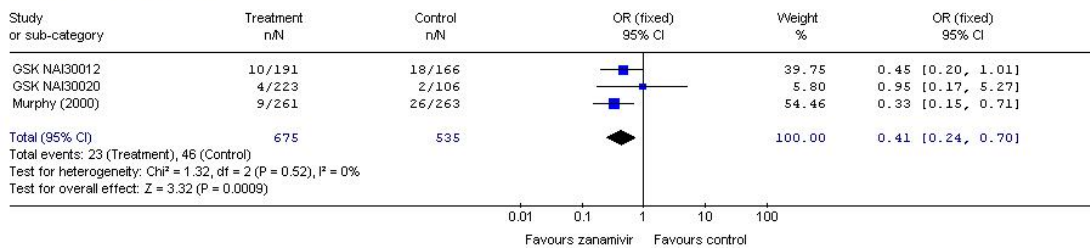
Review: Influenza: Zanamivir
 Comparison: 06 General at risk
 Outcome: 03 Pneumonia (ITT)

Figure 10.28



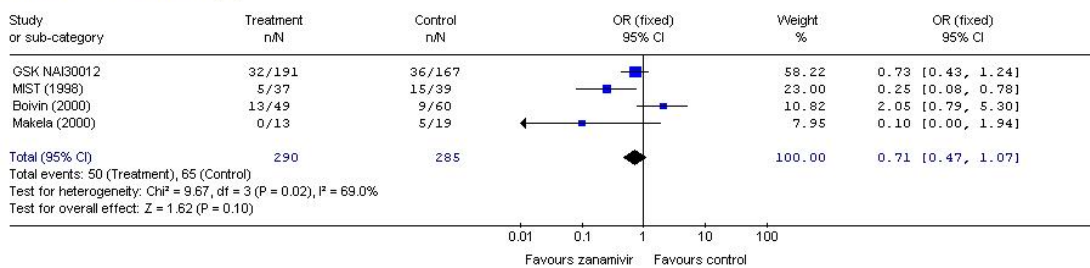
Review: Influenza: Zanamivir
 Comparison: 06 General at risk
 Outcome: 04 Bronchitis (ITT)

Figure 10.29



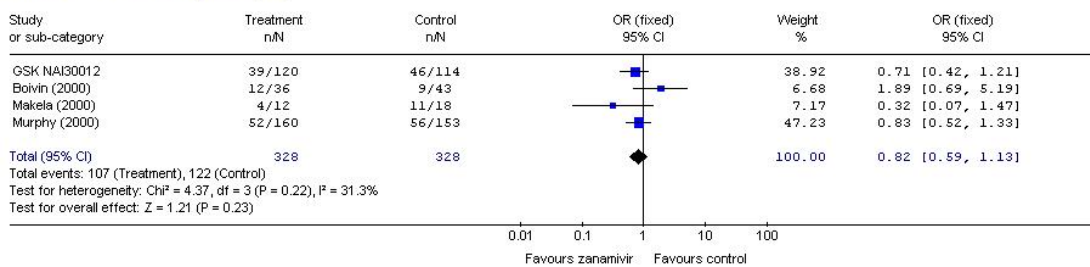
Review: Influenza: Zanamivir
 Comparison: 06 General at risk
 Outcome: 06 Antibiotic use (ITT)

Figure 10.30



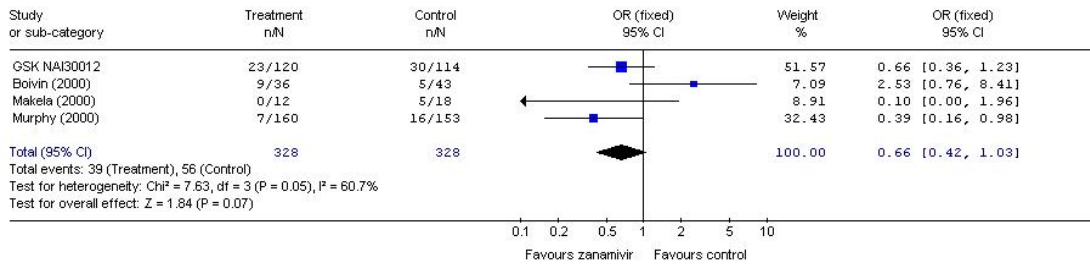
Review: Influenza: Zanamivir
 Comparison: 06 General at risk
 Outcome: 02 Overall complications (ITT)

Figure 10.31



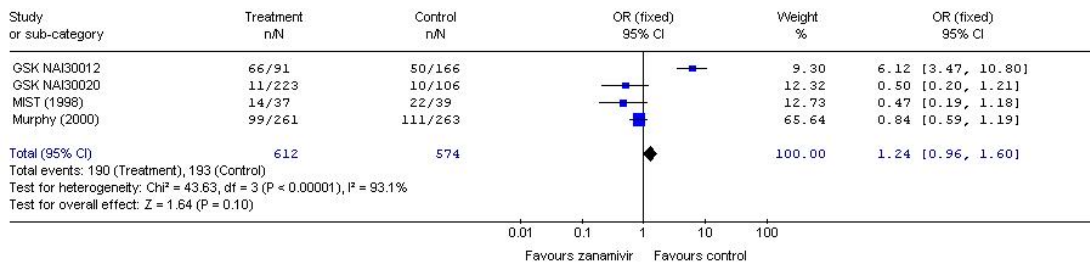
Review: Influenza: Zanamivir
 Comparison: 06 General at risk
 Outcome: 07 Antibiotic use (ITT)

Figure 10.32



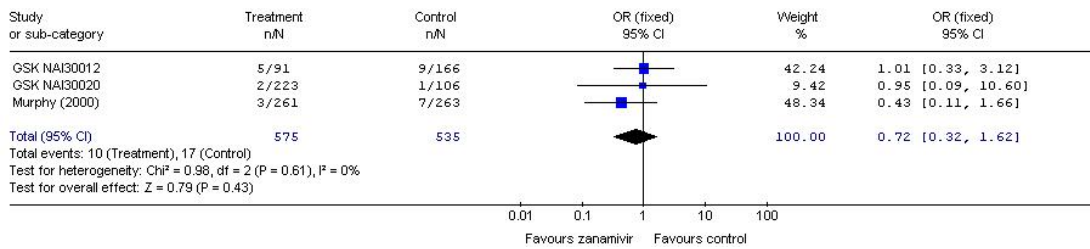
Review: Influenza: Zanamivir
 Comparison: 06 General at risk
 Outcome: 05 Overall adverse events (ITT)

Figure 10.33



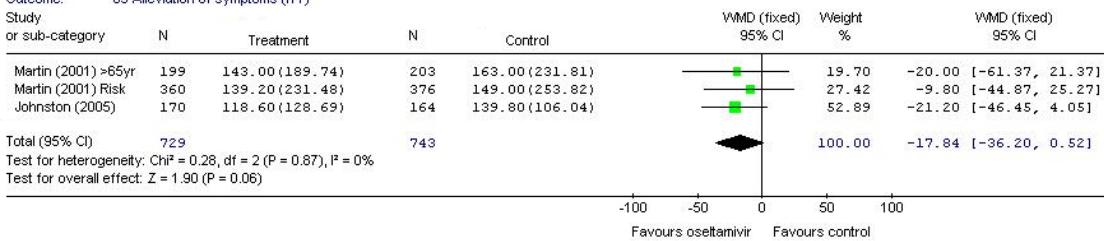
Review: Influenza: Zanamivir
 Comparison: 06 General at risk
 Outcome: 10 Serious adverse events (ITT)

Figure 10.34



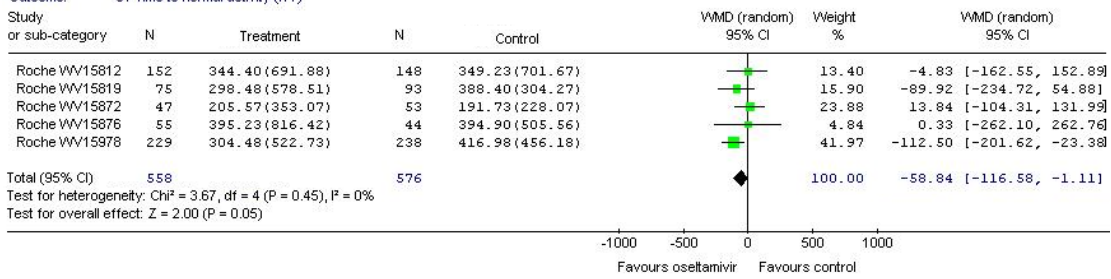
Review: Influenza: Oseltamivir
 Comparison: 06 General at risk
 Outcome: 03 Alleviation of symptoms (ITT)

Figure 10.35



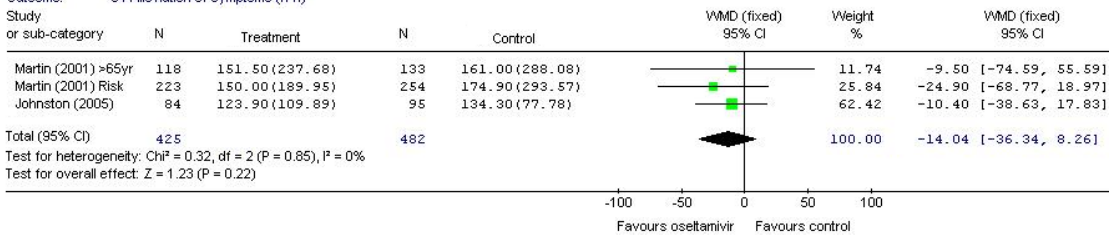
Review: Influenza: Oseltamivir
 Comparison: 06 General at risk
 Outcome: 01 Time to normal activity (ITT)

Figure 10.36



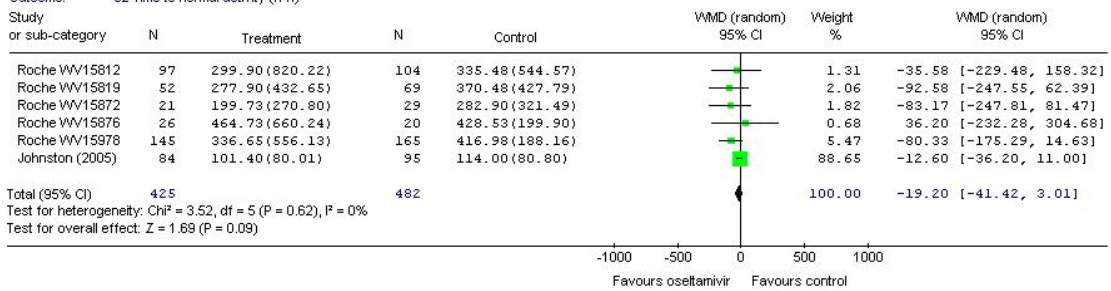
Review: Influenza: Oseltamivir
 Comparison: 06 General at risk
 Outcome: 04 Alleviation of symptoms (ITT)

Figure 10.37



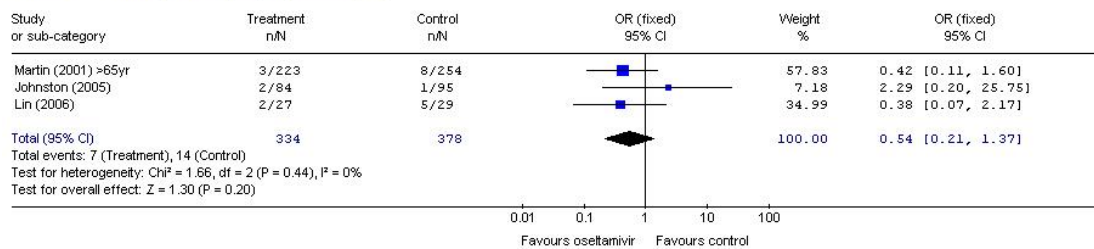
Review: Influenza: Oseltamivir
 Comparison: 06 General at risk
 Outcome: 02 Time to normal activity (ITT)

Figure 10.38



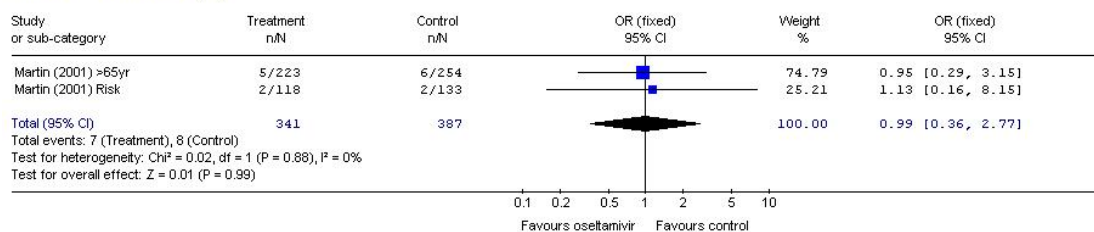
Review: Influenza: Oseltamivir
 Comparison: 06 General at risk
 Outcome: 09 Complications requiring hospitalisation (ITT)

Figure 10.39



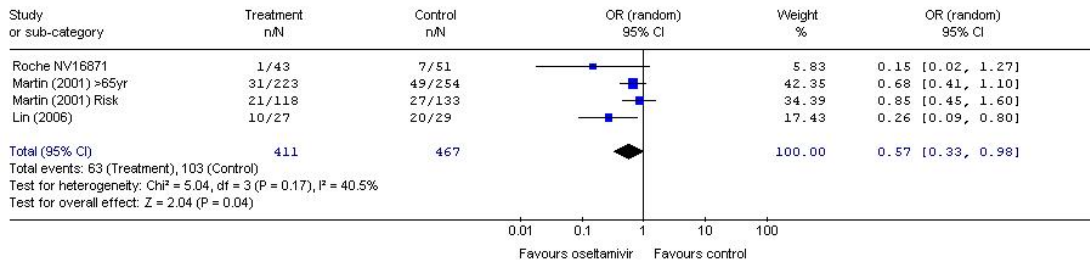
Review: Influenza: Oseltamivir
 Comparison: 06 General at risk
 Outcome: 10 Pneumonia (ITT)

Figure 10.40



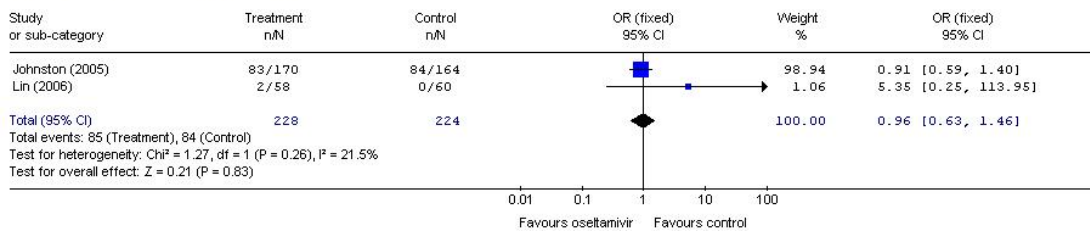
Review: Influenza: Oseltamivir
 Comparison: 06 General at risk
 Outcome: 07 Antibiotic use (ITT)

Figure 10.41



Review: Influenza: Oseltamivir
 Comparison: 06 General at risk
 Outcome: 05 Overall adverse events (ITT)

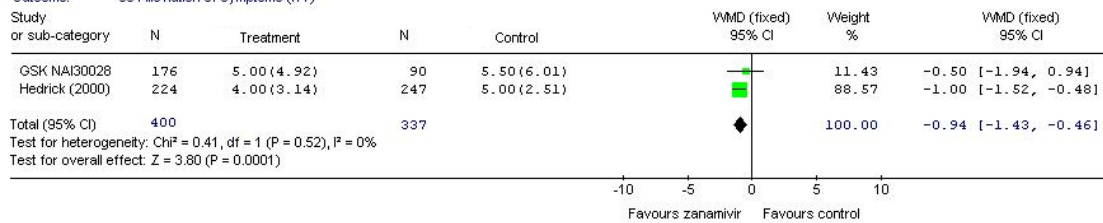
Figure 10.42



Children

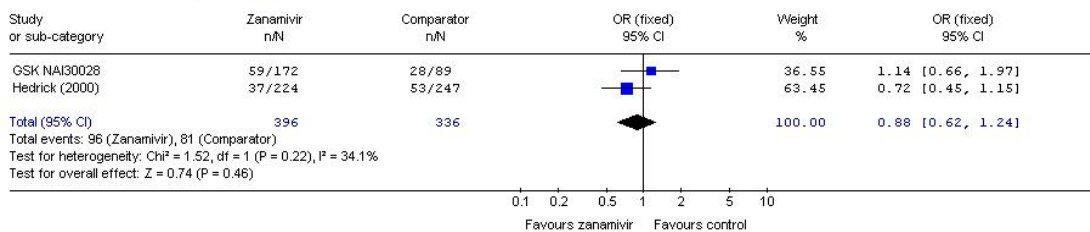
Figure 10.43

Review: Influenza: Zanamivir
 Comparison: 02 Children
 Outcome: 06 Alleviation of symptoms (ITT)



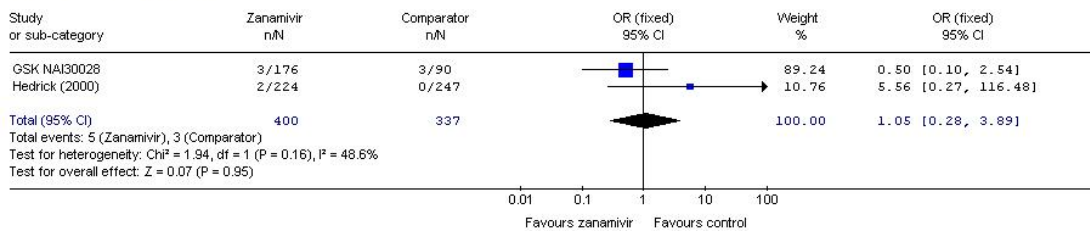
Review: Influenza: Zanamivir
 Comparison: 02 Children
 Outcome: 01 Overall complications (ITT)

Figure 10.44



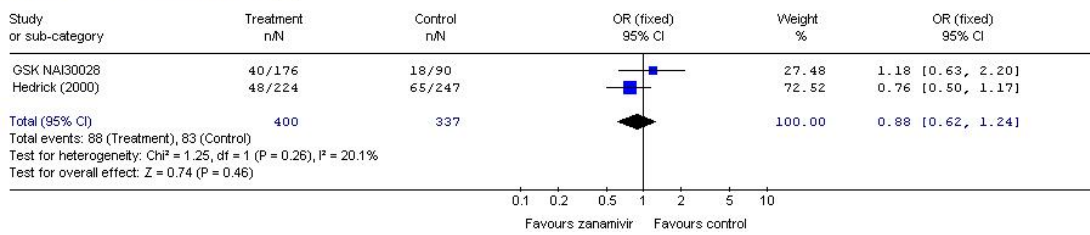
Review: Influenza: Zanamivir
 Comparison: 02 Children
 Outcome: 02 Bronchitis (ITT)

Figure 10.45



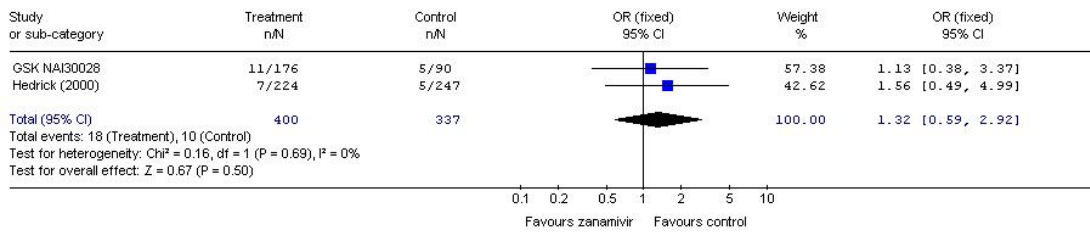
Review: Influenza: Zanamivir
 Comparison: 02 Children
 Outcome: 03 Overall adverse events (ITT)

Figure 10.46



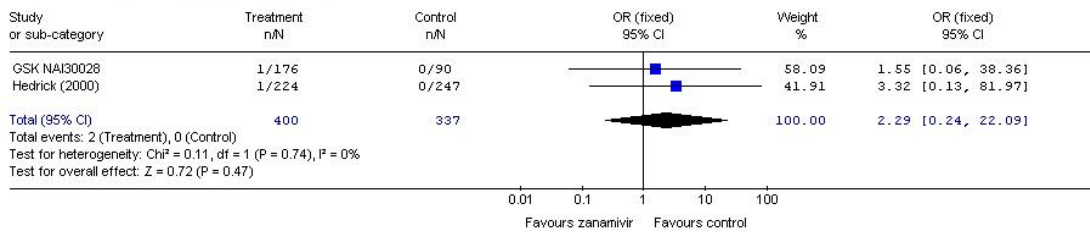
Review: Influenza: Zanamivir
 Comparison: 02 Children
 Outcome: 05 Drug-related adverse events (ITT)

Figure 10.47



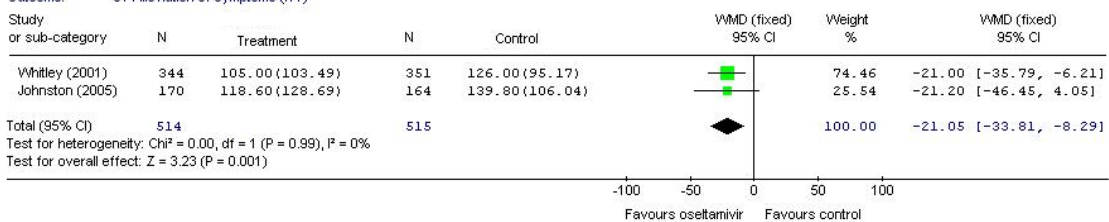
Review: Influenza: Zanamivir
 Comparison: 02 Children
 Outcome: 04 Overall serious adverse events (ITT)

Figure 10.48



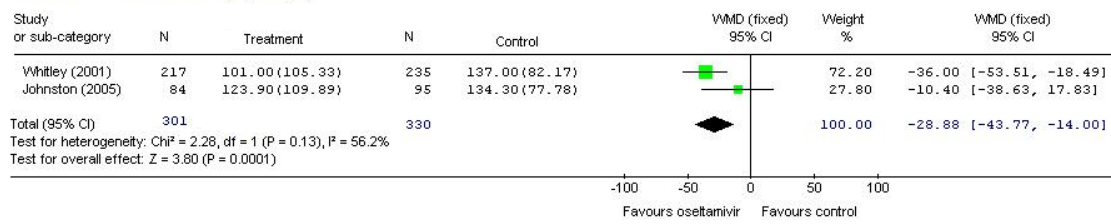
Review: Influenza: Oseltamivir
 Comparison: 02 Children
 Outcome: 01 Alleviation of symptoms (ITT)

Figure 10.49



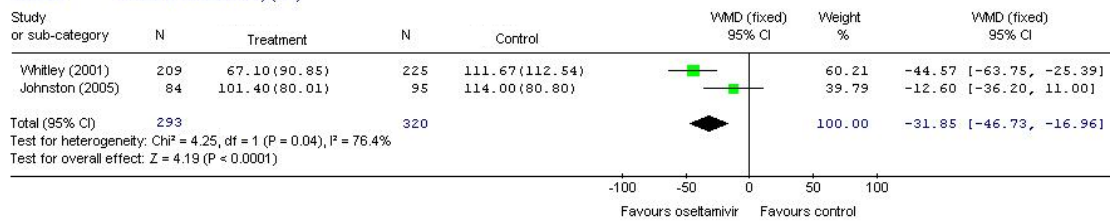
Review: Influenza: Osetamivir
 Comparison: 02 Children
 Outcome: 02 Alleviation of symptoms (ITT)

Figure 10.50



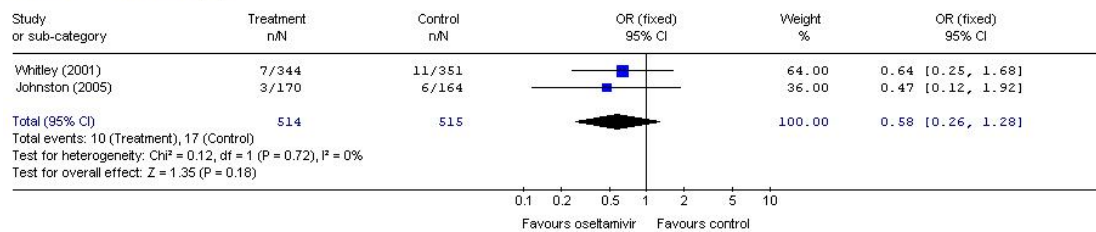
Review: Influenza: Osetamivir
 Comparison: 02 Children
 Outcome: 05 Time to normal activity (ITT)

Figure 10.51



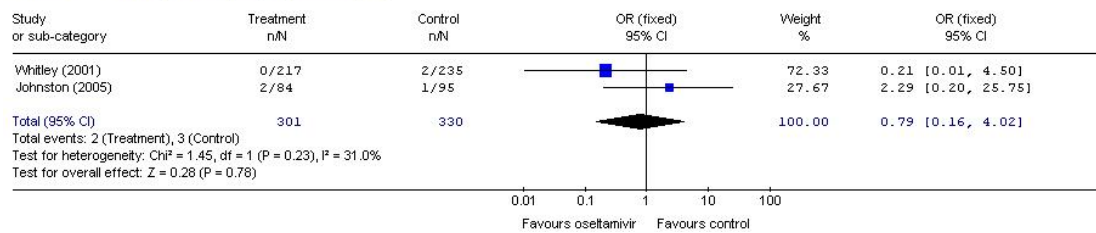
Review: Influenza: Osetamivir
 Comparison: 02 Children
 Outcome: 03 Pneumonia (ITT)

Figure 10.52



Review: Influenza: Osetamivir
 Comparison: 02 Children
 Outcome: 04 Complications requiring hospitalisation (ITT)

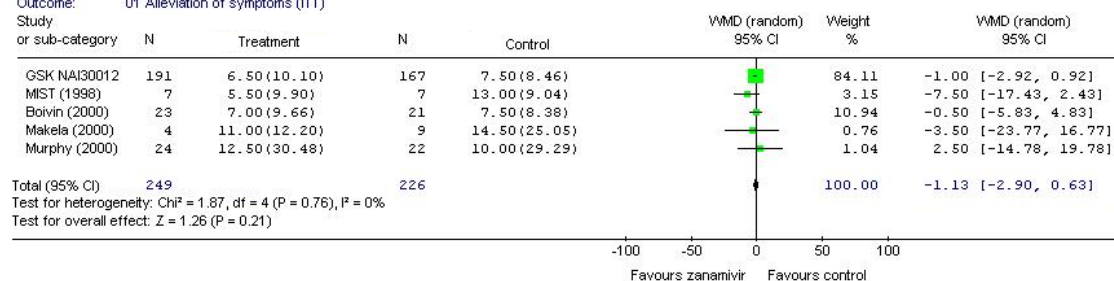
Figure 10.53



Elderly

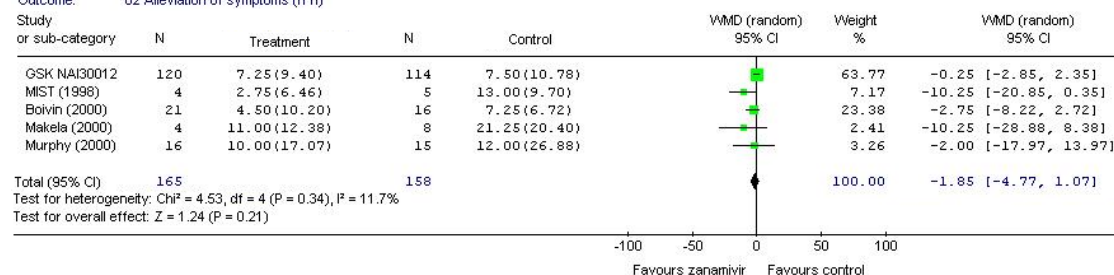
Review: Influenza: Zanamivir
 Comparison: 01 Elderly
 Outcome: 01 Alleviation of symptoms (ITT)

Figure 10.54



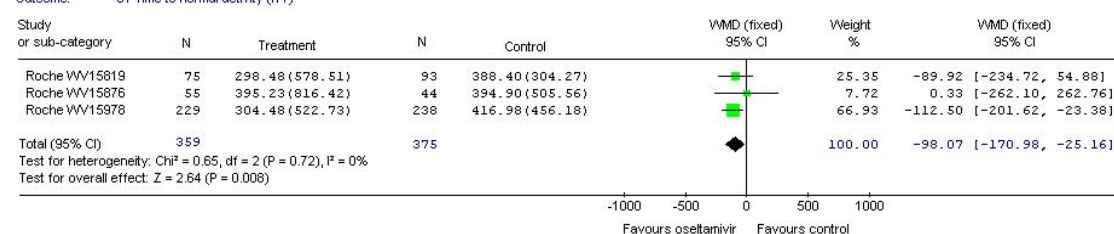
Review: Influenza: Zanamivir
 Comparison: 01 Elderly
 Outcome: 02 Alleviation of symptoms (ITT)

Figure 10.55



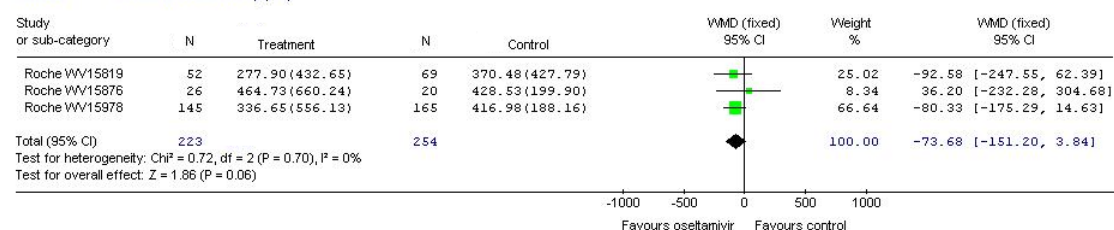
Review: Influenza: Oseltamivir
 Comparison: 01 Elderly
 Outcome: 01 Time to normal activity (ITT)

Figure 10.56



Review: Influenza: Oseltamivir
 Comparison: 01 Elderly
 Outcome: 02 Time to normal activity (ITT)

Figure 10.57



10.7 Bayesian multi-parameter evidence synthesis with indirect comparisons

Winbugs model

Model

```
{
for (i in 1:n.medsymp){
  med.symp[i]~dnorm(ET.med[i], prec.symp[i])
  dev.med[i]<- (med.symp[i] - ET.med[i])*(med.symp[i]-ET.med[i])*prec.symp[i]
  ET.med[i]<-beta[s[i],trt[i],subgrp[i],1]*pow(log(2),1/alpha[s[i],trt[i],1])
}

for (i in (n.medsymp+1):(n.medsymp+n.mednorm)){
  med.norm[i]~dnorm(ET.med[i],prec.norm[i])
  dev.med[i]<- (med.norm[i]-ET.med[i])*(med.norm[i]-ET.med[i])*prec.norm[i]
  ET.med[i]<-beta[s[i],trt[i],subgrp[i],2]*pow(log(2),1/alpha[s[i],trt[i],2])
}

for (i in (n.medsymp+n.mednorm+1):(n.medsymp+n.mednorm+n.nsymp)){
  n.symp[i]~dbin(p.symp[i],N[i])
  rhat[i] <- (0.5+.9999*(p.symp[i]-0.5)) * N[i]
  dev.nsymp[i] <- 2 * (n.symp[i] * (log(n.symp[i])-log(rhat[i])) + (N[i]-n.symp[i]) *
(log(N[i]-n.symp[i]) - log(N[i]-rhat[i])))

  rho[i]<-exp(-pow(X[i]/beta[s[i],trt[i],subgrp[i],1],alpha[s[i],trt[i],1]))

  z[i]<-(0.5-rho[i])/sqrt(rho[i]*(1-rho[i])/N[i])
  phi.z[i]<-phi(z[i])
  z.s[i]<-min(phi.z[i],0.99)
  c[i]<-sqrt(rho[i]*(1-rho[i])/(2*pi*N[i]))*exp((-pow((0.5-
rho[i]),2)*N[i])/(2*rho[i]*(1-rho[i])))
  EP.u[i]<-rho[i]+c[i]/(1-z.s[i])
  EP.l[i]<-rho[i]-c[i]/z.s[i]

  EP.x[i]<-(1-step(ET.med[i]-X[i]))*EP.l[i]+step(ET.med[i]-X[i])*EP.u[i]
  p.symp[i]<- EP.x[i]
  ET.med[i]<-beta[s[i],trt[i],subgrp[i],1]*pow(log(2),1/alpha[s[i],trt[i],1])
}

for (i in
(n.medsymp+n.mednorm+n.nsymp+1):(n.medsymp+n.mednorm+n.nsymp+n.nomed)){
  n.symp[i]~dbin(p.symp[i],N[i])
  rhat[i] <- (0.5+.9999*(p.symp[i]-0.5)) * N[i]
  dev.nsymp[i] <- 2 * (n.symp[i] * (log(n.symp[i])-log(rhat[i])) + (N[i]-n.symp[i]) *
(log(N[i]-n.symp[i]) - log(N[i]-rhat[i])))
  rho[i]<-exp(-pow(X[i]/beta[s[i],trt[i],subgrp[i],1],alpha[s[i],trt[i],1]))
  p.symp[i]<- rho[i]
}

sumdev.med[1]<- sum(dev.med[1:n.medsymp])
sumdev.med[2]<- sum(dev.med[(n.medsymp+1):(n.medsymp+n.mednorm)])
sumdev.nsymp<-
sum(dev.nsymp[(n.medsymp+n.mednorm+1):(n.medsymp+n.mednorm+n.nsymp+n.nomed)])
```

```
sumdev<- sumdev.med[1] + sumdev.med[2] + sumdev.nsymp
```

```
for (j in 1:nstudy){
  for (k in 1:ntrt){
    alpha[j,k,1]~dnorm(a,P.a)I(0,)
    alpha[j,k,2]~dnorm(a,P.a)I(0,)
  }
  gamma[j]~dnorm(g,P.g)
  for (m in 1:n.sg){
    mu[j,m,1]~dnorm(base[m],P.m)
    mu[j,m,2]<-mu[j,m,1] + gamma[j]

    for (k in 1:ntrt){
      log(beta[j,k,m,1])<- mu[j,m,1]+delta[j,k,m,1]
      log(beta[j,k,m,2])<- mu[j,m,2]+ delta[j,k,m,2]
    }
  }

  for (m in 1:n.sg){
    for (Y in 1:2){delta[j,1,m,Y] <- 0 }
    for (k in 2:ntrt) {
      delta[j,k,m,1] ~ dnorm(d[k,m],prec.d)
      delta[j,k,m,2] ~ dnorm(d[k,m],prec.d)
    }
  }
}

for (m in 1:n.sg){
  base[m]~dnorm(0,.2)
  base.pred[m]~dnorm(base[m],P.m)

d[1,m] <- 0
e.d[1,m]<-exp(d[1,m])
for (k in 2:ntrt) {
  d[k,m] ~ dnorm(0,.2)
  e.d[k,m]<-exp(d[k,m])
}
}

P.m<- 1/(sd.m*sd.m)
sd.m~dnorm(0,.2)I(0,)
prec.d<- 1/pow(sigma,2)
sigma~dnorm(0,.2)I(0,)

a~dnorm(1,.1)I(0,)

P.a<- 1/(sd.a*sd.a)
sd.a~dnorm(0,.2)I(0,)

g~dnorm(0,.2)
P.g<- 1/(sd.g*sd.g)
sd.g~dnorm(0,.2)I(0,)

for (m in 1:n.sg){
```

```

        mu.S[m]<- base.pred[m]
        mu.N[m]<- mu.S[m] + g
    }

    for (k in 1:ntrt){
        for (m in 1:n.sg){
            log(mean.S[k,m])<-loggam(1+1/a)+log(beta.S[k,m])
            log(mean.N[k,m])<-loggam(1+1/a)+log(beta.N[k,m])

            log(beta.S[k,m])<- mu.S[m] + d[k,m]
            log(beta.N[k,m])<- mu.N[m] + d[k,m]

            d.pred[k,m] ~ dnorm(d[k,m],prec.d)
            med.S[k, m] <- beta.S[k, m]*pow(log(2), 1/a)
            med.N[k, m] <- beta.N[k, m]*pow(log(2), 1/a)
        }
    }

    for (m in 1:n.sg){
        for (k in 1:ntrt){
            rk[k,m]<-rank(e.d[,m],k)
            best[k,m]<-equals(rk[k,m],1)
            rk.pred[k,m]<-rank(d.pred[,m],k)
            best.pred[k,m]<-equals(rk.pred[k,m],1)
        }
    }

    dum[1]<- code[1]
}

```

Results of Bayesian multi-parameter evidence synthesis with indirect comparisons - excluding 'at risk' children data

Table 10.1: The median and mean (95% credibility intervals (CrI)) number of days to the alleviation of symptoms in the ITT population

Subgroup	Treatment	Probability 'best'	Median (95% CrI)	Mean (95% CrI)
Healthy adults	Placebo	0.00	5.50 (1.99, 12.24)	9.89 (3.60, 22.12)
	Zanamivir	0.06	5.01 (1.80, 11.15)	9.03 (3.25, 20.22)
	Oseltamivir	0.94	4.44 (1.60, 9.93)	7.99 (2.88, 17.91)
'At risk'	Placebo	0.00	8.87 (3.13, 20.08)	15.96 (5.60, 36.14)
	Zanamivir	0.92	7.23 (2.55, 16.39)	13.01 (4.55, 29.46)
	Oseltamivir	0.08	8.36 (2.9, 19.05)	15.04 (5.17, 34.29)
Healthy Children	Placebo	0.00	3.82 (1.20, 9.20)	6.87 (2.16, 16.42)
	Zanamivir	0.75	2.94 (0.91, 7.13)	5.29 (1.65, 12.85)
	Oseltamivir	0.25	3.21 (0.98, 7.78)	5.78 (1.78, 14.04)

Table 10.2: The median and mean difference in days (95% CrI) for the time to alleviation of symptoms in the ITT population

Subgroup	Treatment	Difference in symptom duration	
		Median (95% CrI)	Mean (95% CrI)
Healthy adults	Zanamivir vs. placebo	-0.48 (-1.30, -0.06)	-0.87 (-2.35, -0.10)
	Oseltamivir vs. placebo	-1.06 (-2.58, -0.27)	-1.91 (-4.65, -0.50)
	Zanamivir vs. oseltamivir	0.58 (-0.14, 1.75)	1.04 (-0.26, 3.17)
'At risk'	Zanamivir vs. placebo	-1.64 (-4.19, -0.40)	-2.95 (-7.60, -0.71)
	Oseltamivir vs. placebo	-0.51 (-2.28, 0.86)	-0.92 (-4.10, 1.55)
	Zanamivir vs. oseltamivir	-1.13 (-3.73, 0.39)	-2.03 (-6.77, 0.70)
Healthy Children	Zanamivir vs. placebo	-0.88 (-2.36, -0.17)	-1.58 (-4.27, -0.31)
	Oseltamivir vs. placebo	-0.60 (-1.82, 0.02)	-1.09 (-3.25, 0.03)
	Zanamivir vs. oseltamivir	-0.27 (-1.41, 0.56)	-0.49 (-2.55, 1.00)

Table 10.3: The median and mean (95% CrI) number of days to the alleviation of symptoms in the ITTI population

Subgroup	Treatment	Probability 'best'	Median (95% CrI)	Mean (95% CrI)
Healthy adults	Placebo	0.00	5.27 (2.57, 9.64)	8.77 (4.30, 16.19)
	Zanamivir	0.06	4.58 (2.23, 8.41)	7.63 (3.72, 14.13)
	Oseltamivir	0.94	4.11 (2.00, 7.58)	6.84 (3.33, 12.65)
'At risk'	Placebo	0.00	8.75 (4.22, 16.34)	14.58 (7.02, 27.26)
	Zanamivir	0.95	6.57 (3.15, 12.32)	10.93 (5.21, 20.53)
	Oseltamivir	0.05	7.78 (3.66, 14.70)	12.95 (6.12, 24.59)
Healthy Children	Placebo	0.00	5.83 (2.45, 11.65)	9.71 (4.09, 19.53)
	Zanamivir	0.40	4.49 (1.88, 9.04)	7.48 (3.11, 15.16)
	Oseltamivir	0.60	4.34 (1.79, 8.82)	7.23 (2.99, 14.70)

Table 10.4: The median and mean difference in days (95% CrI) for the time to alleviation of symptoms in the ITTI population

Subgroup	Treatment	Difference in symptom duration	
		Median (95% CrI)	Mean (95% CrI)
Healthy adults	Zanamivir vs. placebo	-0.68 (-1.43, -0.23)	-1.14 (-2.39, -0.39)
	Oseltamivir vs. placebo	-1.16 (-2.27, -0.48)	-1.93 (-3.80, -0.81)
	Zanamivir vs. oseltamivir	0.47 (-0.12, 1.27)	0.79 (-0.20, 2.13)
'At risk'	Zanamivir vs. placebo	-2.19 (-4.44, -0.87)	-3.64 (-7.44, -1.44)
	Oseltamivir vs. placebo	-0.98 (-2.68, 0.30)	-1.62 (-4.48, 0.5)
	Zanamivir vs. oseltamivir	-1.21 (-3.37, 0.27)	-2.02 (-5.64, 0.44)
Healthy Children	Zanamivir vs. placebo	-1.34 (-3.07, -0.33)	-2.23 (-5.13, -0.55)
	Oseltamivir vs. placebo	-1.49 (-3.32, -0.46)	-2.47 (-5.55, -0.76)
	Zanamivir vs. oseltamivir	0.15 (-1.01, 1.53)	0.24 (-1.68, 2.55)

Table 10.5: The median and mean (95% CrI) number of days to the return to normal activities in the ITT population

Subgroup	Treatment	Probability 'best'	Median (95% CrI)	Mean (95% CrI)
Healthy adults	Placebo	0.00	6.49 (2.22, 14.92)	11.69 (3.97, 27.09)
	Zanamivir	0.06	5.92 (2.02, 13.74)	10.67 (3.61, 24.77)
	Oseltamivir	0.94	5.24 (1.79, 12.12)	9.44 (3.19, 22.09)
'At risk'	Placebo	0.00	10.46 (3.49, 24.47)	18.85 (6.26, 44.23)
	Zanamivir	0.92	8.53 (2.85, 20.03)	15.36 (5.09, 36.07)
	Oseltamivir	0.08	9.86 (3.25, 23.19)	17.77 (5.84, 41.71)
Healthy Children	Placebo	0.00	4.51 (1.32, 11.20)	8.12 (2.39, 20.25)
	Zanamivir	0.75	3.47 (1.02, 8.75)	6.25 (1.84, 15.66)
	Oseltamivir	0.25	3.80 (1.09, 9.51)	6.83 (1.97, 17.22)

Table 10.6: The median and mean difference in days (95% CrI) for the time to the return to normal activities in the ITT population

Subgroup	Treatment	Difference in symptom duration	
		Median (95% CrI)	Mean (95% CrI)
Healthy adults	Zanamivir vs. placebo	-0.57 (-1.59, -0.07)	-1.03 (-2.87, -0.12)
	Oseltamivir vs. placebo	-1.25 (-3.13, -0.31)	-2.26 (-5.67, -0.55)
	Zanamivir vs. oseltamivir	0.68 (-0.17, 2.12)	1.23 (-0.31, 3.85)
'At risk'	Zanamivir vs. placebo	-1.64 (-4.19, -0.40)	-2.95 (-7.60, -0.71)
	Oseltamivir vs. placebo	-0.60 (-2.73, 1.00)	-1.08 (-4.90, 1.82)
	Zanamivir vs. oseltamivir	-1.33 (-4.45, 0.45)	-2.4 (-8.09, 0.81)
Healthy Children	Zanamivir vs. placebo	-1.04 (-2.89, -0.19)	-1.87 (-5.25, -0.34)
	Oseltamivir vs. placebo	-0.71 (-2.18, 0.02)	-1.28 (-3.92, 0.03)
	Zanamivir vs. oseltamivir	-0.33 (-1.7, 0.66)	-0.59 (-3.07, 1.19)

Table 10.7: The median and mean (95% CrI) number of days to the return to normal activities in the ITTI population

Subgroup	Treatment	Probability 'best'	Median (95% CrI)	Mean (95% CrI)
Healthy adults	Placebo	0.00	6.82 (3.08, 13.13)	11.37 (5.09, 21.99)
	Zanamivir	0.06	5.94 (2.67, 11.37)	9.90 (4.44, 19.19)
	Oseltamivir	0.94	5.32 (2.39, 10.25)	8.87 (3.96, 17.17)
'At risk'	Placebo	0.00	11.34 (5.11, 22.24)	18.91 (8.41, 37.29)
	Zanamivir	0.95	8.51 (3.75, 16.62)	14.18 (6.27, 27.95)
	Oseltamivir	0.05	10.08 (4.43, 20.13)	16.80 (7.31, 33.59)
Healthy Children	Placebo	0.00	7.56 (2.96, 15.86)	12.60 (4.89, 26.55)
	Zanamivir	0.40	5.82 (2.24, 12.32)	9.70 (3.71, 20.61)
	Oseltamivir	0.60	5.63 (2.16, 11.93)	9.39 (3.59, 19.96)

Table 10.8: The median and mean difference in days (95% CrI) for the time to the return to normal activities in the ITTI population

Subgroup	Treatment	Difference in symptom duration	
		Median (95% CrI)	Mean (95% CrI)
Healthy adults	Zanamivir vs. placebo	-0.89 (-1.94, -0.28)	-1.48 (-3.25, -0.47)
	Oseltamivir vs. placebo	-1.50 (-3.1, -0.58)	-2.50 (-5.18, -0.97)
	Zanamivir vs. oseltamivir	0.61 (-0.15, 1.72)	1.02 (-0.25, 2.88)
'At risk'	Zanamivir vs. placebo	-2.19 (-4.44, -0.87)	-3.64 (-7.44, -1.44)
	Oseltamivir vs. placebo	-1.26 (-3.65, 0.38)	-2.10 (-6.04, 0.64)
	Zanamivir vs. oseltamivir	-1.57 (-4.50, 0.34)	-2.62 (-7.56, 0.56)
Healthy Children	Zanamivir vs. placebo	-1.74 (-4.14, -0.41)	-2.89 (-6.92, -0.68)
	Oseltamivir vs. placebo	-1.93 (-4.44, -0.55)	-3.21 (-7.43, -0.92)
	Zanamivir vs. oseltamivir	0.19 (-1.35, 2.00)	0.32 (-2.24, 3.35)

10.8 Literature review of utility scores for influenza

Study details	Method	Health State	Source	Results	Utility decrements
Burls et al. (2002)	EQ-5D	(i) Flu (ii) No flu	<i>Experts:</i> authors' assumptions.	(i) 0.516 (ii) 0.8	0.284
Griffin et al. (2001)	EQ-5D	(i) Normal health (ii) Flu (during whole illness) (iii) Flu (on worst day)	<i>Patients:</i> sample of 21 retrospectively self-assessed patients aged 18+yrs flu-positive during previous flu season from a UK GP database. <i>Experts</i> (cross-check not used in analysis): panel of 8 UK GPs completed questionnaires on a hypothetical flu-positive 'at risk' patient.	(i) 0.817 (patients), 0.72 (experts) (ii) -0.066 (patients), -0.263 (experts) (iii) -0.342 (patients), not collected (experts)	(i)-(ii) 0.883 (patients), 0.982 (experts) (i)-(iii) 1.159 (patients)
Inonue et al. (2005)	EQ-5D	(i) Flu symptoms (ii) No flu symptoms	<i>Patients:</i> taken from a published Japanese study.	(i) -0.066 (ii) 0.817	0.883
Rothberg et al. (2003a)	EQ-5D	(i) No QoL reduction (ii) QoL reduction due to flu (iii) Complete QoL loss	<i>Patients:</i> daily QoL reductions taken from Griffin et al. (2001).	(i) 0 (ii) -0.883 (iii) -1	0.883
Rothberg et al. (2005)	EQ-5D	(i) No QoL reduction (ii) QoL reduction due to flu (iii) Complete QoL loss	<i>Patients:</i> daily QoL reductions taken from unpublished data from children enrolled in zanamivir RCTs.	(i) 0 (ii) -0.68 (iii) -1	0.68
Husereau et al. (2001)	HUI3	(i) No flu (ii) Flu (outpatient) (iii) Flu (inpatient) (iv) Death	<i>Public:</i> sample of 11 self-assessed healthy adults.	(i) 1 (ii) 0.636 (iii) 0.35 (+5 extra hospital days) (iv) 0	(i)-(ii) 0.364 (i)-(iii) 0.65
Rothberg et al. (2003b)	HUI3	(i) Full health (ii) Flu	<i>Patients:</i> retrospectively collected from a sample of 15 working age patients and health-care workers with a history of flu.	(i) 1 (ii) 0.25	0.75
Mauskopf et al. (2000)	QWB	(i) Flu symptoms (ii) No flu symptoms	<i>Experts:</i> authors' assumptions.	(i) 0.5579 (ii) 1	0.4421
Muenning and Khan (2001)	QWB (base-case), HUI2 (sensitivity analysis)	(i) Flu	<i>Public:</i> taken from a US health survey of 866 individuals.	0.61 (base-case), 0.79 (sensitivity analysis)	0.39 (base-case), 0.21 (sensitivity analysis)
Rothberg and Rose (2005)	QWB	(i) Full health (ii) Flu	<i>Experts:</i> taken from a published US study and from Muenning and Khan (2001)	(i) 1 (ii) 0.6	0.4
Prosser et al. (2005)	TTO	(i) Flu prevention in own 1yr child (ii) Flu prevention in own 14yrs child	<i>Public:</i> telephone interview of sample of 112 adults enrolled in a US health plan asked to trade their own life to prevent flu in their children.	Undiscounted: (i) 68dys (ii) 86dys Discounted at 3%: (i) 29dys (ii) 41dys	Not reported
O'Brien et al. (2003)	VAS	(i) Worst possible health (ii)-(viii). Mean daily health during flu week (ix). Normal health	<i>Patients:</i> daily QoL self-reported by flu infection status over 7 days by 2,207 (69.69% flu-positive) otherwise healthy adults aged 16-64yrs enrolled into 4 oseltamivir RCTs.	Mean daily utility scores reported by flu infection status	Mean daily differences reported over 7 days by flu infection status

Study details	Method	Health State	Source	Results	Utility decrements
Roche submission to NICE (2008)	VAS	(i) Full health (ii) ILI (standard care) (iii) ILI (either NI)	<i>Experts:</i> QoL for standard care was taken from a Dutch study on disability weights. <i>Patients:</i> estimated from self-reported valuations collected for 21dys alongside Roche oseltamivir RCTs.	(i) 1 (ii) 0.811 (iii) 0.904	(i)-(ii) 0.189 (i)-(iii) 0.096
Sander et al. (2004)	3 11-point VAS	(i) Full health (ii) Flu	<i>Experts:</i> taken from a Dutch study on disability weights.	(i) 1 (ii) 0.84	0.16
Sander et al. (2005)	3 11-point VAS	(i) Full health (ii) ILI (standard care) (iii) ILI (oseltamivir) (iv) ILI (zanamivir)	<i>Experts:</i> QoL for no-treatment was taken from a Dutch study on disability weights. <i>Patients:</i> estimated from self-reported valuations collected for 9dys alongside Roche oseltamivir RCTs.	(i) 1 (ii) 0.84 (iii) 0.94 (iv) 0.94	(i)-(ii) 0.16 (i)-(iii) 0.06 (i)-(iv) 0.06
Turner et al. (2003)	VAS	(i) 21/7dys no treatment (ii) 21/7dys zanamivir (iii) 21/7dys oseltamivir (iv) 21/7dys amantadine	<i>Patients:</i> estimated from self-reported valuations collected for 21dys (base-case) and 7dys (sensitivity analysis) from 1,336 patients enrolled in 8 oseltamivir RCTs.	(i) 0.043/0.009 (adults), 0.028/0.006 ('at risk'), 0.043/0.009 (children) (ii) 0.045/0.01 (adults), 0.031/0.007 ('at risk'), 0.044/0.01 (children) (iii) 0.045/0.01 (adults), 0.03/0.007 ('at risk'), 0.045/0.01 (children)	Mean daily differences reported over 21 days by 'at risk' status
Demicheli et al. (2000)	Category rating combined with TTO	(i) Flu and nausea (ii) Full health	<i>Public:</i> sample of 40 British Army soldiers.	(i) -0.95 (ii) 1	1.05
Vindt Holm et al. (2004)	EQ-5D combined with PTO and 3 11-point VAS	(i) Flu (standard care) (ii) Flu (oseltamivir)	<i>Experts:</i> QoL weights were taken from Dutch study on disability weights	Mean daily utility scores reported over 21 days	Mean daily differences reported over 21 days
Smith and Roberts (2002)	Unspecified	(i) Well health (25-54yrs) (ii) Well health (men aged 55-64yrs) (iii) Well health (women aged 55-64yrs) (iv) Well health (65+yrs) (v) Flu (treated) (vi) Flu (untreated) (vii) Non-flu illness	<i>Public:</i> age-adjusted QoL scores for well health were derived from a US population health survey; QoL for untreated flu and non-flu illness were obtained from generic US population-based values. <i>Patients:</i> symptoms reduction rate, estimated at 38% from an oseltamivir RCT, was applied to illness disutility to obtain QoL for flu (treated).	(i) 0.92 (ii) 0.92 (iii) 0.84 (iv) 0.84 (v) 0.783 (vi) 0.65 (vii) 0.65	(i)/(ii)-(v) 0.137 (i)/(ii)-(vi) 0.27 (i)/(ii)-(vii) 0.27 (iii)/(iv)-(v) 0.057 (iii)/(iv)-(vi) 0.19 (iii)/(iv)-(vii) 0.19

10.9 Detailed economic model inputs

No.	Population	Treatment	Distribution	Mean	SE	α	β
Probability ILI is influenza							
<i>Baseline probability ILI is influenza</i>							
1	Children	N/A	Simulation output	0.5643		WinBUGS analysis	
2	Adults & elderly	N/A	Simulation output	0.4107		WinBUGS analysis	
Probability of complication							
<i>Baseline probability of complication</i>							
3	Healthy children	N/A	Beta	0.1344	N/A	2311	14890
4	'at risk' children	N/A	Beta	0.1759	N/A	650	3045
5	Healthy adults	N/A	Beta	0.0755	N/A	6437	78811
6	'at risk' adults	N/A	Beta	0.1217	N/A	2142	15455
7	Elderly	N/A	Beta	0.1092	N/A	1917	15635
<i>Relative risk of complication</i>							
8	Healthy children	Oseltamivir	Log-normal	0.3603	0.5554	N/A	N/A
9	Healthy children	Zanamivir	Log-normal	0.4386	0.5694	N/A	N/A
10	Healthy adults	Oseltamivir	Log-normal	0.3629	0.6085	N/A	N/A
11	Healthy adults	Zanamivir	Log-normal	0.4139	0.5909	N/A	N/A
12	All 'at risk' groups	Oseltamivir	Log-normal	0.4064	0.5390	N/A	N/A
13	All 'at risk' groups	Zanamivir	Log-normal	0.4241	0.5952	N/A	N/A
<i>Probability of RTI complication given patient has complication</i>							
14	Healthy children	N/A	Dirichlet	0.7021	N/A	1697	720
15	'at risk' children	N/A	Dirichlet	0.7704	N/A	520	155
16	Healthy adults	N/A	Dirichlet	0.8656	N/A	5636	875
17	'at risk' adults	N/A	Dirichlet	0.8961	N/A	1941	225
18	Elderly	N/A	Dirichlet	0.8530	N/A	1573	271
<i>Probability of cardiovascular complication given patient has complication</i>							
19	Healthy children	N/A	Dirichlet	0.0000	N/A	0	2417
20	'at risk' children	N/A	Dirichlet	0.0000	N/A	0	675
21	Healthy adults	N/A	Dirichlet	0.0017	N/A	11	6500
22	'at risk' adults	N/A	Dirichlet	0.0134	N/A	29	2137
23	Elderly	N/A	Dirichlet	0.0369	N/A	68	1776
<i>Probability of CNS complication given patient has complication</i>							
24	Healthy children	N/A	Dirichlet	0.0070	N/A	17	2400
25	'at risk' children	N/A	Dirichlet	0.0000	N/A	0	675
26	Healthy adults	N/A	Dirichlet	0.0155	N/A	101	6410
27	'at risk' adults	N/A	Dirichlet	0.0069	N/A	15	2151
28	Elderly	N/A	Dirichlet	0.0239	N/A	44	1800
<i>Probability of renal complication given patient has complication</i>							
29	Healthy children	N/A	Dirichlet	0.0008	N/A	2	2415
30	'at risk' children	N/A	Dirichlet	0.0000	N/A	0	675
31	Healthy adults	N/A	Dirichlet	0.0014	N/A	9	6502
32	'at risk' adults	N/A	Dirichlet	0.0023	N/A	5	2161
33	Elderly	N/A	Dirichlet	0.0092	N/A	17	1827
<i>Probability of 'other' complication given patient has complication</i>							
34	Healthy children	N/A	Dirichlet	0.2900	N/A	701	1716
35	'at risk' children	N/A	Dirichlet	0.2296	N/A	155	520

36	Healthy adults	N/A	Dirichlet	0.1158	N/A	754	5757
37	'at risk' adults	N/A	Dirichlet	0.0813	N/A	176	1990
38	Elderly	N/A	Dirichlet	0.0770	N/A	142	1702
Probability of bronchitis given patient has RTI complication							
39	Healthy children	N/A	Dirichlet	0.0701	N/A	113	1499
40	'at risk' children	N/A	Dirichlet	0.0633	N/A	21	311
41	Healthy adults	N/A	Dirichlet	0.1916	N/A	1057	4461
42	'at risk' adults	N/A	Dirichlet	0.2613	N/A	370	1046
43	Elderly	N/A	Dirichlet	0.3446	N/A	529	1006
Probability of pneumonia given patient has RTI complication							
44	Healthy children	N/A	Dirichlet	0.0180	N/A	29	1583
45	'at risk' children	N/A	Dirichlet	0.0271	N/A	9	323
46	Healthy adults	N/A	Dirichlet	0.0430	N/A	237	5281
47	'at risk' adults	N/A	Dirichlet	0.0438	N/A	62	1354
48	Elderly	N/A	Dirichlet	0.1322	N/A	203	1332
Probability of URTI given patient has RTI complication							
49	Healthy children	N/A	Dirichlet	0.9119	N/A	1470	142
50	'at risk' children	N/A	Dirichlet	0.9096	N/A	302	30
51	Healthy adults	N/A	Dirichlet	0.7655	N/A	4224	1294
52	'at risk' adults	N/A	Dirichlet	0.6949	N/A	984	432
53	Elderly	N/A	Dirichlet	0.5231	N/A	803	732
Probability of otitis media given patient has 'other' complication							
54	Healthy children	N/A	Beta	0.9757	N/A	684	17
55	'at risk' children	N/A	Beta	0.9871	N/A	153	2
56	Healthy adults	N/A	Beta	0.6649	N/A	500	252
57	'at risk' adults	N/A	Beta	0.6250	N/A	110	66
58	Elderly	N/A	Beta	0.2162	N/A	32	116
Proportion of influenza and RSV deaths attributable to influenza (used to weigh probability of complication in scenario 11)							
59	Children	N/A	Beta	0.6579	N/A	25	13
60	Adults	N/A	Beta	0.8011	N/A	733	182
61	Elderly	N/A	Beta	0.7542	N/A	7326	2388
Probability of antibiotics							
Baseline probability of antibiotics given patient has no complication or a non-RTI complication							
62	Children	N/A	Beta	0.2790	N/A	4997	12913.39
63	Adults	N/A	Beta	0.4200	N/A	39622	54716.10
64	Elderly	N/A	Beta	0.5470	N/A	8554	7084.03
Baseline probability of antibiotics given patient has RTI complication							
65	Children	N/A	Beta	0.7370	N/A	2183	779.01
66	Adults	N/A	Beta	0.8140	N/A	6983	1595.62
67	Elderly	N/A	Beta	0.7970	N/A	1527	388.93
Probability of hospitalisation							
Baseline probability of hospitalisation given patient has RTI complication							
68	Healthy children & adults	N/A	Beta	0.1087	N/A	5	41
69	All 'at risk' groups	N/A	Beta	0.1579	N/A	15	80
Baseline probability of stay in ICU given patient has pneumonia							
70	All populations	N/A	Beta	0.0486	N/A	22	431
Probability of mortality							

Baseline probability of mortality given patient has complication							
71	Healthy children	N/A	Fixed	0.0000	N/A	N/A	N/A
72	'at risk' children	N/A	Beta	0.0015	N/A	1	649
73	Healthy adults	N/A	Beta	0.0051	N/A	33	6404
74	'at risk' adults	N/A	Beta	0.0075	N/A	16	2126
75	Elderly	N/A	Beta	0.1168	N/A	224	1693
Cost of treatment							
<i>Baseline cost of treatment</i>							
76	All populations	Usual care	Fixed	£0.00	N/A	N/A	N/A
77	All populations	Oseltamivir	Fixed	£16.36	N/A	N/A	N/A
78	All populations	Zanamivir	Fixed	£16.36	N/A	N/A	N/A
Cost of GP visit							
<i>Baseline cost of GP visit</i>							
79	Children & adults	N/A	Fixed	£31.26	N/A	N/A	N/A
80	Elderly	N/A	Fixed	£34.50	N/A	N/A	N/A
Cost of hospitalisation							
<i>Length of inpatient stay for bronchitis (days)</i>							
81	Children	N/A	Fixed	2.4664	N/A	N/A	N/A
82	Adults	N/A	Fixed	2.5077	N/A	N/A	N/A
83	Elderly	N/A	Fixed	6.5828	N/A	N/A	N/A
<i>Length of inpatient stay for pneumonia (days)</i>							
84	Children	N/A	Fixed	2.9292	N/A	N/A	N/A
85	Adults	N/A	Fixed	7.4115	N/A	N/A	N/A
86	Elderly	N/A	Fixed	14.5126	N/A	N/A	N/A
<i>Length of inpatient stay for URTI (days)</i>							
87	Children	N/A	Fixed	2.1467	N/A	N/A	N/A
88	Adults	N/A	Fixed	3.7665	N/A	N/A	N/A
89	Elderly	N/A	Fixed	11.4650	N/A	N/A	N/A
<i>Length of inpatient stay for ICU (days)</i>							
90	All populations	N/A	Fixed	28	N/A	N/A	N/A
<i>Cost per diem for bronchitis</i>							
91	All populations	N/A	Fixed	£175.00	N/A	N/A	N/A
<i>Cost per diem for pneumonia</i>							
92	All populations	N/A	Fixed	£166.00	N/A	N/A	N/A
<i>Cost per diem for URTI</i>							
93	All populations	N/A	Fixed	£182.00	N/A	N/A	N/A
<i>Cost per diem for ICU</i>							
94	All populations	N/A	Fixed	£1,345.39	N/A	N/A	N/A
Cost of antibiotics							
<i>Cost of antibiotics given patient has no complication or a non-RTI complication</i>							
95	Children	N/A	Fixed	£0.21	N/A	N/A	N/A
96	Adults & elderly	N/A	Fixed	£0.46	N/A	N/A	N/A
<i>Cost of antibiotics given patient has RTI complication</i>							
97	Children	N/A	Fixed	£2.39	N/A	N/A	N/A
98	Healthy adults	N/A	Fixed	£3.71	N/A	N/A	N/A
99	'at risk' adults and elderly	N/A	Fixed	£5.66	N/A	N/A	N/A
Utility decrement from complications							
<i>Utility decrement resulting from bronchitis, URTI, CNS and renal complications, otitis media and GI bleeding</i>							

100	All populations	N/A	Fixed	0.15	N/A	N/A	N/A
<i>Utility decrement resulting from pneumonia</i>							
101	All populations	N/A	Fixed	0.25	N/A	N/A	N/A
<i>Utility decrement resulting from cardiovascular complication</i>							
102	All populations	N/A	Fixed	0.37	N/A	N/A	N/A
Utility decrement from ICU stay							
<i>Utility decrement resulting from ICU stay (applicable for period of illness)</i>							
103	All populations	N/A	Fixed	0.13	N/A	N/A	N/A

10.10 WinBUGs model to estimate the probability that an ILI is influenza

Model

```
{
for(r in 1:n)
{
flu[r] ~ dbin(prob_w[grp[r], yrs[r]], ILI[r])

flu.mi[r] <- ILI[r]*prob_w[grp[r], yrs[r]]
res[r] <- (flu[r]-flu.mi[r])/sqrt(flu.mi[r]*(1-prob_w[grp[r], yrs[r]]))
}

for(i in 1:I)
{
for(j in 1:J)
{
logit(prob_w[i, j]) <- lnO_w[i, j]

lnO_w[i, j] ~ dnorm(lnO_b[i], lnprec_b[i])
}

lnprec_b[i] <- pow(lnsd_b[i], -2)
logit(prob_b[i]) <- lnO_b[i]

lnO_b[i] ~ dnorm(lnO_p, lnprec_p)
lnsd_b[i] ~ dunif(0, 7)
}

for(i in 1:(I-1))
{
for(ii in (i+1):I)
{
lnOR_b[i, ii] <- lnO_b[i]-lnO_b[ii]
}
}

lnprec_p <- pow(lnsd_p, -2)
logit(prob_p) <- lnO_p
MSE <- inprod(res[], res[])/n

lnO_p ~ dflat()
lnsd_p ~ dunif(0, 5)
}
```