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Title: Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67)

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1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

A glossary of technical terms and abbreviations used throughout this report is presented below.

DEFINITION OF TERMS

General terms	
Attack rate	A cumulative incidence rate in a population over time, such as in the circumstances of an epidemic
Meta-analysis	A statistical method by which the results of a number of studies are pooled to give a combined summary statistic.
Post-exposure prophylaxis	Prophylaxis initiated in response to close contact of an individual with another suspected as suffering from influenza. Treatment typically lasts 7 to 10 days following presumed exposure.
Protective efficacy	1 minus the relative risk value, expressed as a percentage
Relative risk	Ratio of the probability of an event occurring in an exposed group relative to a non-exposed or control group
Seasonal prophylaxis	Prophylaxis initiated in response to known circulation of influenza within the community. Treatment typically lasts for 6 weeks.
Symptomatic, laboratory-confirmed influenza	Cases of influenza in which illness is clinically confirmed according to presence of symptoms indicative of influenza and with evidence of infection by the influenza virus, as determined by laboratory methods
Health Economic terms	
Dominated (simple)	Where a given treatment alternative is less effective and more expensive than its

	comparator.
Dominated (extended)	Where the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next more effective comparator.

LIST OF ABBREVIATIONS

ARI	Acute Respiratory Illness
BNF	British National Formulary
CEAC	Cost Effectiveness Acceptability Curve
Cfi	Centre for Infections
CI	Confidence Interval
CNS	Central Nervous System
DASA	Defence Analytical Services Agency
EISS	European Influenza Surveillance Scheme
EQ-5D	Euroqol 5D
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database
GSK	GlaxoSmithKline
HAI	Haemagglutination Inhibition Assay
HIV	Human Immunodeficiency Virus
HPA	Health Protection Agency
HRG	Health Resource Group
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
ILI	Influenza-Like Illness
ITT	Intention-To-Treat
ITU	Intensive Therapy Unit
Mg	Milligram
mL	Millilitre
MOD	Ministry of Defence
MVH	Measurement and Valuation of Health
NAMCS	National Ambulatory Medical Care Survey
NHS	National Health Service
NI	Neuraminidase Inhibitor
NICE	National Institute for Health and Clinical Excellence
ONS	Office for National Statistics
PCR	Polymerase Chain Reaction
PE	Protective Efficacy
PEP	Post-Exposure Prophylaxis
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
QUOROM	Quality Of Reporting Of Meta-analyses

RCGP	Royal College of General Practitioners
RCT	Randomised Controlled Trial
RNA	Ribonucleic Acid
RR	Relative Risk
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infection
SAVE	Simulating Anti-Influenza Value and Effectiveness
SLCI	Symptomatic Laboratory-Confirmed Influenza
SP	Seasonal Prophylaxis
SPC	Summary of Product Characteristics
TTO	Time Trade Off
VAERS	Vaccine Adverse Event Reporting System
VAS	Visual Analogue Scale
WHO	World Health Organisation
WRS	Weekly Returns Service

2. EXECUTIVE SUMMARY

2.1 Background

Influenza is an acute, febrile illness caused by infection of the respiratory system by the influenza virus. Influenza illness is usually self-limiting in otherwise healthy people. In individuals considered to be at high-risk, such as those aged over 65 years or having concomitant disease, the development of influenza carries the risk of increased morbidity, potentially serious influenza-associated complications and mortality.

A Health Technology Assessment of amantadine, oseltamivir and zanamivir for the prophylaxis of influenza was previously reported by Turner *et al.* Since this earlier review was undertaken, the marketing authorisation for zanamivir has been extended to include use of the intervention in the prophylaxis of influenza as well as the treatment of influenza and influenza-like illness. This report presents an updated assessment of new and existing evidence for the clinical and cost-effectiveness of amantadine, oseltamivir and zanamivir in the prevention of influenza.

2.2 Objectives

The objectives of this review were to evaluate the clinical effectiveness of amantadine, oseltamivir and zanamivir in seasonal and post-exposure prophylaxis against influenza and to estimate the incremental cost-effectiveness of the above interventions in comparison to each other and no prophylaxis.

2.3 Methods

A systematic review of evidence relating to the clinical effectiveness of amantadine, oseltamivir and zanamivir in seasonal and post-exposure prophylaxis against influenza was undertaken. An independent health economic model was developed based on a detailed review of existing cost-effectiveness models together with ongoing clinical advice. The model draws together a broad spectrum of evidence relating to the costs and consequences associated with influenza and its prevention. Importantly, where direct evidence concerning the effectiveness of prophylaxis within specific model subgroups was lacking, the model uses effectiveness estimates from mixed subgroups (e.g. effectiveness of oseltamivir and zanamivir as post-exposure prophylaxis taken from studies of households of mixed composition) or extrapolates from other mutually exclusive subgroups (e.g. effectiveness of seasonal prophylaxis using amantadine in adults assumed to be the same in children and elderly individuals). Cost-effectiveness estimates are presented

according to subgroups distinguished by age (children, adults, elderly), risk status (at-risk or otherwise healthy) and vaccination status (vaccinated or unvaccinated). For the purposes of the health economic model, “at-risk” is defined according to the presence of an underlying medical condition; this definition may not necessarily coincide with Department of Health definitions of target groups for vaccination (for example an otherwise healthy adult working in a hospital setting may be eligible for influenza vaccination). The results of the economic analysis are summarised in Section 2.4.2.

2.4 Results

2.4.1 Clinical effectiveness results

Twenty six published references relating to 22 randomised controlled trials (RCTs) were included in the clinical effectiveness review. An additional unpublished report was identified and included in the assessment, resulting in a total of 23 RCTs. A total of 8, 6 and 9 RCTs were included for amantadine, oseltamivir and zanamivir respectively. The quality of the studies identified was highly variable and gaps in the evidence base limited the assessment of the clinical effectiveness of the interventions across population subgroups and settings.

2.4.1.1 Seasonal prophylaxis

Evidence for the use of amantadine in prophylaxis was very limited and drawn from older research of relatively poor quality. Evidence was presented for the efficacy of amantadine in preventing symptomatic, laboratory-confirmed influenza (SLCI) in seasonal prophylaxis in healthy adults (relative risk = 0.40, 95% confidence interval (95%CI) 0.08 to 2.03). Oseltamivir was demonstrated to be effective in preventing SLCI, particularly when used in seasonal prophylaxis in at-risk elderly subjects (relative risk = 0.08, 95% 95%C.I. 0.01 to 0.63). The effectiveness of zanamivir in preventing SLCI was also shown; the preventative efficacy of zanamivir in seasonal prophylaxis was most notable in at-risk adults and adolescents (relative risk = 0.17, 95%C.I. 0.07 to 0.44), and healthy and at-risk elderly subjects (relative risk = 0.20 (95%C.I. 0.02 to 1.72)

2.4.1.2 Post-exposure prophylaxis

As for seasonal prophylaxis, very few data were available for the use of amantadine in post-exposure prophylaxis and were taken from older research of lower quality. A relative risk of 0.10 (95% C.I. 0.03 to 0.34) was reported for the prevention of SLCI in adolescents by post-exposure prophylaxis with amantadine. Oseltamivir was shown to be effective in post-exposure

prophylaxis within households of mixed composition (relative risk = 0.19 (95% C.I. 0.08 to 0.45); whilst the efficacy of zanamivir in post-exposure prophylaxis within households was also reported (relative risk = 0.21 (0.13 to 0.33)).

Interventions appeared to be well tolerated, with a relatively low occurrence of subjects experiencing drug-related adverse events and drug-related withdrawals. Very limited evidence was available for the effectiveness of the interventions in preventing complications, hospitalisations and in minimising length of illness and time to return to normal activities. No clinical effectiveness data could be identified for health-related quality of life or mortality outcomes.

2.4.2 Summary of cost-effectiveness findings

2.4.2.1 Seasonal prophylaxis

Seasonal prophylaxis for healthy children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the healthy children subgroup. The proposed reduction in the price of zanamivir does not affect this finding. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £44,000 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis produces the greatest level of net benefit is expected to be around 0.97.

Seasonal prophylaxis for at-risk children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the at-risk children subgroup. Again, the proposed reduction in the price of zanamivir does not affect this finding. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £17,000 per QALY gained for at-risk children who have not been vaccinated. For at-risk children who have previously been vaccinated, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be in excess of £50,000 per QALY gained. The cost-effectiveness estimates for oseltamivir are based on efficacy data which have been drawn from a trial of seasonal prophylaxis in healthy adults. Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that oseltamivir is optimal in unvaccinated at-risk children is approximately 0.70 (this probability is also 0.70 when the proposed price reduction for zanamivir is included). Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that oseltamivir is optimal in unvaccinated at-risk

children is around 0.94 (probability = 0.91 when the proposed price reduction for zanamivir is included). For at-risk children who have previously been vaccinated, the probability that no prophylaxis is optimal at £30,000 per QALY gained is approximately 0.96 or higher.

Seasonal prophylaxis for healthy adults

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the healthy adult subgroup. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £148,000 per QALY gained for healthy adults who have not been vaccinated and greater than £427,000 per QALY gained for healthy adults who have been vaccinated. These estimates are based on a trial of oseltamivir as seasonal prophylaxis in healthy adults. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is close to 1.0, irrespective of vaccination status.

Seasonal prophylaxis for at-risk adults

Based on the current list price for zanamivir, the model suggests that both amantadine and zanamivir are ruled out of the analysis in at-risk adults. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £64,000 per QALY gained in unvaccinated at-risk adults and around £187,000 per QALY gained in previously vaccinated at-risk adults. These estimates are based on a trial of oseltamivir as seasonal prophylaxis in healthy adults. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis produces the greatest amount of net benefit is close to 1.0.

When the proposed price reduction for zanamivir is included in the analysis for at-risk adults, zanamivir is no longer dominated. The incremental cost-effectiveness of seasonal prophylaxis using zanamivir versus no prophylaxis is expected to be around £53,000 per QALY gained in unvaccinated at-risk adults and £157,000 per QALY gained in at-risk adults who have previously been vaccinated. The incremental cost-effectiveness of oseltamivir is expected to be around £108,000 per QALY gained in unvaccinated at-risk adults and around £314,000 per QALY gained in previously vaccinated at-risk adults. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is around 0.99 for unvaccinated at-risk adults and close to 1.0 for previously vaccinated at-risk adults.

Seasonal prophylaxis for healthy elderly

For healthy elderly individuals, amantadine and zanamivir are expected to be dominated or extendedly dominated. The proposed reduction in the price of zanamivir does not affect this result. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in healthy elderly individuals who have not been vaccinated is expected to be around £50,000 per QALY gained. For previously vaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £120,000 per QALY gained. These estimates are based on a trial of oseltamivir as seasonal prophylaxis in elderly individuals. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is expected to be optimal is close to 1.0 (this probability is around 0.97 and 1.0 when the proposed price reduction for zanamivir is included in the analysis for unvaccinated and vaccinated subgroups respectively).

Seasonal prophylaxis for at-risk elderly

For at-risk elderly individuals, amantadine and zanamivir are expected to be extendedly dominated despite the proposed reduction in the price of zanamivir. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in at-risk elderly individuals who have not been vaccinated is expected to be around £38,000 per QALY gained. For previously vaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £94,000 per QALY gained. These estimates are based on a trial of oseltamivir as seasonal prophylaxis in elderly subjects. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is around 0.77 or higher.

The simple sensitivity analysis suggests that the cost-effectiveness of seasonal prophylaxis using amantadine, oseltamivir and zanamivir is sensitive to assumptions regarding the influenza attack rate, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community, the risk of hospitalisation in uncomplicated cases, and the discount rate.

2.4.2.2. Post-exposure prophylaxis

Post-exposure prophylaxis for healthy children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the healthy children subgroup. For unvaccinated healthy children, the

incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £23,000 per QALY gained at the current list price, and around £19,000 per QALY gained when the proposed price reduction for zanamivir is included in the analysis. For vaccinated healthy children, the incremental cost-effectiveness of zanamivir is expected to be at least £59,000 per QALY gained; this estimate includes the proposed price reduction for zanamivir. These cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). Based on the current list price for zanamivir, the probability that zanamivir is optimal in unvaccinated healthy children is expected to be 0.15 and 0.45 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the proposed price reduction is included in the analysis, the probability that zanamivir is optimal in unvaccinated healthy children is expected to be 0.47 and 0.79 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. For the vaccinated subgroup, the probability that no prophylaxis is optimal at a threshold of £30,000 per QALY gained is close to 1.0 (probability = 0.99 when the proposed price reduction for zanamivir is included).

For children under the age of 5 years, oseltamivir is the only licensed antiviral prophylaxis option. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £24,000 per QALY gained and £74,000 per QALY gained in unvaccinated and vaccinated groups respectively.

Post-exposure prophylaxis for at-risk children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the at-risk children subgroup. For unvaccinated at-risk children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8,000 per QALY gained at the current list price, and around £6,000 per QALY gained when the proposed price reduction for zanamivir is included in the analysis. For vaccinated at-risk children, the incremental cost-effectiveness of zanamivir is expected to be around £28,000 per QALY gained at the current list price, and £23,000 per QALY gained when the proposed price reduction is included in the analysis. Again, these cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). Based on its current list price, the probability that zanamivir is optimal in unvaccinated at-risk children is expected to be 0.67 and 0.73 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the

proposed price reduction is included in the analysis, the probability that zanamivir is optimal in unvaccinated at-risk children is expected to be 0.85 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. Based on the current list price for zanamivir, the probability that zanamivir is optimal in vaccinated at-risk children is expected to be 0.08 and 0.31 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the proposed price reduction is included in the analysis, the probability that zanamivir is optimal in unvaccinated at-risk children is expected to be 0.26 and 0.65 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively.

For at-risk children under the age of 5 years, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £9,000 per QALY gained for unvaccinated at-risk children and around £29,000 per QALY gained for vaccinated at-risk children.

Post-exposure prophylaxis for healthy adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the healthy adult subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated healthy adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £34,000 per QALY gained. For previously vaccinated healthy adults, the incremental cost-effectiveness of oseltamivir is expected to be around £104,000 per QALY gained. These cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). The probability that oseltamivir is optimal in unvaccinated otherwise healthy adults is expected to be around 0 and 0.19 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. For healthy adults who have previously been vaccinated, the probability that oseltamivir is optimal is close to zero at a willingness to pay threshold of £30,000 per QALY gained.

Post-exposure prophylaxis for at-risk adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the at-risk adult subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated at-risk adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £13,000 per QALY gained. For previously vaccinated at-risk adults, the incremental cost-effectiveness of oseltamivir is expected to be around £44,000 per QALY gained. These cost-utility estimates are based on effectiveness

data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). Based on the current list price for zanamivir, the probability that oseltamivir is optimal in unvaccinated at-risk adults is 0.89 and 0.84 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively (probability = 0.59 when the proposed price reduction for zanamivir is included in the analysis). For at-risk adults who have previously been vaccinated, the probability that no prophylaxis is optimal is around 0.96 at a willingness to pay threshold of £30,000 per QALY gained (probability = 0.95 when the proposed price reduction for zanamivir is included).

Post-exposure prophylaxis for healthy elderly

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the healthy elderly subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £11,000 per QALY gained. For previously vaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir is expected to be around £28,000 per QALY gained. These cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). Based on the current list price for zanamivir, the probability that oseltamivir is optimal in unvaccinated healthy elderly individuals is 0.87 and 0.82 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively (probability = 0.62 when the proposed price reduction for zanamivir is included in the analysis). For healthy elderly individuals who have previously been vaccinated, the probability that oseltamivir is optimal is 0.09 and 0.50 or at willingness to pay thresholds of £20,000 per QALY gained and £30,000 per QALY gained respectively (probability = 0.07 and 0.38 when the proposed price reduction for zanamivir is included in the analysis).

Post-exposure prophylaxis for at-risk elderly

Amantadine and zanamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the at-risk elderly subgroup. For unvaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8,000 per QALY gained. For vaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir is expected to be around £22,000 per QALY gained. Again, these cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and

adults). The probability that oseltamivir is optimal in unvaccinated at-risk elderly individuals is around 0.83 and 0.77 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained (this probability is around 0.60 when the proposed price reduction for zanamivir is included in the analysis). For vaccinated at-risk elderly individuals, the probability that oseltamivir is optimal is 0.35 and 0.78 at willingness to pay thresholds of £20,000 per QALY gained and £30,000 per QALY gained respectively (these probabilities are 0.25 and 0.54 when the proposed price reduction for zanamivir is included in the analysis).

The simple sensitivity analysis suggests that the cost-effectiveness of post-exposure prophylaxis using amantadine, oseltamivir and zanamivir is sensitive to assumptions regarding the influenza attack rate, the level of resistance against oseltamivir, assumptions regarding the comparative efficacy of oseltamivir and zanamivir, the efficacy of influenza vaccination, multiple prescribing of prophylaxis to contact cases, the risk of hospitalisation in uncomplicated cases, and the discount rate.

2.5 Discussion and conclusions

The clinical effectiveness data used to inform the cost-effectiveness modelling was limited for a number of population subgroups. This should be borne in mind in the interpretation of the review findings. Additional consideration should be paid to the occurrence of adverse events attributable to amantadine and the issue of resistance to antivirals amongst influenza isolates, which, although not directly reflected within the trials identified for inclusion in the systematic review, are factors which may have an important influence on the effectiveness of antiviral prophylaxis in clinical practice. Variation in the levels of resistance to antivirals amongst influenza isolates was taken into account in the cost-effectiveness analysis. Although the base case assumes oseltamivir resistance to be zero (since current levels of resistance to oseltamivir were considered sufficiently low to warrant exclusion from the base case), multiple sensitivity analyses were undertaken in order to assess the impact of variation in levels of resistance amongst influenza strains to the interventions under study. It should be noted that in the 2 weeks preceding completion of this assessment report, the Health Protection Agency issued a press release stating that approximately 5% (8/162) of H1N1 influenza tested isolates were resistant to oseltamivir. However, further research and monitoring is required to fully assess the impact of this resistance. The sensitivity analysis undertaken using the economic model suggests that low levels of resistance are likely to have only a minor impact upon the cost-effectiveness of oseltamivir. However, increasing levels of resistance to oseltamivir do have the capacity to dramatically influence the conclusions of the

economic analysis. It is therefore centrally important that the results of the economic analysis are interpreted in the light of current levels of influenza activity and resistance.

A number of uncertainties are apparent within the evidence base. Issues included variation in the quality of trials in terms of internal validity, external validity, attributes of study design and clarity of reporting. There was a lack of data available for a number of subgroups under study. The absence of head-to-head RCTs meant that a direct comparison of the effectiveness of the interventions was not possible. The weaknesses inherent within in the clinical evidence base are directly relevant to the interpretation of the health economic model results; these weaknesses rendered the use of more advanced statistical analyses inappropriate. A central area of uncertainty within the evidence base concerns the paucity of robust preference-based valuations of the impact of influenza and influenza prophylaxis on health-related quality of life.

A number of areas for further research are warranted:

1. Additional RCTs of influenza prophylaxis in subgroups for which data are currently lacking (as described in Section 8)
2. RCTs in which the follow-up period extends beyond the duration of prophylaxis
3. Head-to-head RCTs in which the clinical effectiveness of amantadine, oseltamivir and/or zanamivir in different subgroups are directly compared
4. Quality of life studies to inform future economic decision modelling
5. Further research concerning the incidence and management of complications caused by influenza.

3. BACKGROUND

3.1. Description of health problem

Influenza

Influenza is an acute febrile respiratory infection caused by the influenza virus. Cases typically occur in a seasonal pattern, with localised epidemics during the winter months. Influenza is highly contagious and easily transmitted from person to person. Illness is generally self-limiting but bacterial complications may arise. Such complications can be life-threatening in nature, particularly in the elderly and in individuals with co-morbidities. Worldwide pandemics of influenza may occur when a major new subtype arises, often originating from avian influenza. Circumstances of pandemic influenza and avian influenza are beyond the scope of this review.

Symptoms of influenza

Common symptoms of influenza include respiratory symptoms such as sneezing, runny nose, cough, sore throat and coryza, and systemic symptoms such as fever, malaise, myalgia, chills and headache. There may also be gastrointestinal symptoms such as nausea, vomiting and diarrhoea. The duration of the acute illness is usually around 3 to 4 days, but cough and malaise may persist for 1 to 2 weeks. It is also possible for individuals to be asymptomatic whilst infected with the influenza virus.^{1,2}

The symptoms of influenza can also result from a number of other infectious diseases, known as influenza-like illnesses (ILIs). These can be caused by adenoviruses, rhinovirus, respiratory syncytial virus, parainfluenza virus and bacterial infections. Confirmation of influenza infection requires laboratory methods such as viral culture or serological examination of antibody titres.

Prognosis, complications and mortality

Influenza infection can cause unpleasant symptoms for 1 to 2 weeks but is usually self-limiting and does not generally require treatment in otherwise healthy adults. However, influenza can lead to complications including secondary bacterial infection. Complications are more common in certain at-risk groups, including those aged over 65 years, infants beyond the age when maternally derived antibodies provide protection (and those with congenital abnormalities), and individuals with co-morbidities such as chronic respiratory disease (including asthma and chronic obstructive pulmonary disease), cardiovascular disease, chronic renal disease, diabetes mellitus, or immunosuppression.²

Complications of influenza are often respiratory, including primary viral pneumonia, secondary bacterial pneumonia, bronchitis, bronchiolitis in children, exacerbations of asthma and chronic respiratory disease, and otitis media. Additionally, influenza can cause a range of non-respiratory symptoms and complications, including febrile convulsions, toxic shock syndrome, Reye's syndrome, encephalopathy, transverse myelitis, pericarditis and myocarditis. Some of these complications may require hospitalisation and can be life-threatening, especially in the elderly or those with underlying disease.^{1,2}

The presence of complications increases the risk of mortality due to influenza. Mortality risk is highest in individuals who are elderly or have co-morbidities. Estimates of deaths thought to occur each year due to influenza in the UK range from 12,000 to 13,800.^{3,4,5} The UK epidemic of 1989–1990 was estimated to have caused 29,000 excess deaths.¹

The influenza virus

Influenza is an orthomyxovirus, consisting of a lipid membrane surrounding a matrix protein shell and a core consisting of seven or eight RNA-nucleoprotein complexes. There are three serotypes of influenza virus - influenza A, B and C - which differ in their core proteins. Influenza A and B are responsible for nearly all influenza-associated clinical illnesses. The influenza virus contains two surface glycoproteins, which act as powerful antigens: haemagglutinin (H antigen) and neuraminidase (N antigen). Haemagglutinin facilitates the entry of the virus into cells of the respiratory epithelium, whilst neuraminidase facilitates the release of newly produced viral particles (virions) from infected cells. An ion channel protein is also embedded in the lipid membrane; in influenza A this is the M2 protein and in influenza B it is the NB protein. The influenza virus infects epithelial cells of the upper and lower respiratory tract, attaching to the cell membranes, invading the host cell and using the host cell machinery to reproduce. New viral particles are released by lysing (breaking open) the host cells, which damages the epithelium and increases susceptibility to secondary bacterial infections.⁶

Influenza strains and subtypes

The WHO classification system for influenza is based on the antigenic type of the nucleoprotein core (A, B or C), the geographical location of first isolation, the strain serial number, the year of isolation, and (for influenza A) the haemagglutinin (H) and neuraminidase (N) subtypes, with each item separated by a slash; for example, A/Wuhan/359/95 (H3N2).

New strains and subtypes of influenza are produced as a result of ‘antigenic drift’ and ‘antigenic shift’. Antigenic drift arises from gene mutations causing changes in the amino acid sequence of haemagglutinin or neuraminidase, the main antigens associated with immunity, leading to changes in the antigenic nature of the virus, ie. a new strain of influenza (within a subtype). Antigenic drift is associated with annual outbreaks, as the virus is able to infect individuals who had developed immunity to previous strains. Many individuals are likely to retain partial immunity, although infants have little or no immunity. Influenza A undergoes antigenic drift to a greater extent than influenza B.

Antigenic shift is said to occur when an entirely new subtype of influenza A is introduced into the population, causing disease and onward human-to-human transmission. Antigenic shift occurs when the H and/or N of the new subtype is introduced into humans from the avian reservoir of infection, mostly ducks that serve as a reservoir for 16 different subtypes of H and 9 subtypes of N for the influenza A virus. Other animal reservoirs may also be implicated in antigenic shift. Antigenic shift occurred in 1918 when a H1N1 influenza A virus adapted to man. It occurred in 1957 and 1968 when the genomes of the circulating human viruses were mixed with those of avian origin by genetic reassortment – this process of ‘gene shuffling’ occurs during dual infections with influenza A viruses of differing subtypes. Antigenic shift results in ‘pandemic influenza’ because populations across the world have little or no immunity to the new strains. Pandemics cause a very high morbidity and mortality burden;⁷ the 1918–1919 pandemic estimated to have caused up to 40 million deaths worldwide. Pandemics originate mostly in Asia where chickens, ducks, pigs and humans live in very close proximity and where other social factors favour inter-species transmission of virus. However, as discussed above, pandemic influenza and avian influenza are not considered within this review.

Transmission of influenza

Influenza virus is highly contagious and easily passed from person to person. The virus is spread by virus-laden respiratory secretions. Most infections appear to be transmitted by droplets that are expelled during coughing and sneezing, rather than by aerosols. The incubation period is 1 to 3 days. People with influenza may begin shedding virus 1 to 2 days before symptoms appear. Nasal shedding peaks about 48 hours after onset of symptoms and adults usually remain infectious for up to 1 week (and up to 2 weeks in children; viral shedding may also be prolonged in immunocompromised individuals).²

Epidemiology

Seasonal outbreaks of infection with influenza occur most years during the winter months in the northern hemisphere. The UK influenza season may run from week 40 to week 25, but occurs typically between December and March.⁸ Illnesses resembling influenza that occur in the summer are usually due to other viruses.⁸ Infections with influenza A account for approximately 80% of outbreaks, whilst influenza B accounts for approximately 20%.⁹ Comparative studies indicate that A/H3N2 infections produce more severe illness than A/H1N1 and that influenza B is intermediate in severity.² Typically, there is an annual outbreak which appears abruptly, peaks within 2 to 3 weeks and lasts for around 5 to 7 weeks. Successive or overlapping waves of infection by different subtypes of influenza A or by influenza A and B may result in a more prolonged period of disease activity.¹⁰

Influenza is a common condition that may affect all age groups. However, the risk of an individual contracting the disease depends on a number of factors, including the virulence of the circulating strain, the natural level of immunity (which depends on past exposure to influenza virus or vaccination, and the degree of cross-immunity from these to the circulating strain), health status, age (both those over 65 years and the very young are at increased risk), and living arrangements. Influenza outbreaks can occur within establishments where several people live or work in close proximity; for example, residential homes, hospitals, schools and prisons. In addition, the virus is transmitted quite frequently between individuals who live in the same house. Many studies worldwide have shown that the highest attack rates occur in young children and that school-age children play a central role in the dissemination of influenza in households and the community.¹⁰

Incidence

Influenza activity during recent years is illustrated in Figures 1 and 2 below. The rate of general practitioner consultations for influenza-like illness (ILI) is monitored in the UK, and thresholds for use in England are defined by the Health Protection Agency (HPA) as follows:⁸

Baseline rate:	Fewer than 30 new GP consultations per 100,000 population per week
Normal seasonal activity:	30-200 new GP consultations per 100,000 population per week
Epidemic activity:	Greater than 200 new GP consultations per 100,000 population per week

The thresholds for Wales are slightly different, whereby the baseline rate is fewer than 25 new GP consultations per 100,000 population per week, normal seasonal activity relates to 25-100 new consultations, and epidemic activity is greater than 400 new consultations per 100,000 population per week.

It should be noted that, since influenza activity varies from season to season, attack rates, complication and mortality rates would also be anticipated to vary.

Figure 1: RCGP weekly consultation rate for influenza-like illness, England: 2007/08, 2006/07 and 1999/2000 (HPA)¹¹

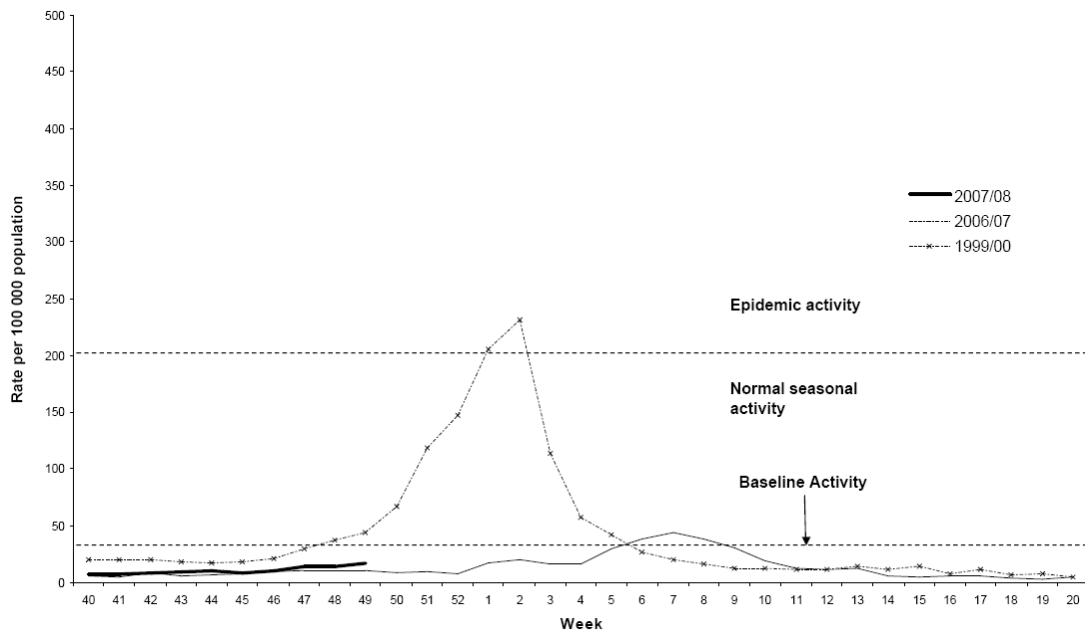
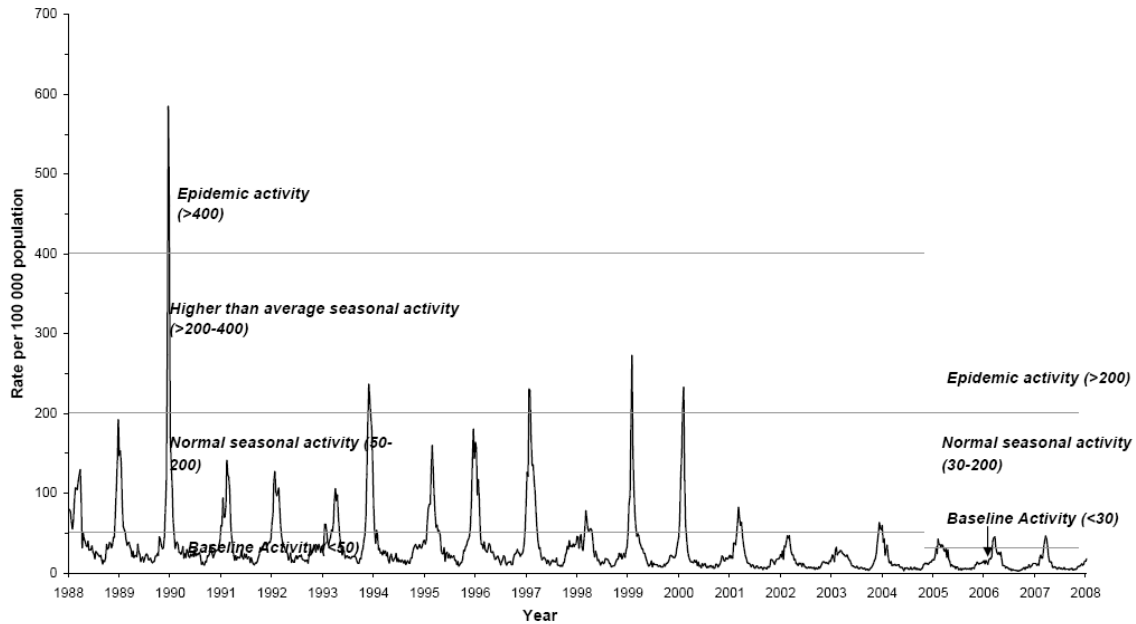


Figure 2: RCGP weekly consultation rate for influenza-like illness, England, 1988 to 2007/8 (HPA)⁸



Impact of influenza and significance for the NHS

For most people, influenza generally causes illness lasting 1 to 2 weeks. A proportion of individuals may experience asymptomatic infection or mild illness. However, the disease can lead to complications and mortality, particularly in the elderly or those with certain co-morbidities.

In terms of resource implications, influenza causes an increase in general practice consultations, medical treatment and hospitalisations, as well as increased absence from work. In primary care, adults aged 15-64 years account for most consultations for influenza-related illness. In a large UK study of subjects who had one or more diagnoses of influenza or ILI recorded within the General Practitioner Research Database (GPRD), 59.4% received prescription medications, the most frequently prescribed being antibiotics (45.2%) and antipyretics/analgesics (22.5%).¹² Patients with influenza were approximately six times more likely to use prescription medications than a matched control sample.¹² The incidence of consultations due to influenza across the study period were reported as being 14.5 per 1000 person-years.¹² Complications arising from influenza may require hospitalisation, particularly in elderly people with underlying cardiopulmonary disorders.¹³

The prevention of influenza also has resource implications for the NHS. In the UK, recommended groups for influenza vaccination include people at risk of complications from influenza (those

aged over 65 years, individuals with chronic respiratory disease, chronic cardiovascular disease, chronic renal disease, chronic liver disease, chronic neurological disease, diabetes mellitus, the immunosuppressed, individuals with HIV infection, people in residential homes (elderly or other long-stay)), the carers of dependents whose welfare would be put at risk should their carer fall ill, healthcare workers involved directly in patient care and can be considered for social care workers directly involved in care and household contacts of immunosuppressed individuals.¹⁴ The requirement for influenza vaccination has also been extended to poultry workers, in order to reduce the risk of the development of a potentially serious new variant as a result of co-infection with avian and human influenza strains.¹⁵ Therefore, the guidelines for vaccination cover both healthy individuals and people with underlying medical conditions. Prophylaxis with the antiviral drug oseltamivir is currently recommended by NICE for at-risk persons who are not adequately protected by vaccination and have been exposed to influenza (or at-risk persons living in residential homes who have been exposed to influenza, irrespective of vaccination status), provided that the individual can start taking oseltamivir within 48 hours of exposure to influenza.¹⁶ These guidelines are described in more detail in Section 3.3.3.

Measurement of influenza activity in the community

Influenza has no pathognomonic features and can manifest itself, as can other respiratory viruses, in a range of ways, such as the common cold, bronchitis, bronchiolitis, exacerbations of asthma or COPD, pneumonia, croup and febrile convulsions. Therefore, the level of influenza activity in a community is quantified by a combination of two factors: i) the number of cases of illness due to ILI (e.g. the number of clinic visits due to ILI or absences from school or work), and ii) the laboratory-based identification of influenza virus in samples from individuals with ILI.

In 1947, the World Health Organisation (WHO) established a global influenza surveillance system (a network of laboratories) to monitor the emergence and spread of new strains of influenza. The information generated by this system aids the development of vaccines against currently-circulating influenza strains. Vaccination is an important aspect of influenza prophylaxis and the degree of match between vaccine and circulating strains within a particular season has important implications for the control of influenza activity. In the UK, the Health Protection Agency (HPA) monitors and records the incidence of seasonal flu and uptake of seasonal flu vaccine. The Centre for Infections (CfI) conducts surveillance of flu activity in the UK, carries out laboratory tests to identify which strains of flu are in circulation, and communicates this information to health professionals and to the public.⁸

Diagnosis of influenza

Influenza-like illness can be defined clinically according to symptoms; the exact definition used varies, with different trials of influenza prevention using a range of indicators, but often includes a raised temperature (usually $\geq 37.8^{\circ}\text{C}$) and/or symptoms such as cough, headache, sore throat or myalgia.

To determine whether an individual case of influenza-like illness is true influenza, presence of the influenza virus must be determined in a laboratory test. This may consist of the isolation of influenza virus from a nose and throat swab or nasopharyngeal wash taken from the patient, via either viral culture or polymerase chain reaction (PCR). In addition, serum samples from the patient may be tested for the presence of influenza-specific antibodies via a haemagglutination inhibition assay (HAI); influenza infection is usually defined as a 4-fold or higher increase in influenza-specific HAI titre between baseline and post-infection serum samples (known as seroconversion). Many influenza studies use both viral culture and HAI serum testing, whilst some also use PCR, and generally a positive result on one or more of the tests is taken to indicate influenza infection. However, laboratory confirmation of influenza would not routinely be carried out on people presenting to their general practitioner with ILI.¹

3.2. Current service provision

3.2.1. Management of disease

The symptoms of influenza and other ILI are often self-limiting and require no medical intervention. Over-the-counter medications are available for symptomatic relief of influenza. The presence of secondary complications of influenza typically requires treatment including antibiotics, and may require hospitalisation.

NICE currently recommends zanamivir and oseltamivir for the treatment of at-risk adults who present with ILI and who can start therapy within 48 hours of the onset of their symptoms.¹⁷ Oseltamivir is recommended for the treatment of children who present with ILI and who can start therapy within 48 hours of the onset of symptoms.¹⁷ At risk individuals are defined within the NICE guidance as those who:

- have chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)
- have significant cardiovascular disease (excluding people with hypertension only)

- have chronic renal disease
- are immunocompromised
- have diabetes mellitus
- are aged 65 years or older.¹⁷

It should be noted that the current guidance for influenza vaccination differs to that outlined above in that, in addition to the at-risk groups above, vaccination is recommended for patients with chronic liver disease, chronic neurological disease and also for individuals who live within long-stay residential care facilities, carers, healthcare workers and poultry workers.^{18,19,15}

3.2.2 Current service cost

There is very limited evidence concerning the total costs of treating influenza and ILI in the UK. The current value of the UK antiviral market for the prophylaxis and treatment of influenza has been estimated to be approximately £800,000, of which around 89% is attributable to oseltamivir.²⁰ However, the true cost of managing influenza is likely to be considerably higher due to the additional costs of vaccination, and the management of secondary complications arising from influenza infection.

3.2.3 Variation in services/and/or uncertainty about best practice

There is relatively little antiviral usage in the UK, potentially attributable lower levels of virus activity and/or consultation rates compared with previous decades. In contrast, the use of oseltamivir is much greater in Japan.

It should be noted that the market authorisations for the use of antiviral post-exposure prophylaxis stipulate that prophylaxis should be initiated within a specified period of exposure to an index case. This stipulation requires that patients present to their GP promptly, the timescale of which will be impacted upon by an individual's propensity to seek medical care and issues relating to access to GP services.

There is variation in terms of the uptake of vaccination in indicated subgroups. Recent monitoring data from the HPA suggests that the uptake of influenza vaccination is around 79% in individuals aged over 65 years, and around 42% in at-risk individuals aged under 65 years.

3.2.4. *Relevant national guidelines*

NICE has issued guidance relating to the use of amantadine and oseltamivir in prophylaxis²¹ and zanamivir, oseltamivir and amantadine in the treatment of influenza.¹⁷ These recommendations are outlined in detail in Section 3.3.3.

In addition to national policy for influenza vaccination in at-risk groups, vaccination against influenza for people aged 65 years and above was also promoted within the National Service Framework for Older People.²² and for people with coronary heart disease in the National Service Framework for Coronary Heart Disease.²³

3.3 Description of technology under assessment

3.3.1 *Summary of interventions*

The clinical and cost-effectiveness of amantadine, oseltamivir and zanamivir in the prophylaxis of influenza have been evaluated in this assessment. The following section of the report summarises the product characteristics of each of these interventions in turn using the Summary of Product Characteristics (SPC) for each drug^{24,25,26,27,28,29} (obtained from the electronic Medicine Compendium at www.medicines.org.uk) and information from the British National Formulary (BNF).¹⁴

3.3.1.1 Amantadine (Lysovir®, Alliance Pharmaceuticals)

a) Description of intervention

Amantadine is a symmetrical C-10 primary amine with a cage-like structure, which, in hydrochloride salt form, is water-soluble.³⁰ Amantadine hydrochloride exerts an antiviral effect against influenza type A by means of inhibition of the M2 ion channel, which results in the blocking of viral replication.³⁰ The antiviral activity of amantadine is restricted to influenza A. In addition, amantadine has weak dopamine agonist activity.

b) Licensed indications

Amantadine hydrochloride is indicated for:

- the treatment of and prophylaxis against signs and symptoms caused by influenza A infection (as Lysovir®, Alliance Pharmaceuticals)
- the treatment of Parkinson's disease (but not drug-induced extrapyramidal symptoms) (as Symmetrel®, Alliance Pharmaceuticals)
- the treatment of *herpes zoster* (as Symmetrel®, Alliance Pharmaceuticals)

c) Dosage and administration

Lysovir® is available as reddish brown hard gelatine capsules containing 100mg of amantadine hydrochloride, which are ingested orally. Symmetrel is also available as 50mg/5ml syrup.

Prophylaxis

Adults and children over 10 years: 100 mg daily for as long as protection from influenza is required, usually for up to 6 weeks *or* with influenza vaccination for 2 to 3 weeks after vaccination.

Treatment

Adults and children over 10 years: 100 mg daily for 4 to 5 days. Treatment should be initiated within 48 hours of the onset of symptoms.

Adults: 100 mg daily for the recommended period

Children aged 10 to 15 years: 100 mg daily for the recommended period

Children under 10 years of age: Dosage not established

Adults over 65 years of age: Due to the longer elimination half-life and reduced capacity for renal clearance of amantadine in elderly patients, a reduced dose of less than 100 mg daily or 100mg given at intervals of greater than one day may be appropriate.

Patients with renal impairment: Dosage should be adjusted by reducing total daily dose or by increasing dosage interval in line with clearance of creatinine. Guidance is as follows:

<i>Creatinine clearance (ml/min)</i>	<i>Dose</i>
< 15	Lysovir contra-indicated
15-35	100 mg every 2 to 3 days
> 35	100 mg daily

d) Contra-indications

Amantadine hydrochloride is contra-indicated in patients who:

- have epilepsy
- have a history of gastric ulceration
- have severe renal impairment
- are pregnant, wish to become pregnant or are breast-feeding
- have known hypersensitivity to amantadine or any excipients

e) Cautions

Amantadine hydrochloride should be administered with caution to patients who:

- have hepatic impairment
- have renal impairment
- have congestive heart disease (as the drug may cause exacerbation of oedema)
- experience confusion or hallucinations
- have underlying psychiatric disorders
- are elderly
- are receiving concomitant medications with potential to affect the CNS

Abrupt withdrawal of amantadine therapy should be avoided in patients with Parkinson's disease. It should be noted that, whilst resistance to amantadine is well-documented,³⁰ it has been reported that levels of resistance amongst influenza isolates have risen dramatically on an international scale.³¹ Development of resistance can occur relatively rapidly during treatment and can lead to the failure of prophylaxis, for example, within the management of outbreaks of influenza in long-term care settings.³²

f) Adverse events

Adverse events associated with amantadine hydrochloride include anorexia, nausea, nervousness, insomnia, dizziness, inability to concentrate, convulsions, hallucinations, blurred vision, gastrointestinal effects, livedo reticularis, peripheral oedema and skin rashes. It has been documented that adverse effects can occur frequently amongst recipients.³³ Central nervous system adverse events have been described as occurring most notably within the elderly population.

3.3.1.2 Oseltamivir (Tamiflu®, Roche)

a) Description of intervention

Oseltamivir is a neuraminidase inhibitor that exerts antiviral activity against influenza A and B viruses.³⁴ The drug inhibits viral release, preventing subsequent infection of adjacent cells. The SPC reiterates that oseltamivir is not a substitute for vaccination and that use should take into account official recommendations and variability of epidemiology and impact across patient populations and geographical locations.

b) Licensed indications

Oseltamivir is indicated for:

- the post-exposure prophylaxis of influenza in patients aged 1 year and above having had contact with a clinically diagnosed influenza index case when influenza is circulating in the community. The SPC states that the administration of oseltamivir should be decided on a case by case basis and that seasonal prophylaxis in subjects aged 1 year and above may be considered in exceptional circumstances (such as in the case of mismatch between vaccine and circulating strains of influenza or in the event of a pandemic)
- the treatment of influenza in patients aged 1 year and above presenting with influenza symptoms when influenza is circulating in the community. Treatment is effective when initiated within 48 hours of onset of first symptoms

c) Dosage and administration

Tamiflu® is administered orally and is available as grey/yellow capsules containing 75 mg of oseltamivir (as phosphate), capsules containing 45 mg of oseltamivir (as phosphate), capsules containing 30 mg of oseltamivir (as phosphate) and as a powder (as phosphate) (12 mg/ml) for reconstitution with water as an oral suspension. The administration of 75 mg doses can be made up of one 75 mg capsule *or* one 30 mg capsule plus one 45 mg capsule *or* one 30 mg dose plus one 45 mg dose of suspension. It should be noted that the BNF lists only the 75 mg dose of Tamiflu in capsule form. The administration of suspension is recommended in patients who are not able to swallow capsules. It is recommended in the SPC that powder for oral suspension should be constituted by a pharmacist before dispensing to the patient.

Prophylaxis

Prophylaxis should be initiated as soon as possible within 48 hours of exposure to the index case.

Post-exposure prophylaxis:

Adults and adolescents over 13 years: 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

Children aged 1 to 13 years: body-weight under 15 kg, 30 mg once daily, body-weight 15 to 23 kg, 45 mg once daily, body-weight 23 to 40 kg 60 mg once daily, body-weight over 40 kg, adult dose

Seasonal prophylaxis:

During a community outbreak of influenza, the recommended dose is 75 mg once daily for up to 6 weeks.

Dose adjustment is recommended for patients with severe renal impairment as follows:

<i>Creatinine clearance (ml/min)</i>	<i>Dose</i>
> 30	75 mg once daily
> 10 to \leq 30	75 mg every second day or 30 mg suspension once daily or 30 mg capsules once daily
\leq 10	Not recommended
Dialysis patients	Not recommended

Treatment

Treatment should be initiated as soon as possible within 48 hours of onset of symptoms.

Adults and adolescents over 13 years: 75 mg every 12 hours for 5 days

Children aged 1 to 13 years: body-weight under 15 kg, 30 mg every 12 hours, body-weight 15 to 23 kg, 45 mg every 12 hours, body-weight 23 to 40 kg, 60 mg every 12 hours, body-weight over 40 kg, adult dose

Dose adjustment is recommended for patients with severe renal impairment as follows:

<i>Creatinine clearance (ml/min)</i>	<i>Dose</i>
> 30	75 mg twice daily
> 10 to \leq 30	75 mg once daily or 30 mg suspension twice daily or 30 mg capsules twice daily
\leq 10	Not recommended
Dialysis patients	Not recommended

No adjustment of dose is required in the elderly, with the exception of patients with severe renal impairment. There is insufficient evidence to recommend dosage adjustment in children with renal impairment.

d) Contra-indications

Oseltamivir is contra-indicated in patients who:

- have hypersensitivity to oseltamivir or any of the excipients

e) Cautions

Oseltamivir should be administered with caution to patients who:

- have renal impairment
- are pregnant or breast-feeding
- have conditions of such severity or instability that imminent hospitalisation may be required
- are immunocompromised
- have chronic cardiac and/or respiratory disease

Dose should be reduced if creatinine clearance in patients is less than 10 to 30 ml/min and administration should be avoided if creatinine clearance is less than 10 ml/min.

f) Adverse events

Adverse events associated with oseltamivir include nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, headache, fatigue, insomnia, dizziness, conjunctivitis, epistaxis, skin rashes, and - in very rare cases - hepatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis. Neuropsychiatric disorders in children have also been reported.

3.3.1.3 Zanamivir (Relenza®, GlaxoSmithKline)

a) Description of intervention

Zanamivir is a neuraminidase inhibitor that inhibits the replication of influenza A and B viruses.³⁴ It is noted in the SPC that zanamivir is not a substitute for vaccination, as protection only lasts for as long as the drug is administered, and that the use of zanamivir should be decided on a case by case basis according to circumstances and the population in need of protection. The SPC recommends that the drug should only be used when reliable epidemiological data confirms the circulation of influenza in the community. Use of zanamivir should take into account official recommendations, epidemiological variation and varying impact of influenza across patient populations and geographical locations.

b) Licensed indications

Zanamivir is indicated for:

- the post-exposure prophylaxis of influenza A and B in adults and children aged 5 years and above who have had contact with a clinically diagnosed case of influenza in a household. Relenza® may be considered for use in seasonal prophylaxis in exceptional

circumstances, for example when there is mismatch between circulating or vaccine strains or in the event of a pandemic.

- the treatment of influenza A and B in adults and children aged 5 years and above presenting with influenza-like illness with influenza is active in the community.

c) Dosage and administration

Relenza® is available in the form of pre-dispensed dry powder for inhalation in blisters containing zanamivir at 5 mg/blister delivered via oral inhalation using a *Diskhaler*® device. Each delivered inhalation (quantity released via mouthpiece of the Diskhaler) contains 4.0 mg zanamivir.

Prophylaxis

Post-exposure prophylaxis

Adults and children aged 5 years and above: 10 mg once daily (ie. 2 inhalations) for 10 days

Prophylaxis should be initiated as soon as possible and within 36 hours of exposure to an infected index case.

Seasonal prophylaxis

During an epidemic, prophylaxis may be administered.

Adults and children aged 12 years and above (as recommended within the BNF)¹⁸: 10 mg once daily for up to 28 days.

Treatment

Adults and children aged 5 years and above: 10 mg twice daily for 5 days

Treatment should be initiated as soon as possible and within 48 hours of onset of symptoms in adults and within 36 hours of onset of symptoms in children.

No dose modification is required for individuals with renal or hepatic impairment or for elderly patients.

d) Contra-indications

Zanamivir is contra-indicated in patients who:

- are pregnant or breast-feeding
- are hypersensitive to any ingredient of the preparation

e) Cautions

Zanamivir should be administered with caution to patients who:

- have asthma and chronic pulmonary disease
- have uncontrolled chronic illness
- are immunocompromised
- are pregnant

Other inhaled drugs, such as asthma medication, should be administered before zanamivir.

f) Adverse events

The following adverse events associated with zanamivir are described as occurring very rarely: bronchospasm, respiratory impairment, angioedema, urticaria and skin rashes.

3.3.2. *Identification of important subgroups*

A number of important subgroups exist for consideration in relation to the use of antivirals for influenza prophylaxis. Subgroups viewed to be at-risk of developing influenza-associated complications were described in Section 3.1. Within the guidance issued by NICE for the prophylaxis²¹ and treatment¹⁷ of influenza, populations viewed to be at-risk include individuals who:

- *are* aged 65 years and above
- *or* have chronic lung disease (including asthma and chronic obstructive pulmonary disease)
- *or* have significant heart disease (excluding people with hypertension only)
- *or* have chronic renal disease
- *or* have diabetes mellitus
- *or* are immunocompromised

3.3.3. *Current usage in the NHS*

Guidance was issued by NICE relating to the use of oseltamivir and amantadine in the prophylaxis of influenza²¹ and for the use of zanamivir, oseltamivir and amantadine for the treatment of influenza.¹⁷ These guidance documents were issued in accordance with the expectation that vaccination would continue to be the mainstay of influenza prevention. Issued guidance relates solely to circumstances where it is known that influenza A or B is circulating in the community. To this end, NICE recommended that community-based virological systems

should be used to monitor the circulation of influenza virus in the community. Issued guidance does not pertain to the circumstances of a pandemic, impending pandemic or to the situation of the emergence of a widespread epidemic of a new influenza strain, to which there is little or no community resistance.

‘At-risk’ groups were defined according to NICE guidance as described in Section 3.3.2.

Prophylaxis

NICE recommended that oseltamivir should be used in the prevention of influenza as follows:

- For individuals who are aged 13 years and above,
- *and* belong to an at-risk group,
- *and* are not effectively protected by vaccination (for example, individuals may not have received an influenza vaccination for that season, vaccination may be contraindicated or has yet to take effect, or in circumstances where vaccination has been undertaken but there is a mismatch between vaccine and circulating strains)
- *and* have been in close contact with an index case with influenza-like illness
- *and* can start taking oseltamivir within 48 hours of contact with the index case

- For individuals who are aged 13 years and above
- *and* belong to an at-risk group (whether or not they have been vaccinated)
- *and* live in a residential care establishment where another individual has influenza-like illness (resident or staff member)
- *and* can start taking oseltamivir within 48 hours of contact with the index case

For the purposes of the guidance, a residential care establishment was classed as a location where an at-risk person lived long-term in order to receive continuing care alongside other individuals with care needs. Exposure to ILI was defined as having close contact with an individual who resides in the same home environment as a person who has been experiencing symptoms of ILI.

NICE did not recommend that oseltamivir should be used in post-exposure prophylaxis of influenza in healthy people aged under 65 years. The use of oseltamivir in seasonal prophylaxis was not recommended. The use of amantadine in post-exposure and seasonal influenza prophylaxis was not recommended.

Treatment

It was recommended that amantadine should not be used in the treatment of influenza and that zanamivir or oseltamivir should not be used in the treatment of individuals who are healthy and not at risk of developing complications from influenza.

The use of zanamivir and oseltamivir in line with their licensed indications was recommended for the treatment of:

- adults (aged over 12 years) belonging to an ‘at-risk’ group
- *who* present with influenza-like illness
- *and* can begin treatment within 48 hours of the onset of symptoms

The use of oseltamivir in line with licensed indications was recommended for the treatment of:

- children (aged over 1 year) belonging to an ‘at-risk’ group
who present with influenza-like illness
and can begin treatment within 48 hours of the onset of symptoms

It should be noted that, although the use of amantadine in the prophylaxis and treatment of influenza was not recommended by NICE, this drug is also licensed for the treatment of Parkinson’s disease and *herpes zoster*.

3.3.4 Anticipated costs associated with intervention

The costs associated with amantadine, oseltamivir and zanamivir are dependent on the setting for the prophylaxis, the mode of administration and the age of the patient (oseltamivir only). Acquisition costs for post-exposure prophylaxis and seasonal prophylaxis are presented in Tables 1 and 2 respectively. The capsule/tablet forms of prophylaxis are likely to be most relevant to adult populations as these allow for more precise measurements of dosage; for oseltamivir in children aged under 13 years, dosage is usually adjusted according to body weight. Prophylaxis is typically given to children under 13 years in suspension form based on body mass. It should be noted that whilst the BNF only lists 75mg capsules and suspension, the SPC accessed via the electronic Medicine Compendium²⁹ (www.medicines.org.uk) cites the additional availability of 30mg and 45mg capsules of oseltamivir. Amantadine, oseltamivir and zanamivir are self-administered and do not require administration by a healthcare professional. It should be noted that diagnostic testing for influenza is not standard practice in the UK and is unlikely to represent a relevant cost associated with these products. The reader should also note that in November

2007, the manufacturer of zanamivir (GSK) applied to the Department of Health for a price modulation of two of their drugs, one of which was zanamivir. The current list price for zanamivir is £24.55 (5 disks, 4 blisters per disk); the new proposed price for zanamivir is £16.55 (Personal communication: Toni Maslen, Health Outcomes Programme Leader, GSK). This proposed price reduction for zanamivir was approved by the Department of Health with effect from the 1st February 2008 but was not listed in the BNF (No. 54)¹⁴ at the time of submission of this report.

Table 1: Estimated post-exposure prophylaxis acquisition costs

Regimen	Age (yrs)	Prophylaxis days/course	Mg/dose	Doses/day	Mg/course	Doses/pack	Packs required	Cost/pack	Cost/course
amantadine (5-cap pack, lysovir)	> 10	10	100	1	1000	5	2	£2.40	£4.80
amantadine (14-cap pack, lysovir)	> 10	10	100	1	1000	14	1	£4.80	£4.80
amantadine (56-cap pack, symmetrel)	> 10	10	100	1	1000	56	1	£16.88	£16.88
amantadine (150mL syrup, symmetrel)	> 10	10	100	1	1000	15	1	£5.55	£5.55
oseltamivir (cap) - adults	> 13	10	75	1	750	10	1	£16.36	£16.36
oseltamivir (suspension) - adults	> 13	10	75	1	750	12	1	£16.36	£16.36
oseltamivir (suspension) - children < 15kg	< 14	10	30	1	300	30	1	£16.36	£16.36
oseltamivir (suspension) - children 15-23kg	< 14	10	45	1	450	20	1	£16.36	£16.36
oseltamivir (suspension) - children 23-40kg	< 14	10	60	1	600	15	1	£16.36	£16.36
oseltamivir (suspension) - children > 40kg	< 14	10	75	1	750	12	1	£16.36	£16.36
zanamivir (powder)	> 5	10	10	1	100	10	1	£24.55	£24.55

Table 2: Estimated seasonal prophylaxis acquisition costs

Regimen	Age (yrs)	Prophylaxis days/course	Mg/dose	Doses/day	Mg/course	Doses/pack	Packs required	Cost/pack	Cost/course
amantadine (5-cap pack, lysovir)	> 10	42	100	1	4200	5	9	£2.40	£21.60
amantadine (14-cap pack, lysovir)	> 10	42	100	1	4200	14	3	£4.80	£14.40
amantadine (56-cap pack, symmetrel)	> 10	42	100	1	4200	56	1	£16.88	£16.88
amantadine (150mL syrup, symmetrel)	> 10	42	100	1	4200	15	3	£5.55	£16.65
amantadine following vaccination (5-cap pack, lysovir)	> 10	21	100	1	2100	5	5	£2.40	£12.00
amantadine following vaccination (14-cap pack, lysovir)	> 10	21	100	1	2100	14	2	£4.80	£9.60
amantadine following vaccination (56-cap pack, symmetrel)	> 10	21	100	1	2100	56	1	£16.88	£16.88
amantadine following vaccination (150mL syrup, symmetrel)	> 10	21	100	1	2100	15	2	£5.55	£11.10
oseltamivir (cap) – adults	> 13	42	75	1	3150	10	5	£16.36	£81.80
oseltamivir (suspension) – adults	> 13	42	75	1	3150	12	4	£16.36	£65.44
oseltamivir (suspension) - children < 15kg	< 14	42	30	1	1260	30	2	£16.36	£32.72
oseltamivir (suspension) - children 15-23kg	< 14	42	45	1	1890	20	3	£16.36	£49.08
oseltamivir (suspension) - children 23-40kg	< 14	42	60	1	2520	15	3	£16.36	£49.08
oseltamivir (suspension) - children > 40kg	< 14	42	75	1	3150	12	4	£16.36	£65.44
zanamivir (powder)	> 5	28	10	1	280	10	3	£24.55	£73.65

4. DEFINITION OF THE DECISION PROBLEM

NICE has previously issued guidance on the use of amantadine and oseltamivir for the prevention of influenza.¹⁶ When the original NICE guidance was issued, the licensed indications for zanamivir did not extend to its use as prophylaxis. Marketing authorisation has since been issued for the use of zanamivir for the prophylaxis of influenza. This review presents an updated assessment of new and existing evidence for amantadine and oseltamivir, and an assessment of the clinical effectiveness and cost-effectiveness of zanamivir for the prophylaxis of influenza in England and Wales.

4.1 Decision problem

The decision problem has been defined as follows:

Interventions

Three prophylactic interventions are included in this assessment:

- 1) Amantadine (Lysovir® or Symmetrel®, Alliance Pharmaceuticals)
- 2) Oseltamivir (Tamiflu®, Hoffman La Roche Pharmaceuticals)
- 3) Zanamivir (Relenza®, GlaxoSmithKline Pharmaceuticals)

Relevant comparators

Amantadine, oseltamivir and zanamivir are compared against each other and against no prophylaxis (in which subjects received any of the following: placebo, no treatment or expectant treatment following onset of symptomatic influenza).

Populations and relevant subgroups

The interventions are evaluated in the post-exposure prophylaxis and seasonal prophylaxis settings. In the post-exposure setting, the assessment evaluates the clinical effectiveness and cost-effectiveness of the interventions in adults and children who have been exposed to a clinically diagnosed case of influenza. In reality, effectiveness would be in terms of exposure to an index

case with influenza-like illness (ILI), which may or may not subsequently be confirmed as influenza. Post-exposure prophylaxis was considered in the prevention of transmission of influenza from index cases to household contacts and in outbreak control within establishments where members of a community live or work in close proximity, for example within long-term care settings and boarding schools. In the seasonal setting, the assessment evaluates the clinical effectiveness and cost-effectiveness of the interventions in adults and children for whom seasonal prophylaxis would be appropriate in exceptional circumstances. In this case, exceptional circumstances relate to a high degree of mismatch between the circulating influenza virus and vaccine strains; as noted in Section 4.2, the effectiveness of influenza prophylaxis in pandemic situations is beyond the remit of this assessment.

The clinical effectiveness and cost-effectiveness of influenza prophylaxis for people who are at a higher risk of influenza infection or complications was considered. Where evidence was available, vaccination status was also taken into consideration.

4.2. Overall aims and objectives of assessment

The objectives of the assessment are:

- To evaluate the clinical effectiveness of amantadine, oseltamivir, and zanamivir in the prophylaxis of influenza in terms of cases prevented, complications prevented, health-related quality of life, mortality, hospitalisations prevented, length of influenza illness, and time to return to normal activities.
- To evaluate the incidence and impact of treatment-related adverse events.
- To estimate the incremental cost-effectiveness of amantadine, oseltamivir and zanamivir in comparison to each other and no prophylaxis.
- To identify gaps in the existing evidence base and those areas requiring further primary research.
- To estimate the annual cost to the NHS.

As outlined within the scope and noted in Section 4.1., the remit of this assessment does not include the circumstances of a pandemic, impending pandemic, or a widespread epidemic of a

new strain of influenza to which there is little or no community resistance. The economic analysis considers a 'typical' influenza season as well as the potential impact of higher attack rates and vaccine mismatch. The interventions are appraised according to their licensed indications, with guidance to be issued in accordance with relevant marketing authorisations.

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

A systematic review of the clinical effectiveness of amantadine, oseltamivir and zanamivir for influenza prophylaxis was undertaken according to the general principles recommended in the QUOROM statement.³⁵ Methods for the review are detailed below.

5.1.1. Identification of studies

Systematic searches were undertaken to identify studies relating to the clinical effectiveness of amantadine, oseltamivir and zanamivir in the prevention of influenza A and B. The search strategy comprised the following main elements:

- searching of electronic databases listed below
- contact with experts in the field
- handsearching of bibliographies of retrieved papers
- scanning of electronic archives of key journals for relevant evidence published within the preceding 12 months (searched October 2007)

a) Sources searched

The electronic databases searched included MEDLINE; Medline in Process; EMBASE; Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, BIOSIS, CINAHL, DARE, NHS EED and HTA databases; OHE HEED, NRR (National Research Register); Science Citation Index; Current Controlled Trials; Clinical Trials.gov. Searches were undertaken in July 2007. Sponsor submissions to NICE were also handsearched.

b) Keyword strategies

The search strategies included subject headings and free text terms, combined using Boolean logic, to identify all published and unpublished data relating to the prevention of influenza A and B. The Medline search strategy is presented in Appendix 1.

c) Search restrictions

Searches were restricted by publication type to controlled clinical trials, systematic reviews and economics or quality of life studies. Searches were not restricted by the date of publication or by language.

5.1.2. *Inclusion and exclusion criteria*

The following inclusion criteria were used to identify relevant studies for inclusion in the assessment.

Population:

- adults and children who have been exposed to a clinically diagnosed case of influenza (which may or may not be true influenza)
- adults and children for whom seasonal prophylaxis would be appropriate in exceptional circumstances, such as in the event of mismatch between the circulating influenza virus and vaccine strains. For the purposes of this assessment, we have considered healthy and at-risk children, adults and the elderly.

Interventions:

The following medications used for influenza prophylaxis administered in line with current UK marketing authorisations:

- Amantadine
- Oseltamivir
- Zanamivir

Trials of these interventions in seasonal prophylaxis and post-exposure prophylaxis (both in prevention of the transmission of influenza within households and in outbreak control in settings where individuals live or work in close proximity) were included in the review. Trials in which interventions were used in prophylaxis against experimentally-induced influenza in line with licensed indications were also included. The results of these challenge studies should be interpreted with caution due to their limited external validity. These studies are presented to provide a comprehensive review of the effectiveness of prophylaxis; these studies were not used to inform the health economic model.

Comparators:

Interventions were compared against each other and no prophylaxis (in which subjects received any of the following: placebo, no treatment or expectant treatment following onset of symptomatic influenza).

Outcomes:

- cases prevented (measured in terms of symptomatic, laboratory-confirmed influenza or, in the absence of this outcome, clinical illness and/or infection)
- complications prevented
- adverse events
- health-related quality of life (HRQoL)
- mortality
- hospitalisations prevented
- length of influenza illness
- time to return to normal activities
- cost and cost-effectiveness (See Section 6)

Study types:

- Randomised controlled trials (RCTs)

If evidence was not available from RCTs, other study types would have been considered according to the hierarchy of evidence. Systematic reviews were not included in the analysis, but were handsearched to identify randomised controlled trials meeting the inclusion criteria of this review and retained for discussion.

The following exclusion criteria were used:

- Intervention medications not used in accordance with their licensed indications
- Studies only published in languages other than English

Based on the above inclusion/exclusion criteria, study selection was undertaken by one reviewer, with involvement of a second reviewer when necessary to provide consensus on inclusion or exclusion of studies.

5.1.3. Data abstraction strategy

Data were extracted with no blinding to authors or journal. Data was extracted by one reviewer using a standardised form. Any studies giving rise to uncertainty were reviewed independently by a second reviewer, and discrepancies, for example where studies were not clearly reported, were resolved by discussion. All data abstraction was checked and confirmed by a second reviewer.

5.1.4. *Critical appraisal strategy*

The quality of included randomised controlled studies was assessed using quality criteria based on those developed by the NHS Centre for Reviews and Dissemination;³⁶ these are presented in Appendix 2. The purpose of such quality assessment was to provide a narrative account of trial quality for the reader. Quality assessment was confirmed by a second reviewer.

5.1.5. *Methods of data synthesis*

The pre-specified outcomes defined in Section 5.1.1 were presented within a narrative synthesis. Where quantitative synthesis was considered to be appropriate, statistical meta-analysis was undertaken using a random effect model using RevMan software (version 4.2.10) in order to calculate pooled estimates for relative risks for outcomes of interest. The presence of heterogeneity within the identified evidence and the lack of any head-to-head direct comparative RCTs of antiviral prophylaxis were considered to preclude the use of sensitivity analyses and mixed treatment comparisons.

Efficacy data are presented as relative risks (RR) and protective efficacy (PE = 1 minus RR, expressed as a percentage). Where the RR or PE values were not described in the study publication, or where the value differed (usually only by a small margin) from that calculated from the formula below, the RR was calculated by the Assessment Group using the following formula (and marked with †):

$$RR = (a/(a+c))/(b/(b+d))$$

where a = event present for treatment group, b = event present for control group, c = event absent for treatment group, and d = event absent for control group.

Where publications have reported a 95% confidence interval (95% C.I.) around the RR or PE, these have been presented. Where no C.I. was published, it was calculated using the following formula (and marked with †):

$$SE [\ln(RR)] = \text{square root } [(1/a - 1/(a+c) + 1/b - 1/(b+d))].$$

$$\text{Lower 95\% confidence limit for RR} = \exp [\log RR - 1.96 \times SE [\ln(RR)]]$$

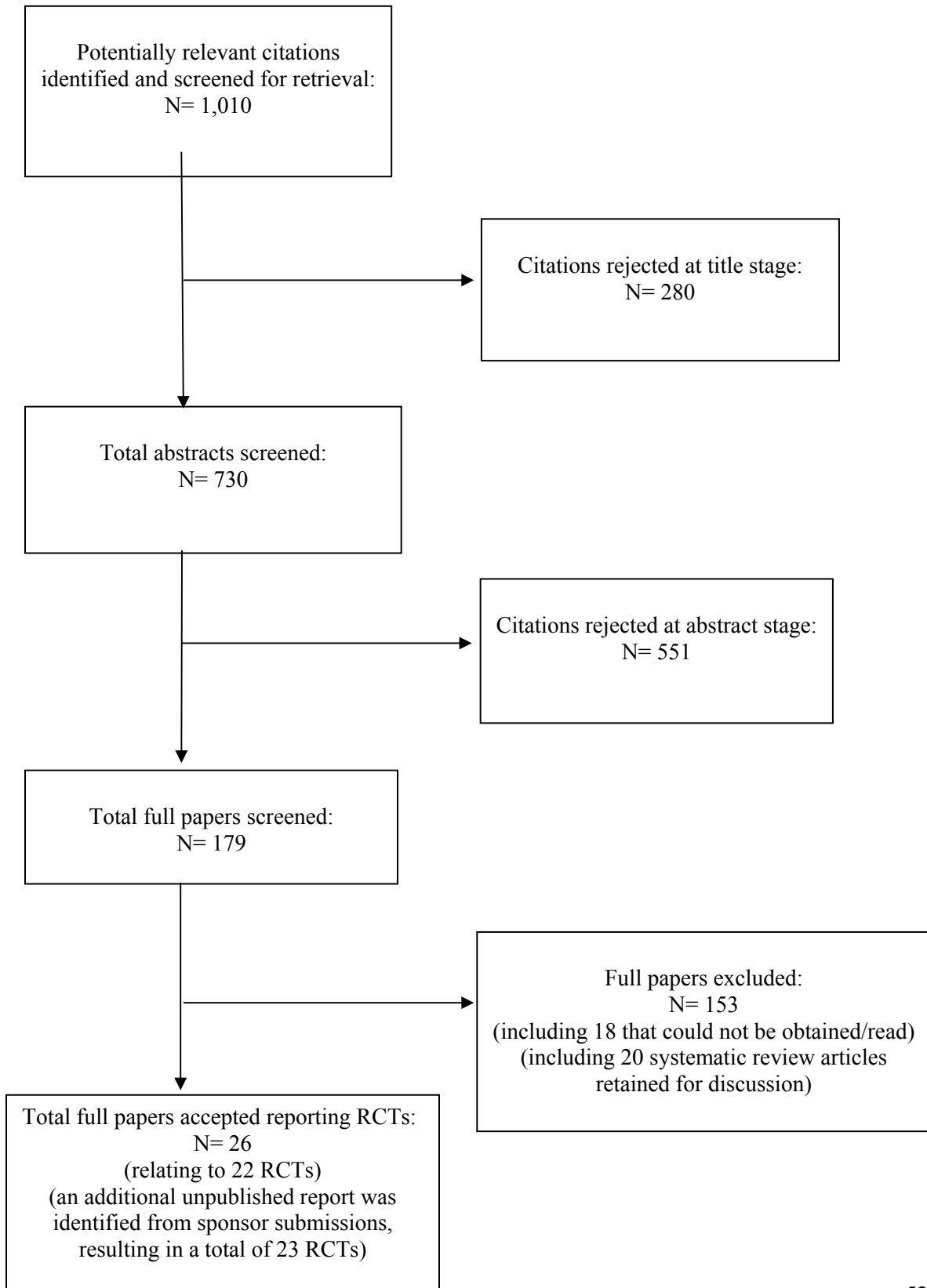
$$\text{Upper 95\% confidence limit for RR} = \exp [\log RR + 1.96 \times SE [\ln(RR)]].$$

5.2 Results

5.2.1 Quantity and quality of research available

As a result of the searches outlined above, a total of 1,010 citations were identified, following removal of duplicates, and were screened for inclusion in the review of clinical effectiveness (see Figure 3). Two hundred and eighty citations were rejected at the title stage, yielding 730 abstracts for screening, of which 551 were rejected upon examination of the abstract. Of 179 full papers retrieved, 153 were excluded (of which 18 were not available for retrieval by information specialists or could not be read as they were not available in English). Of these, seven citations were excluded, since the full text was not available in English.^{37,38,39,40,41,42,43} Of the articles that could not be obtained, it is unlikely that these were likely to be relevant for inclusion, as they appeared to be conference abstracts and discussion papers. Papers that were excluded after close scrutiny are presented in Appendix 6, together with the justification for their exclusion. Twenty systematic reviews were identified; these were handsearched and retained for discussion. Twenty six citations relating to 22 RCTs were included in the review of clinical effectiveness. One additional unpublished report was provided as evidence as part of the submissions by sponsors and is also presented.⁴⁴

Figure 3: QUOROM diagram of study inclusion and exclusion in clinical effectiveness review



5.2.1.1 Quantity of research available

A total of 26 published references presenting findings from a total of 22 RCTs were considered relevant for inclusion in the review of clinical effectiveness of amantadine, oseltamivir and zanamivir for the prophylaxis of influenza. An additional unpublished report was identified in the sponsor submissions and included in the assessment, resulting in a total of 23 RCTs.⁴⁴ One included reference⁴⁵ was a report of a pooled analysis of data relating to post-exposure prophylaxis of influenza using oseltamivir and zanamivir based on included trials.^{46,47,48,49} No ongoing trials or trials due to report were identified in searches that met the inclusion criteria. All included articles are described below and grouped by intervention.

Amantadine

A total of 8 full papers reporting 8 RCTs investigating the prophylactic use of amantadine against influenza were identified. Characteristics of these studies are presented in Table 3.

The original HTA review reported by Turner *et al.*¹⁰ assessed the use of amantadine in influenza prophylaxis in children (aged under 18 years) and the elderly (aged over 65 years) only, as a Cochrane review of the use of amantadine in adults had recently been reported.⁵⁰ This Cochrane review has been subsequently updated³³ and was handsearched to identify any additional citations for inclusion in the current review. Turner *et al.*¹⁰ identified 3 trials of amantadine prophylaxis undertaken in children.^{51,52,53} However, these studies and an additional trial⁵⁴ are not included in this technology assessment report, as the dosage of amantadine is not established in children under 10 years of age according to licensed indications. Two prevention trials in the elderly were also included in the original assessment.^{55,56} Of these studies, only the findings presented by Pettersson and co-authors⁵⁵ are included in this update, whilst the trial reported by Leeming *et al.*⁵⁶ was excluded, as twice the currently licensed dose was administered to participants.

An additional 7 trials of amantadine prophylaxis were identified by our searches. These included two studies that evaluated seasonal prophylaxis in healthy adults.^{57,58} Further trials described amantadine prophylaxis in outbreak control in healthy adolescents in a boarding school⁵⁹ and in adults in semi-isolated engineering school populations.^{60,61} A further 3 reports of the prophylactic efficacy of amantadine against experimentally-induced influenza were identified.^{62,57,63} One of these papers presented results from 2 separate trials examining the use of amantadine in seasonal prophylaxis and experimentally-induced influenza studies.⁵⁷

Four trials included in the Cochrane review of amantadine and rimantadine in influenza A in adults³³ have been included in our assessment.^{55,61,59,57} Justifications of study exclusions are reported in Appendix 6.

An abstract was available in English for a double-blind, placebo-controlled trial by Plesnik *et al.*,³⁸ which suggested that amantadine at 100mg/day reduced the incidence of serologically-confirmed infection and was well tolerated. However, since the full text was not available in English, this citation could not be included and is not presented in the review.

Table 3: Characteristics of included amantadine prophylaxis RCTs

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
Reuman <i>et al.</i> , 1989	Healthy unvaccinated adults aged 18 to 55 years living in the community	T1: Amantadine 100mg/day n=159 T2: Placebo n=159	Seasonal	Presumed 6 weeks	E.I. DuPont de Nemours and Company, Inc.	Reuman <i>et al.</i> , 1989 ⁵⁷
Aoki <i>et al.</i> , 1986	Healthy adults in a military setting, (age not defined) 6 to 8 individuals in each study year immunised against influenza in previous years	T1: Amantadine 100mg/day, 1980-81 n=74, 1981-82: under 28 yrs n= 21, over 29 yrs n=29, 1982-83 n=46 T2: Placebo: 1980-81 n=48, 1981-82: under 28 yrs n=16, over 29 yrs n=18, 1982-83 n=33	Seasonal	39 days (1980-81) 32 days (1982-83)	National Health Research and Development Program of Canada and The Canadian Foundation for the Advancement of Clinical Pharmacology	Aoki <i>et al.</i> , 1986 ⁵⁸
Pettersson <i>et al.</i> , 1980	Elderly subjects (mean ages T1=77.4 yrs, T2=79.0 yrs) living in a residential home, vaccination status unclear, but discussion states no adequate vaccine available	T1: Amantadine 100mg/day, randomised n=94, completing study n=89 T2: Placebo, randomised n=101, completing study n=99	Seasonal	9 weeks	Medica Ltd. & Orion Diagnostica Ltd.	Pettersson <i>et al.</i> , 1980 ⁵⁵
Payler & Purdham, 1984	Adolescent males (13 to 19 yrs old) in boarding school setting, 87% vaccinated	T1: Amantadine 100mg/day randomised n=299, final analysis n=267 T2: No specific treatment randomised n=307, final analysis n=269	Outbreak control	14 days	Study medication supplied by Ciba-Geigy Pharmaceuticals	Payler & Purdham, 1984 ⁵⁹

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
Smorodintsev <i>et al.</i> , 1970a, b	Male adults (recruitment pool aged 18 to 30 yrs) (presumed healthy) in semi-isolated engineering school populations	<p>T1: Amantadine 100mg/day (50.7% of 10,053), assigned to group n=5092, onset of influenza prior to dosing n=441, n=4559 regularly or irregularly taking amantadine.</p> <p>T2: Placebo (31.6% of 10,053), assigned to group n=3175, onset of influenza prior to dosing n=307, n=2804 receiving placebo (3175 minus 307=2868, 2804 included in analysis.</p> <p>T3: Internal control: individuals at the same engineering schools as the amantadine and placebo groups, but living at home rather than at the school; received no prophylaxis (10.0% of 10,053) n=1011</p> <p>T4: External control: individuals at an 8th engineering school; received no prophylaxis (7.7% of 10,053), assigned to group n=775</p>	Outbreak control	5 of 7 populations dosed for 30 days, 2 populations dosed for 12 days	Study medication supplied by E.I. DuPont de Nemours and Company, Inc.	Smorodintsev <i>et al.</i> , 1970a, b ^{60,61}

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
Reuman <i>et al.</i> , 1989	Healthy unvaccinated adults aged 18 to 40 years	T1: Amantadine 100mg/day n=20 T2: Placebo n=19	Experimentally-induced influenza	8 days (3 days pre-challenge and 5 days post-challenge)	E.I. DuPont de Nemours and Company, Inc.	Reuman <i>et al.</i> , 1989 ⁵⁷
Sears & Clements, 1987	Healthy adults aged 18 to 40 years	T1: Amantadine 100mg/day n=22 T2: Placebo n=22	Experimentally-induced influenza	8 days	E.I. DuPont de Nemours and Company, Inc.	Sears & Clements, 1987 ⁶³
Smorodintsev <i>et al.</i> , 1970c	Healthy adults (age not defined)	T1: Amantadine 100mg/day n=19 T2: Placebo n=31	Experimentally-induced influenza	12 days (24 hours before challenge and daily for 11 days)	Study medication supplied by E.I. DuPont de Nemours and Company, Inc.	Smorodintsev <i>et al.</i> , 1970c ⁶²

Oseltamivir

Nine references (of which 6 were reported in full papers and a further 3 were abstracts) were identified that investigated the use of oseltamivir in prophylaxis against influenza in 6 original RCTs. Characteristics of these trials can be seen in Table 4.

Four oseltamivir prevention trials were covered in the original HTA review;¹⁰ these were studies WV15825,^{64,65} WV15673,⁶⁶ WV15697⁶⁶ and WV15799.⁴⁹ Data for each of the trials WV15673 and WV15697 were reported in the publication by Hayden *et al.*⁶⁶ both individually and combined across the 2 studies. All of these trials are included in the current assessment. Three additional publications present findings of an RCT published subsequent to the HTA review¹⁰ by Hayden *et al.*, 2004^{48,67,68} examining the efficacy of oseltamivir in post-exposure prophylaxis within households. A further paper describes a trial of experimentally-induced influenza.⁶⁹ An additional publication⁴⁵ describes a pooled analysis of data from oseltamivir post-exposure prophylaxis trials, which are already included in the review.^{46,47,48,49}

An abstract in English was obtained for the trial by Kashiwagi *et al.*⁴¹ in which oseltamivir was administered to healthy adults at 75mg once daily versus placebo for 6 weeks. This trial was previously reviewed by Jefferson *et al.*⁷⁰ However, the report was not available in full in English and was therefore excluded from this review.

Table 4: Characteristics of included oseltamivir prophylaxis trials

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
WV15825	At-risk elderly subjects living in a residential home (mean age T1=81 yrs, T2=82 yrs) (98% with concomitant disease in each group), T1: 80.4% vaccinated T2: 80.1% vaccinated	T1: Oseltamivir 75 mg once daily n=276 T2: Placebo n=272	Seasonal	6 weeks	Hoffman-La Roche	Peters <i>et al.</i> , 2001 ^{64, 65}
WV15673	Healthy unvaccinated adults aged 18 to 65 yrs living in the community. Conducted at study sites in Virginia, USA	T1: Oseltamivir 75 mg once daily n=268 T2: Placebo n=268	Seasonal	6 weeks	Hoffman-La Roche	Hayden <i>et al.</i> , 1999a ⁶⁶
WV15697	Healthy unvaccinated adults aged 18 to 65 yrs living in the community. Conducted at study sites in Texas and Kansas City, USA	T1: Oseltamivir 75 mg once daily n=252 T2: Placebo n=251	Seasonal	6 weeks	Hoffman-La Roche	Hayden <i>et al.</i> , 1999a ⁶⁶

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
WV15799	Subjects of mixed age and health status living in households. Adults and children aged 12 years and above (as contacts), Contacts of all index cases; T1: 11.4% vaccinated. T2: 13.9% vaccinated Index cases did not receive treatment.	T1: Oseltamivir 75mg once daily n=493 T2: Placebo n=462	Post-exposure prophylaxis	7 days	Hoffman-La Roche	Welliver <i>et al.</i> , 2001 ⁴⁹
WV16193	Subjects of mixed age and health status. Adults and children aged 1 year and above. Contacts:: T1: 8% vaccinated T2: 7% vaccinated Index cases in both arms received treatment with oseltamivir 75mg twice daily for 5 days.	Oseltamivir: prophylaxis (PEP) vs. treatment on influenza onset (expectant treatment); index cases in both groups received treatment. T1: Oseltamivir prophylaxis 75mg daily for 10 days, n=400 T2: Oseltamivir treatment on influenza onset (expectant treatment) 75mg twice daily for 5 days (less in children), n=392	Post-exposure prophylaxis	10 days	Hoffman-La Roche	Hayden <i>et al.</i> , 2004 ^{48,67,68}

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
Hayden <i>et al.</i> , 2000	Healthy adults aged 18 to 65 yrs	T1: Oseltamivir 75mg once daily n=19 T2: Placebo n=19	Experimentally- induced influenza	7 days (1 day before challenge and 6 days after)	Hoffman-La Roche	Hayden <i>et al.</i> , 2000 ⁶⁹

Zanamivir

A total of 10 published reports of 8 original RCTs were included in the assessment, of which 8 were full papers and 2 abstracts providing further reports of included studies. A further trial was identified within the sponsor submissions and is included, giving a total of 9 RCTs.⁴⁴ These are presented in Table 5.

Turner and colleagues¹⁰ evaluated 5 zanamivir prevention trials: studies NAIA2010,⁷¹ NAIA3005,^{72,73} NAIA30010,⁴⁶ NAIA2009⁷⁴ and NAIB2009.⁷⁴ NAIA2009 and NAIB2009 were reported as a single trial in the published literature. All of these trials are included in the present assessment, with the exception of trial NAIA2010 reported by Schilling *et al.*,⁷¹ due to the use of a dose of zanamivir at a level that was twice that of current licensed indications.

An additional 6 citations relating to zanamivir were identified by the systematic searches for inclusion in the clinical effectiveness review. Findings from a trial of zanamivir seasonal prophylaxis in at-risk adolescents and adults have been presented.⁷⁵ A report of the use of zanamivir in post-exposure prophylaxis within households has also been published,⁴⁷ whilst two additional papers and one abstract provide reports of the use of zanamivir in outbreak control in at-risk elderly subjects within long-term care settings.^{76,77,78} An additional paper describes a pooled analysis of data from zanamivir post-exposure prophylaxis trials which are already included in the review.⁴⁵

Table 5: Characteristics of included zanamivir prophylaxis trials

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
NAIA3005	Healthy adults (aged 18 to 64 years) from University communities, T1: 14% vaccinated T2: 14% vaccinated	T1: Zanamivir 10mg once daily n=553 T2: Placebo n=554	Seasonal	28 days	Glaxo Wellcome	Monto <i>et al.</i> , 1999a ^{72,73}
GSK study 167-101	Healthcare workers aged 18 years and above	T1: Zanamivir 10mg once daily n=161 T2: Placebo n=158	Seasonal	28 days	GlaxoSmithKline	Sponsor submission ⁴⁴
NAI30034	At-risk adolescents and adults (aged 12 yrs and above). High-risk defined as age 65 yrs and above or chronic disorders of pulmonary or cardiovascular system or diabetes mellitus. T1: 67% vaccinated T2: 68% vaccinated	T1: Zanamivir 10mg once daily n=1678 randomised, n=1595 completed study T2: Placebo n=1685 randomised, n=1594 completed study	Seasonal	28 days	GlaxoSmithKline	LaForce <i>et al.</i> , 2007 ⁷⁵

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
NAI30031	Subjects of mixed age and health status. Adults and children aged 5 years and above (as contacts). Index cases: T1: 8% vaccinated, T2: 5% vaccinated, Contact cases: T1: 11% vaccinated, T2: 10% vaccinated Index cases did not receive treatment.	T1: Zanamivir 10mg once daily n=661 T2: Placebo n=630	Post-exposure prophylaxis	10 days	GlaxoSmithKline	Monto <i>et al.</i> , 2002 ⁴⁷
NAI30010	Subjects of mixed age and health status. Adults and children aged 5 years and above. Contacts: T1: 14% vaccinated, T2: 18% vaccinated Index cases were randomised to zanamivir twice daily or placebo.	T1: Zanamivir inhaled 10mg daily n=414 T2: Placebo n=423	Post-exposure prophylaxis	10 days	Glaxo Wellcome	Hayden <i>et al.</i> , 2000 ⁴⁶
NAIA2009 NAIB2009	Subjects of mixed age and health status. Unvaccinated adults and children aged 13 to 65 years (as contacts). Index cases did not receive treatment.	T1: Zanamivir 10mg inhaled daily n=144 T2: Placebo n=144	Post-exposure prophylaxis	5 days	Presumed Glaxo Wellcome	Kaiser <i>et al.</i> , 2000 ⁷⁴

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
NAIA3004	At-risk elderly subjects in long-term care (mean age T1=66.8 yrs, T2=67.2 yrs) (84 to 85% at-risk of complications) T1: 9.6% vaccinated, T2: 8.8% vaccinated	T1: Zanamivir once daily n=242 T2: Placebo n=252	Outbreak control	14 days	Glaxo Wellcome	Ambrozaitis <i>et al.</i> , 2005 ^{76,77}
NAIA3003	At-risk elderly subjects in long-term care (mean age T1=76.3 yrs, T2=74.8 yrs) (96 to 100% at risk of complications) T1: 99% vaccinated, T2: 92% vaccinated	T1: Zanamivir 10 mg once daily n=12 for influenza B outbreak T2: Placebo n=13 for influenza B outbreak	Outbreak control	14 days	Glaxo Wellcome	Gravenstein <i>et al.</i> , 2005 ⁷⁸

5.2.1.2 Quality of included research

The quality of the evidence included within the assessment was variable in terms of study design characteristics and clarity of reporting. Key study quality characteristics are summarised and presented in Appendices 3, 4 and 5.

Amantadine

The quality of the included 8 RCTs relating to the prophylactic use of amantadine was relatively poor. No new amantadine prevention trials published since the original HTA assessment¹⁰ were identified. A considerable number of the older amantadine trials utilised a dose of 200mg/day as opposed to the currently licensed adult dose of 100mg/day¹⁸ and were therefore not considered to be suitable for inclusion in this review (See Section 5.1.2). Other amantadine prevention trials incorporated use of doses of the drug in line with the current license, alongside inappropriate doses, but did not present data appropriate for inclusion separately and were therefore also excluded. Details of these studies can be seen in the table of excluded studies (see Appendix 6).

Much of the amantadine prophylaxis evidence was not reported clearly, with a lack of detail for example on methods of randomisation of study subjects.^{57,59,60,61,63,62} It was unclear in a number of trials whether allocation of treatment group was concealed.^{57,58,55,59,63,62} Only study publication failed to clearly state the number of participants randomised.⁶² As only one report presented details of baseline characteristics of participants,⁵⁵ it was generally not possible to assess whether baseline comparability between treatment groups had been achieved. It is therefore possible that potentially confounding variables may not have been adequately balanced amongst participants randomised to each trial arm. An additional 4 publications failed to state the eligibility criteria for participation in the trials.^{55,60,61,62} A number of co-interventions were identified with the potential to affect outcomes, including vaccination,^{57,58,59,60,61} intake of medications that may affect study outcomes,⁶³ and previous exposure to the experimental challenge strain.⁶² The blinding of participants, those administering the intervention and outcome assessors was similarly difficult to judge and whilst many publications reported that a double-blind design was used, no further details were presented. Whilst all studies included at least 80% of randomised participants in the final analysis and only one study failed to report reasons for participants withdrawal,^{60,61} adherence to the intention-to-treat analysis was variable between studies.

Oseltamivir

The quality of the oseltamivir prophylaxis evidence presented was considerably more robust in terms of study design and reporting than that for amantadine. However, the randomisation methods used and concealment of allocation was unclear in the reporting of some studies.^{49,48,68,67,69} All studies stated the number of participants randomised, and only one report failed to clearly describe baseline characteristics and eligibility criteria,⁶⁹ with all others judged to have achieved baseline comparability amongst subjects. A number of authors identified vaccination status,^{64,66,49,48} and recent use of antivirals^{64,48} or antibiotics⁴⁸ as potentially confounding co-interventions. Clarity of reporting of blinding was variable amongst studies, whilst one study was described as being open-label in design.^{48,68,67} All studies retained at least 80% of randomised subjects for use in the analysis and all, with the exception of 2 reports,^{64,69} presented reasons for withdrawal, but the analysis of only two studies could be considered to adhere to the intention-to-treat principle.^{48,68,67}

Zanamivir

The evidence base for the use of zanamivir in prophylaxis against influenza could also be considered to have a greater degree of internal validity than the trials of amantadine prophylaxis. However, there was a lack of detail on methods of randomisation^{47,46,74} and concealment of allocation.^{46,74,76,77} All studies outlined the number of subjects who were randomised to each group and described baseline characteristics, with baseline comparability considered to have been reached to varying degrees in all trials. Baseline comparability was considered to be relatively weaker in one trial.⁷⁸ Vaccination status^{72,75,47,46,76,78} and recent use of antivirals^{46,76,78} were identified as co-interventions. More information was available on blinding procedures used in the zanamivir research (with additional information obtained from sponsor submissions) than for oseltamivir and amantadine prophylaxis trials, although there were some gaps in reporting in a number of studies.^{72,73,75,47,46,74} However, all studies included over 80% of randomised subjects in analyses, described reasons for withdrawal and all utilised intention-to-treat analysis.

5.2.2 Assessment of effectiveness

Critical review and synthesis of information

The outcomes considered in the clinical effectiveness review of the interventions used in influenza prophylaxis included cases prevented, complications prevented, adverse effects of treatment, health-related quality of life, mortality, hospitalisations prevented, length of influenza illness, time to return to normal activities and cost and cost-effectiveness. Not all of these

outcomes were represented in the identified clinical effectiveness trials included in the review; none of the included studies reported outcomes relating to health-related quality of life or mortality. The primary outcome reported in the majority of included trials related to cases of influenza prevented as measured in terms of the incidence of symptomatic, laboratory-confirmed influenza (SLCI). Where SLCI data were not presented – typically in older trials of relatively lower quality - cases prevented by prophylaxis within trials were described in terms of clinical influenza, acute respiratory disease and/or infection.^{63,62,58,60,61} The efficacy of prophylaxis in preventing cases of SLCI was most frequently reported as a protective efficacy statistic (1 minus the relative risk, expressed as a percentage). Whilst a minority of papers presented some SLCI data by influenza type, the numbers of observed cases were too small to allow meaningful estimates of efficacy to be made by influenza type and therefore the total numbers of cases of SLCI are presented. These values are tabulated where appropriate within the data synthesis. In a small number of trials, this evidence was categorised by subgroup, in terms of age, risk (according to age and health status) and vaccination status and are presented where available. The majority of trials also presented information on the occurrence of adverse events amongst participants, which is presented in text format, due to the large degree of variability in adverse events reported. A limited amount of information was reported relating to complications prevented, hospitalisations prevented, length of influenza illness and time to return to normal activities.

5.2.2.1 Amantadine

The included evidence focusing on amantadine prophylaxis against influenza was taken from relatively older trials of lower quality that were conducted across a broad range of population subgroups. There was considerable variability between trials in terms of vaccination levels, setting and duration of prophylaxis. Eight references reporting 8 randomised controlled trials were identified. The Cochrane review investigating amantadine and rimantadine in influenza A incorporated the use of meta-analysis in their analysis.³³ However, the large degree of heterogeneity and variation in primary outcomes used in terms of cases prevented between the studies included in our review would suggest that the use of statistical meta-analysis would be inappropriate; as such, the results of these trials are presented in the form of a narrative synthesis.

Evidence for amantadine prophylaxis in children under 10 years is not presented in this systematic review, as such data were excluded as amantadine dosage is not established in this age group according to licensed indications. The limited evidence that exists relating specifically to

this younger age group was reported within the original HTA review.¹⁰ No clinical trial evidence relating to the use of amantadine in the paediatric population has been subsequently published.

5.2.2.1.1 Seasonal prophylaxis with amantadine

Seasonal prophylaxis in healthy adults

Two trials by Reuman *et al.*⁵⁷ and Aoki *et al.*⁵⁸ examining the use of amantadine in seasonal prophylaxis in healthy adults were identified and included in the systematic review of clinical effectiveness.

The RCT conducted by Reuman *et al.*⁵⁷ was undertaken in a healthy, unvaccinated adult population aged 18 to 55 years. Whilst this study also investigated the effects of amantadine at doses of 50mg and 200mg daily, only data relating to the use of the drug at the licensed dose of 100mg per day are presented here. The reporting of the duration of the intervention is unclear within the reporting of this trial; it is assumed from the description of the trial methods to be over a period of 6 weeks. Subjects were excluded if chronic disease and abnormal clinical history and physical examination were evident prior to study entry. Clinical symptoms with influenza A infection were observed in 5 of 159 subjects in the placebo group (3.1%) and 2 of 159 subjects (1.3%) in the amantadine at 100mg/day dosage group (relative risk 0.40[†], 95% C.I. 0.08[†] to 2.03[†]). The authors described a higher rate of adverse events in the treatment group receiving the higher dose of 200mg daily but no differences between the arms receiving the licensed dose of 100mg/day and placebo. Total adverse events were reported at a rate of 49/159 (31%) versus 47/159 (30%) in the placebo and amantadine arms respectively. Gastrointestinal adverse events occurred in 8% of subjects in each arm (12/159 for each arm). CNS-related adverse events were observed in 14% of amantadine-treated subjects (23/159) and 16% (25/159) of subjects in the placebo arm. One subject of 159 in the placebo arm (0.6%) withdrew as a result of adverse events; no withdrawals were described in the amantadine 100mg/day group. However, adherence to amantadine was relatively poor, with 49% of the amantadine-dosed participants and 58% of the placebo arm taking less than the total allotted tablets. This study suggests that the use of amantadine at the lower dose results in fewer adverse effects but the low influenza attack rate does not allow meaningful conclusions to be drawn in relation to the efficacy of amantadine in preventing influenza illness and infection.

A study in which amantadine was administered to healthy military personnel for seasonal prophylaxis over 2 seasons for 32 days and 39 days respectively was reported by Aoki *et al.*⁵⁸ As

discussed in Section 5.1.2, only data comparing effects in treatment arms receiving amantadine at a dose of 100mg per day or placebo are presented in this review. Reasons for the unequal numbers in each treatment arm are unclear. Six to 8 individuals per study season were described as being vaccinated in previous years (proportions not estimable). Primary outcomes reported related to the proportion of participants who developed acute respiratory tract infection, classification of disease and adverse effects. No differences in the incidence or classification of acute respiratory illness (ARI) were observed between the treatment arms. The trial findings were not reported clearly, in that 1 subject in 1980-81 and 2 subjects in the 1982-83 seasons are stated as developing acute influenza A but no further detail was presented concerning the treatment arm in which these cases developed. However, the observed attack rates were so low that meaningful comparison of efficacy between arms is limited. In the 1980-81 season, withdrawals due to adverse effects were reported at a frequency of 1/49 (2.0%) in the placebo group and 1/75 (1.3%) in the amantadine at 100mg/day group. In 1982-83, these rates were described as 1/34 (2.9%) in the placebo group and 1/47 (2.1%) in the amantadine 100mg/day group. No amantadine-related differences in adverse effects were observed between the placebo and amantadine 100mg/day groups (no further data were presented).

Seasonal prophylaxis in the elderly

A single trial by Pettersson *et al.*⁵⁵ in which amantadine was used for seasonal prophylaxis in elderly subjects was included in the systematic review. Whilst the trial also investigated amantadine prophylaxis in different population groups and settings, the only data for amantadine administered in line with licensed indications and therefore suitable for inclusion related to residents of a home for the elderly who received amantadine at a dose of 100mg/day versus placebo over a period of 9 weeks. The vaccination status of subjects was not clearly described in the trial publication, although it was stated in the discussion of the report that no adequate vaccine was available at the time of study; this suggests that the population could be considered unprotected by vaccination. Primary outcomes were reported in terms of the incidence of serologically-confirmed influenza infection, incidence of respiratory infections and adverse events. No data were reported for the incidence of serologically-confirmed influenza infection or incidence of respiratory infections in the elderly study population, as there was no evidence of an influenza epidemic in this group. Amantadine prophylaxis was described as being terminated in 5 of 94 (5.3%) and 2 of 101 (2.0%) subjects in the amantadine versus placebo arms respectively. Whilst this evidence would suggest a potentially higher incidence of adverse events in the amantadine arm, a range of apparently non-drug-related reasons were cited for termination,

including one fracture of caput femoris, two deaths attributable to carcinoma and myocardial infarction, no reason given in one case and compliance and practical issues in a further two cases. One case of GI symptoms and one of chest pains were cited in the placebo arm.

5.2.2.1.2 Post-exposure prophylaxis with amantadine

Post-exposure prophylaxis in households

No studies investigating the use of amantadine in the prevention of influenza in household contacts of influenza-infected index cases were identified for inclusion in the systematic review.

Outbreak control in healthy adults and adolescents

Two trials were identified in which amantadine was used for the control of influenza outbreaks. The trial reported by Payler and Purdham⁵⁹ was undertaken in adolescent males in a boarding school, of whom 87% (525/606) were vaccinated for that season. Subjects were randomised to receive either amantadine at 100mg/day for 14 days or no treatment. In this study, the control arm was not placebo-controlled. However, it is unlikely that a lack of blinding would impact upon the reported incidence of SLCI, due to the nature of the manifested infectious illness and requirement of infection confirmed by laboratory tests. The incidence of clinical influenza was reported as being 7/267 (2.6%) in the amantadine arm versus 42/269 (15.6%) in the control group ($P < 0.001$, relative risk 0.17[†], 95% C.I. 0.08[†] to 0.37[†]). The incidence of clinical influenza that was laboratory-confirmed was 3/267 (1.1%) in the subjects receiving amantadine compared with 29/269 (10.8%) in the control group ($P < 0.001$), resulting in a protective efficacy of 90% (95% C.I. 0.66[†] to 0.97[†]). Of the 3 subjects developing symptomatic, laboratory-confirmed influenza in the amantadine arm, 2 subjects were described as being vaccinated, whilst one subject was not. No information was given for the control arm. Urticaria was reported in 1 of 267 participants receiving amantadine (0.4%), whilst no adverse events were observed in the control group. The authors observed that 8 of the 9 subjects who developed laboratory-confirmed influenza A 3 days after the 14 day prophylactic period had ceased had received amantadine, highlighting that protection against influenza is not extended beyond the prophylactic period.

The second included RCT of amantadine in outbreak control was presented by Smorodintsev *et al.*^{60,61} The composition of the study population was not clearly reported but appears to have consisted of healthy unvaccinated adults based in semi-isolated engineering schools. Five of 7 schools were dosed for 30 days, whilst 2 schools were dosed for 12 days. The reporting of the study was very unclear, with conflicting descriptions of the vaccination status of populations

varying from unvaccinated to partially vaccinated. In subjects regularly or irregularly receiving drug medication, clinical influenza occurred at rates of 214/4559 (4.7%), and 224/2804 (8.0%) in the amantadine and placebo groups respectively (relative risk 0.59[†], 95% C.I. 0.49[†] to 0.70[†]). Of 400 influenza cases that were selected at random, severity of symptoms in the amantadine group was reported as 56.0% mild and 9.0% severe; whilst symptoms were described as 38.0% mild and 19.0% severe in the placebo group (P< 0.01 for severe symptoms, P< 0.001 for mild symptoms), demonstrating milder disease in the amantadine-treated group. No further information was provided on the manner in which symptoms were classed as mild or severe. Mean duration of overall illness was shorter in the amantadine versus placebo group (P< 0.05). A subset of non-ill subjects (n=1825) were questioned about adverse effects, which occurred in 7.2% (94/1313) and 5.1% (26/512) of those questioned from the amantadine and placebo groups respectively, showing a non-significant 2.1% excess in the amantadine group. Statistically-significant (at 5%) excesses in dyspepsia (1.72%) and sleep disturbances (1.14%) were noted in the amantadine-dosed subjects. The applicability of this evidence is considerably hindered by poor reporting and lack of detail on population baseline characteristics. However, some limited evidence of the efficacy of amantadine in preventing and shortening the duration and severity of clinical influenza disease and for a higher rate of adverse effects as a result of amantadine receipt were presented.

Outbreak control in the elderly

No studies investigating the use of amantadine in outbreak control in elderly populations were identified.

5.2.2.1.3 Prophylaxis with amantadine against experimentally-induced influenza

Three further trials of amantadine prophylaxis, in which subjects were challenged experimentally with influenza virus, were included in the systematic review.^{57,63,62}

Reuman *et al.*⁵⁷ undertook an RCT to determine the efficacy of amantadine in preventing experimentally-induced influenza A. Whilst the use of doses of amantadine at 50mg/day and 200mg/day were also investigated, only data relating to the use of data relevant to the review for amantadine at 100mg/day and placebo are presented within this systematic review. Subjects were healthy, unvaccinated adults aged 18 to 40 years. Individuals who had a pre-study abnormal clinical history and physical examination or chronic disease were excluded from participation. Infection was noted in 18/19 (95%) placebo subjects and in 12/20 (60%) of amantadine-dosed subjects (P=0.012). SLCI was observed in a lower proportion of subjects, in 11/19 (58%) in the

placebo arm and in 3/20 (15%) in the amantadine arm ($P=0.0055$), resulting in a relative risk of 0.26 (95% C.I. 0.09[†] to 0.79[†]) and a protective efficacy of 74%. Amantadine at all doses was described as suppressing respiratory symptoms on days 2 to 6 following viral challenge and systematic symptoms on days 2 and 3 post-challenge. Total length of illness was not reported. Total adverse events judged to be potentially drug-related occurred in 50% of placebo subjects and 80% of subjects receiving amantadine at 100mg/day ($P=0.27$). These were stated as being mostly mild and transient and related to the GI and CNS systems. Three adverse events were rated as severe, comprising two cases of severe headache, of which one occurred in each treatment arm, and one case of dream abnormality in a subject receiving amantadine. No withdrawals were made in the placebo or amantadine at 100mg/day arms.

Further evidence of the use of amantadine prophylaxis against experimentally-induced influenza A was published by Sears & Clements.⁶³ Healthy, unvaccinated adult subjects aged 18 to 40 years were randomised to receive either amantadine at 100mg/day or placebo over a period of 8 days. Infection was serologically-confirmed in 77% (17/22) of amantadine subjects and 91% (20/22) of the placebo group. Influenza illness was observed in 2/22 (9.1%) of those subjects receiving amantadine and 9/22 (40.9%) of subjects receiving placebo, yielding a protective efficacy of 78% ($P < 0.04$) and a relative risk of 0.22[†] (95% C.I. 0.05[†] to 0.91[†]). Severity of illness was also less in the amantadine-dosed group. The authors stated that no adverse events were reported in the amantadine-dosed group.

Smorodintsev *et al.*⁶² demonstrated the efficacy of amantadine at the lower dose of 100mg/day versus the previously used dose of 200mg/day and placebo in the prevention of experimentally-induced influenza A in healthy medical student volunteers. Only data in which the licensed dose of 100mg/day and placebo are compared are presented here. A protective efficacy of 42% against clinical influenza was reported for amantadine at 100mg/day versus placebo (10/19 in the amantadine arm, 28/31 in the placebo arm; relative risk 0.58, 95% C.I. 0.37[†] to 0.91[†]). This increased to a protective efficacy of 86% against serologically-confirmed influenza (1/19 in the amantadine arm, 12/31 in the placebo arm; relative risk 0.14[†], 95% C.I. 0.02[†] to 0.96[†]). No adverse effect data were reported specifically comparing amantadine at the licensed dose against placebo; however no drug-related side effects were reported overall.

5.2.2.1.4 Adherence to amantadine prophylaxis

Four trials presented evidence of varying levels of adherence to the study protocols. Payler and Purdham stated that only 2% of their subjects did not take amantadine,⁵⁹ whilst 85% (number of subjects not reported) of participants in an additional trial of outbreak control were reported as taking amantadine without interruption over the study period, suggesting a relatively high level of adherence.⁶⁰ However, Reuman *et al.*⁵⁷ reported that approximately half of their study participants did not take all of the allotted study treatment (49% and 58% of amantadine and placebo groups). The study by Aoki *et al.*⁵⁸ utilised laboratory testing of samples taken from tested study participants and demonstrated that 9% and 21% of subjects who had been randomised to receipt of amantadine and were tested in different study seasons showed no drug in samples.⁵⁸

5.2.2.1.5 Viral resistance to amantadine

No trials presented data on analysis of sensitivity of viral isolates to amantadine (see Section 5.2.2.1.6).

5.2.2.1.6 Discussion of amantadine prophylaxis

As noted in the review by Jefferson *et al.*,⁷⁹ the evidence base relating to amantadine in prophylaxis against influenza was comparatively old and relatively poor in terms of study quality and reporting. The resulting data should therefore be interpreted with caution.

Owing to low attack rates, evidence of efficacy against SLCI in seasonal prophylaxis was limited. One study of amantadine used in outbreak control⁵⁹ suggested high efficacy against SLCI in a boarding school setting and demonstrated that protection against influenza is not conferred beyond the prophylactic period. Limited evidence for a lower incidence of clinical influenza and milder disease of shorter duration was presented.^{60,61} Some evidence relating to the efficacy of amantadine in preventing experimentally-induced infection and SLCI was also identified. As such challenge studies are undertaken under experimental rather than clinical conditions, data drawn from these studies should be interpreted with caution with respect to external validity and applicability to clinical effectiveness, particularly with respect to the nature of challenge and the comparability of subjects in terms of pre-challenge antibody titres. However, as the evidence concerning amantadine prophylaxis against naturally-acquired influenza is sparse, it was considered useful to present the findings of the use of the drug in accordance with licensed indications against the development of experimentally-induced influenza in healthy adults, in order to supplement the evidence base presented here. Very limited interpretation can be made

concerning the impact of vaccination status on the efficacy of amantadine prophylaxis, although the study reported by Payler and Purdham⁵⁹ demonstrated that a small number of cases of SLCI developed in both vaccinated and unvaccinated subjects in the amantadine-treated arm.

Withdrawals due to adverse events and illness were similar in amantadine and placebo groups, whilst adverse effects were similar in both groups, with the exception of the trial reported by Smorodintsev *et al.*^{60,61} and the experimental challenge study by Reuman *et al.*,⁵⁷ both of which demonstrated a higher incidence of adverse effects in the amantadine-treated subjects. Severe adverse effects also appeared to be higher in the amantadine-treated group.⁵⁷

None of the amantadine prophylaxis trials included in this review reported the assessment of sensitivity of influenza isolates to amantadine. However, as noted in Section 3.3.1.1, reports of the increasing emergence of amantadine-resistant influenza A strains³¹ present a significant challenge to the clinical effectiveness of amantadine in prophylaxis against influenza and must be taken into account during the interpretation of the evidence presented in the clinical effectiveness review.

5.2.2.2 Oseltamivir

Nine references reporting 6 original RCTs of oseltamivir for the prophylaxis of influenza were identified.

5.2.2.2.1 Seasonal prophylaxis with oseltamivir

Seasonal prophylaxis in children

No evidence that specifically relates to seasonal prophylaxis in children was identified.

Seasonal prophylaxis in healthy adults

Two RCTs investigating oseltamivir for seasonal prophylaxis were reported by Hayden *et al.*⁶⁶ The two trials were identically-designed multicentre studies undertaken in healthy, unvaccinated adults aged 18 to 65 years; the first of which was undertaken in Virginia (WV15673) and the second at sites in Texas and Kansas City (WV15697). Prophylaxis was administered for 6 weeks. Oseltamivir administered to subjects at a dose of 75 mg once daily conferred a protective efficacy against SLCI of 84% (95% C.I. 53 to 96) in trial WV15673 and a non-significant protective efficacy of 50% (95% C.I. -55 to 94) in trial WV15697. The authors reported a pooled estimate for protective efficacy against SLCI of 76% (95% C.I. 46 to 91; relative risk = 0.24). When a

meta-analysis of the data reported separately for each trial was undertaken by the Assessment Group, the relative risk of developing influenza for oseltamivir versus placebo was 0.27 (95% C.I. 0.09 to 0.83). Total withdrawals occurred in 21/519 (4%) of the placebo and 17/520 (3%) of the oseltamivir subjects. Withdrawals due to adverse effects or intercurrent illness occurred in 8/520 (1.5%) of the oseltamivir 75mg/daily group and in 10/519 (1.9%) of the placebo group. Upper gastrointestinal adverse effects were higher in subjects receiving oseltamivir at 75 mg/day (12.1%) versus placebo (7.1%) (difference 5.0%, 95% C.I. 1.4 to 8.6%). Vomiting occurred in a higher proportion of subjects receiving the oseltamivir dose (2.5%) versus placebo (0.8%) (difference 1.7%, 95% C.I. 0.2 to 3.3%).

Seasonal prophylaxis in the elderly

Peters *et al.*^{64,65} presented the results from study WV15825, an RCT of oseltamivir in seasonal prophylaxis in a frail, elderly population residing within a residential care setting. Prophylaxis with oseltamivir at 75 mg once daily for 6 weeks resulted in a 92% protective efficacy for SLCI (P=0.002). When incidence in solely the vaccinated population was analysed, a protective efficacy of 91% against SLCI (P=0.003) was observed. For all individuals, receipt of oseltamivir resulted in an 86% relative reduction in secondary influenza complications (where complications included bronchitis (4/272), pneumonia (3/272) and sinusitis (1/272) in the placebo arm and bronchitis (1/276) in the oseltamivir group) (P=0.037). In subjects with laboratory-confirmed influenza, the relative reduction in secondary complications was 78% (P=1.14). Withdrawals due to adverse events or illness were at rates of 6.5% (18/276) and 4.0% (11/272) in the oseltamivir and placebo arms respectively. Similar proportions of subjects in each group experienced mild to moderate adverse events (around 60%); however most of these were not considered by the study investigators to be drug-related. Headaches occurred at a higher frequency in the oseltamivir group vs. placebo (8.3% vs 5.5%) and gastrointestinal adverse events were also more common amongst individuals receiving oseltamivir (14.9% vs 12.9%).

Table 6: Oseltamivir for seasonal prophylaxis in healthy unvaccinated adults: WV15673 and WV15697 (Hayden *et al.*, 1999a)⁶⁶

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. in oseltamivir group	No. in oseltamivir group with an event	RR (95% C.I.)
Symptomatic, laboratory-confirmed influenza	WV15673	268	19	268	3	0.16 (0.04, 0.47)
Symptomatic, laboratory-confirmed influenza	WV15697	251	6	252	3	0.50 (0.06, 1.55)
	Pooled (random effect)					0.27 (0.09 to 0.83) (P=0.21, I ² =35.4%)

Table 7: Oseltamivir for seasonal prophylaxis in at-risk elderly subjects in residential care (80% vaccinated): WV15825 (Peters *et al.*, 2001)⁶⁴

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. in oseltamivir group	No. in oseltamivir group with an event	RR (95% C.I.)
Symptomatic, laboratory-confirmed influenza	WV15825	272	12	276	1	0.08 (0.01 [†] , 0.63 [†])
Vaccinated subjects only	WV15825	218	11	222	1	0.09 (0.01 [†] , 0.69 [†])

5.2.2.2.2 Post-exposure prophylaxis with oseltamivir

Post-exposure prophylaxis in mixed households

Two RCTs, WV15799⁴⁹ and trial WV16193 reported by Hayden *et al.*^{48,67,68} investigating oseltamivir in the prevention of influenza in household contacts of index cases were identified.

Welliver *et al.*⁴⁹ randomised household contacts of index cases to receive either 75 mg of oseltamivir once daily or placebo for 7 days. Index cases did not receive antiviral treatment in either trial arm. Children under 12 years of age were excluded as contacts, but were eligible as index cases. A minor point is that subjects aged ≥ 12 years received the adult dose of 75 mg once daily, whilst dosing according to bodyweight is recommended in subjects aged less than 13 years. Whilst individuals with well-controlled co-morbidities were eligible for participation in the study, potential subjects with cancer, immunosuppression or chronic renal or liver disease were excluded. Prophylaxis resulted in a protective efficacy amongst individual contacts of all index cases of 89% (95% C.I. 71 to 96, $P < 0.001$). For individual contacts of influenza-positive index cases only, the protective efficacy was also 89% (95% C.I. 67 to 97, $P < 0.001$). Withdrawals due to adverse effects or illness occurred in 2/461 (0.4%) in the placebo arm and 5/494 (1.0%) oseltamivir subjects. Gastrointestinal adverse effects were reported in 7.2% of the placebo and 9.3% of the oseltamivir subjects, whilst nausea was evident in 2.6% and 5.5% of the placebo and oseltamivir subjects respectively. No abnormal results for safety or vital signs and no serious adverse events were observed.

A randomised, open-label trial (WV16193) in adults and children aged 1 year and above undertaken by Hayden *et al.*^{48,67,68} and published subsequent to the original assessment¹⁰ investigated the use of oseltamivir (75mg once daily) in post-exposure prophylaxis in household contacts of index cases for 10 days versus expectant treatment, in which oseltamivir (75mg twice daily) was administered for 5 days upon the onset of influenza illness in contacts. In both trial arms, index cases received treatment. Post-exposure prophylaxis with oseltamivir for 10 days in individual household contacts resulted in a protective efficacy against SLCI of 73% (95% C.I. 47 to 86), when including all households irrespective of whether the index case developed influenza. For individual contacts of influenza-positive index cases, the corresponding protective efficacy was lower, at 68% (95% C.I. 35 to 84). The proportion of contacts with laboratory-confirmed influenza with at least one secondary complication was broadly comparable between the post-exposure prophylaxis group and subjects receiving expectant treatment (7% (3/46) versus 5% (4/75)); however the more severe respiratory complications occurred in the expectant treatment

arm only. The median time from start of treatment to alleviation of symptoms in contacts was also shorter in the post-exposure prophylaxis (n=10) versus expectant treatment arm (n=33) (5.5 hrs (0-87) versus 39.8 hrs (0-627) (P=0.103)). Fewer contacts with laboratory-confirmed influenza in the post-exposure prophylaxis arm were bed-bound compared with subjects in the expectant treatment group (7% (3/46) versus 28% (21/75)), demonstrating a milder form of disease. Withdrawals due to adverse events occurred at a rate of 1/410 (0.2%) in the post-exposure prophylaxis arm and at 4/402 (1.0%) in the expectant treatment arm. Nausea was more common in subjects receiving oseltamivir for post-exposure once daily versus treatment twice daily (8% vs. 7%). However, vomiting was more frequent in the expectant treatment arm (10% vs. 4.5%).

When the data for SLCI in the mixed adults and children populations from the Welliver *et al.*⁴⁹ and Hayden *et al.*⁴⁸ trials were pooled by meta-analysis using random effects, the resulting relative risk amongst household contacts of all index cases was 0.19 (95% C.I. 0.08 to 0.45), equating to a protective efficacy of 81%. For contacts of influenza-infected index cases only, the corresponding pooled relative risk was 0.21 (95% C.I. 0.08 to 0.58) and the resulting protective efficacy was 79%. A pooled relative risk for withdrawals generated by the Assessment Group yielded a relative risk of 0.85 (95% C.I. 0.09 to 7.72), favouring treatment.

An additional pooled analysis of data from the trials by Welliver *et al.*⁴⁹ and Hayden *et al.*⁴⁸ was reported by Halloran *et al.*,⁴⁵ who presented a pooled estimate of protective efficacy of oseltamivir post-exposure prophylaxis against illness of 81% (95% C.I. 35 to 94) and an 80% reduction in infectiousness (95% C.I. 48 to 72). The secondary analysis by Halloran *et al.* also assessed pathogenicity of influenza in the treatment and control arms of the household post-exposure prophylaxis trials. Pathogenicity was defined as the ability of the virus to cause disease in an infected person. It was calculated as the number of contacts with symptomatic laboratory-confirmed influenza (SLCI) divided by the number of contacts with laboratory-confirmed influenza infections (symptomatic or asymptomatic). Pathogenicity was lower amongst subjects treated with oseltamivir compared with control. In the study by Welliver *et al.*,⁴⁹ reported pathogenicity in the control group was 34/60 (57%) and in the oseltamivir group, 4/33 (12%); these data included contacts, regardless of whether the index case was influenza-positive. In the study by Hayden *et al.*,⁴⁸ pathogenicity in the control group was 33/75 (44%) and in the oseltamivir group, 10/46 (22%); note that for this study only data for contacts with an influenza-positive index case were available for this analysis.

In the trials reported by Hayden *et al.*⁴⁸ and Welliver *et al.*⁴⁹ it was noted that, in some instances, the strain of influenza with which the contact cases were infected did not match that of the index case, thus indicating that illness was not transmitted from the index case but from a source external to the household setting.

Table 8: Oseltamivir for post-exposure prophylaxis in households: WV15799 (Welliver *et al.*, 2001)⁴⁹ and WV16193 (Hayden *et al.*, 2004)⁴⁸

Outcome	Trial	Total no. in placebo group	No. in control group with an event	Total no. in oseltamivir group	No. in oseltamivir prophylaxis group with an event	RR (95% C.I.)
Symptomatic, laboratory-confirmed influenza in contacts of all index cases	WV15799	462	34	493	4	0.11 (0.04, 0.29)
	WV16193	392	40	400	11	0.27 (0.14, 0.53)
	Pooled (random effect)					0.19 (0.08 to 0.45) (P=0.15, I ² =52.9%)
Symptomatic, laboratory-confirmed influenza in contacts of influenza-positive index cases	WV15799	206	26	209	3	0.11 (0.03, 0.33)
	WV16193	258	33	244	10	0.32 (0.16 to 0.65)
	Pooled (random effect)					0.21 (0.08 to 0.58) (P=0.13, I ² =56.3%)

Table 9: Oseltamivir for post-exposure prophylaxis in paediatric household contacts (1 to 12 years): WV16193 (Hayden *et al.*, 2004)⁴⁸

Outcome	Trial	Total no. in placebo group	No. in control group with an event	Total no. in oseltamivir group	No. in oseltamivir prophylaxis group with an event	RR (95% C.I.)
Symptomatic, laboratory-confirmed influenza in contacts of all index cases	WV16193	111	21	104	7	0.36 (0.15, 0.84)
Symptomatic, laboratory-confirmed influenza in contacts of influenza-positive index cases	WV16193	74	18	55	6	0.45 (0.18, 1.13)

Post-exposure prophylaxis in paediatric household contacts

Clinical outcomes from the trial by Hayden *et al.*⁴⁸ were also reported separately for paediatric household contacts aged 1 to 12 years. It should be noted that this study allocated doses according to the child's age banding, rather than bodyweight as recommended by the BNF.¹⁸ However, subsequent analysis has shown that the dosages used were broadly equivalent to those approved.⁸⁰ For individual contacts of all index cases, the protective efficacy against SLCI was 64% (16 to 85) (relative risk= 0.36). When contacts of influenza-infected index cases only were included in the analysis, the protective efficacy dropped to 55% (-13 to 82) (relative risk = 0.45). Amongst paediatric cases, vomiting was more common in the expectant treatment group (20% versus 10%). No children withdrew due to adverse events.

Outbreak control

No studies describing the use of oseltamivir for control of influenza outbreaks were identified.

5.2.2.2.3 Prophylaxis with oseltamivir against experimentally-induced influenza

A single trial by Hayden *et al.*⁶⁹ of oseltamivir used in accordance with licensed indications in prophylaxis against experimentally-induced influenza B in healthy adults was identified. Influenza B infection was observed at rates of 17/19 (89%) in the oseltamivir group and 16/19 (84%) in the placebo group (relative risk 1.06[†], 95% C.I. 0.83[†] to 1.36[†]). Symptoms of upper respiratory tract illness were present in 2/19 (11%) oseltamivir subjects compared with 4/19 (21%) in the placebo arm (relative risk 0.50[†], 95% C.I. 0.10[†] to 2.41[†]), whilst fever was observed in 1/19 (5%) and 2/20 (10%) in the oseltamivir versus placebo groups respectively (relative risk 0.53[†], 95% C.I. 0.05[†] to 5.34[†]). No serious adverse effects were reported. Adverse effects related to study treatment occurred in 1/19 (5.3%) of subjects in each group. No treatment-related adverse effects were observed during the off-treatment follow-up period.

5.2.2.2.4 Adherence to oseltamivir prophylaxis

Adherence to the study regimens was reasonably high. In one study, 7% percent of placebo subjects and 11% of those in the oseltamivir arm were reported as taking less than 80% of study medication.⁶⁴ In another study, 53% of both oseltamivir and placebo arms took 100% of the prescribed doses taken, according to returned capsules.⁶⁶ In the study by Welliver *et al.*,⁴⁹ fewer than 1% of contacts in both placebo and oseltamivir arms did not take the allocated treatment.

5.2.2.2.5 Viral resistance to oseltamivir

A number of trials tested viral isolates for resistance to oseltamivir in vitro and found no evidence of reduced sensitivity (see Section 5.2.2.2.6).^{66,49,48,69}

5.2.2.2.6 Discussion of oseltamivir evidence

The trials included in this systematic review suggest that oseltamivir has a relatively high protective efficacy against SLCI in healthy adults. The protective efficacy against SLCI was notably high amongst the frail elderly living in residential care, amongst whom a clear reduction in influenza-associated complications was also observed. The efficacy against SLCI was broadly equivalent in vaccinated and unvaccinated individuals. The evidence for oseltamivir in post-exposure prophylaxis in the household setting has been reinforced by the publication of an additional trial⁴⁸ since the original assessment.¹⁰ Oseltamivir conveys a high protective efficacy against SLCI in household contacts and any resulting disease appears to be milder and of shorter duration.⁴⁸ As in the Cochrane review by Matheson *et al.*⁸¹ of neuraminidase inhibitors in the prevention of influenza in children, only one RCT, trial WV16193,⁴⁸ in which data relating specifically to children were presented was identified. Prophylaxis in paediatric contacts was demonstrated to be reasonably effective. An experimental challenge study also demonstrated a lower incidence of illness in subjects receiving prophylaxis.

Withdrawals due to adverse events and illness were similar in both groups in all trials, bar one,⁶⁴ which demonstrated a slightly higher incidence in frail, elderly subjects receiving oseltamivir. Two studies suggested that gastrointestinal adverse effects were marginally higher amongst the oseltamivir-treated subjects.^{66,49}

No evidence of reduced sensitivity of viral isolates to oseltamivir was obtained. A number of publications have postulated that levels of resistance to neuraminidase inhibitors have been low.^{82,83,84} However, additional reports from Japan⁸⁵ and Europe⁸⁶ (including the UK) have demonstrated the emergence of oseltamivir-resistance influenza A strains. Recent surveillance data⁸⁷ from within the UK have indicated that approximately 5% of influenza A (H1N1) isolates were oseltamivir-resistant, but no conclusions were drawn by the Health Protection Agency with regards to the clinical significance of this finding, stating a requirement for further research. The clinical effectiveness evidence for the use of oseltamivir in prophylaxis against influenza should therefore be interpreted in light of the above reports of emerging resistance.

5.2.2.3 Zanamivir

Ten published articles presenting the results from 8 RCTs were identified for inclusion in the systematic review of clinical effectiveness. An additional unpublished report was identified in the sponsor submissions and included in the assessment, resulting in a total of 9 RCTs. Only the use of inhaled zanamivir is considered within this assessment, hence trial arms in which doses of intranasal zanamivir were administered were excluded.

5.2.2.3.1 Seasonal prophylaxis with zanamivir

Seasonal prophylaxis in children

No data specifically relating to seasonal prophylaxis in children were identified.

Seasonal prophylaxis in healthy adults

Study NAIA3005 reported by Monto *et al.*^{72,73} evaluated the use of zanamivir in seasonal prophylaxis in healthy adults aged 18 to 64 years and demonstrated a 68%[†] protective efficacy against SLCI (95% C.I. 37%[†], 83%[†]). When the unvaccinated subjects were analysed as a subgroup, the protective efficacy was 60% (95% C.I. 24 to 80). Potential symptoms relating to drug use were reported by 75% of subjects in both arms. Adverse effects considered by the authors to be potentially drug-related were observed in 5% (27/554) of the placebo and 5% (30/553) of the zanamivir group, of which less than 1% in each arm was classed as severe. Total withdrawals occurred in 3% (17/554) and 2% (10/553) of the placebo and zanamivir arms. Potentially drug-related withdrawals were made in 1.3% of the placebo and 0.7% of the zanamivir groups. A conference abstract⁷³ presenting further information on the trial stated that significantly less time was missed from work in the zanamivir group (mean hours lost 1.4 versus 0.6 hours, P=0.001). Total productive time lost was also less in the zanamivir group (1.8 versus 3.0 hours, P=0.001). The authors stated that the trial was undertaken during a season in which the predominant circulating influenza A strain did not match the administered vaccine, demonstrating efficacy of prophylaxis during a circumstance of strain mismatch.

An unpublished report of a randomised, double-blind, placebo-controlled trial, presented as part of the sponsor submissions, described the use of zanamivir in seasonal prophylaxis in adult healthcare workers (who were presumed to be healthy in the current assessment).⁴⁴ No statistical significance between treatment groups in the development of SLCI was observed (3/160 versus 6/156 in zanamivir and placebo arms respectively in non-vaccinated set, P=0.3314). Adverse events occurred at similar rates in the zanamivir (67.7%) and placebo (62.2%) arms, of which

1.2% in the zanamivir and 1.3% in placebo subjects were considered to be drug-related. One serious adverse event, that was not judged to be drug-related, occurred in a zanamivir-treated subject.

Seasonal prophylaxis in at-risk adolescents and adults

Since the original HTA assessment was undertaken,¹⁰ a large scale study of zanamivir seasonal prophylaxis in community-dwelling adolescents and adults aged 12 years and above at risk of complications of influenza has been published.⁷⁵ High-risk was defined as being aged 65 years and above or having chronic pulmonary or cardiovascular diseases or diabetes mellitus. For the ITT population assessed for the development of SLCI during days 1 to 28 of prophylaxis, a protective efficacy of 83% was observed (relative risk=0.17, 95% C.I. 0.07 to 0.44, $p < 0.001$). For the per-protocol population, this value dropped to 75% (relative risk=0.25, 95% C.I. 0.09 to 0.70, $p=0.014$). Protective efficacies against the development of SLCI during days 2 to 28 and 3 to 28 of the prophylactic period were 81% and 80% respectively. Data were also presented by high-risk condition, with relative risk values calculable for various subgroups: subjects with respiratory disease (relative risk=0.18, 95% C.I. 0.05[†] to 0.61[†]), with cardiovascular disease (no events in zanamivir group) and with diabetes (no events in diabetes group). When presented according by age, the incidence of SLCI was lower in the zanamivir group versus placebo group in subjects aged both below and above 50 years (50 years and above: zanamivir: 1/1276 (0.08%), placebo: 9/1270 (0.71%); below 50 years: zanamivir: 3/402 (0.75%), placebo: 14/415 (3%).⁴⁴ Relative risks were also calculable by vaccination status, with relative risks of 0.17 (95% C.I. 0.02[†] to 1.41[†]) and 0.17 (95% C.I. 0.05[†] to 0.58[†]) of developing SLCI in vaccinated and unvaccinated subjects respectively. Confirmed influenza with complications was observed in 0.06% of zanamivir subjects and in 0.48% of those in the placebo arm, giving a relative risk of 0.12 (95% C.I. 0.02 to 0.73). Zanamivir was well tolerated, with no significant differences in total adverse effects between the two groups, with 51% in each group (placebo: 851/1685 and zanamivir: 850/1678). Potentially drug-related adverse events were observed in 9% and 10% of the placebo and zanamivir arms respectively. Drug-related serious adverse events occurred in 2/1685 of placebo subjects (0.12%, cardiac arrhythmia and dyspnoea/cough) and 1/1678 of zanamivir subjects (0.06%, acute resistant asthmatic bronchitis/acute rhinositis). Subjects with respiratory disease with any adverse event were observed in 59% of each group (405/684 and 412/695 in zanamivir and placebo arms respectively).⁴⁴ Subjects with cardiovascular disease for whom any adverse event was reported were evident in 48% (159/331) and 49% (149/307) of the placebo arms.⁴⁴ Diabetic subjects with any adverse event were observed in 62% of the zanamivir

group (223/359) and 52% of the placebo group (191/370).⁴⁴ There were 39 hospitalisations in the ITT population after the study start; 19 in the placebo group and 20 in the zanamivir group.⁴⁴ The mean length of stay across those subjects hospitalised was 3.8 days in placebo-treated subjects, compared with 3.3 days in zanamivir-treated subjects.⁴⁴ Mean values of 0.4 vs 0.3 days in placebo and zanamivir groups over which subjects were incapacitated or confined to bed demonstrated no significant difference between arms.⁴⁴ Median time to alleviation of symptoms was shorter in the zanamivir group than placebo (2.5 versus 4.0 days).

Seasonal prophylaxis in the elderly

Trial NAI30034⁷⁵ also evaluated the efficacy of zanamivir in seasonal prophylaxis in subjects aged 65 years and above. Of these, 13% had respiratory disease, 15% had cardiovascular disease, 9% had diabetes and 10% had two or three of the above risk factors.⁴⁴ SLCI was observed in 1/946 and 5/950 of zanamivir and placebo group subjects respectively, resulting in a relative risk of 0.20 (0.02[†] to 1.72[†]). Amongst subjects aged over 65 years, the proportions experiencing any adverse events were 53% in each group (498/946 and 501/950 in zanamivir and placebo arms respectively).⁴⁴

Table 10: Zanamivir for seasonal prophylaxis in healthy adults: NAIA3005 (Monto *et al.*, 1999)⁷² and GSK study 167-101

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. In zanamivir group	No. in zanamivir group with an event	RR (95% C.I., and p-value if available)
Symptomatic, laboratory-confirmed influenza	NAIA3005	554	34	553	11	0.32 (0.17 [†] , 0.63 [†])
Symptomatic, laboratory-confirmed influenza in unvaccinated subjects only	NAIA3005	No data	No data	No data	No data	0.40 (0.20 to 0.76, p=0.004)
Symptomatic, laboratory-confirmed influenza in unvaccinated subjects only	GSK study 167-101 ⁴⁴	156	6	160	3	0.49 (0.12 [†] to 1.92 [†] , P=0.3314)

Table 11: Zanamivir for seasonal prophylaxis in at-risk adults and adolescents (67 to 68% vaccinated): NAI30034 (LaForce *et al.*, 2007)⁷⁵

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. in zanamivir group	No. in zanamivir group with an event	RR (95% C.I., and p-value if available)
Symptomatic, laboratory-confirmed influenza in all cases	NAI30034	1685	23	1678	4	0.17 (0.07 to 0.44)
Symptomatic, laboratory-confirmed influenza in vaccinated subjects	NAI30034	1141	6	1116	1	0.17 (0.02 [†] to 1.41 [†])
Symptomatic, laboratory-confirmed influenza in unvaccinated subjects	NAI30034	544	17	562	3	0.17 (0.05 [†] to 0.58 [†])
Symptomatic, laboratory-confirmed influenza in subjects with respiratory disease	NAI30034	695	17	684	3	0.18 (0.05 [†] to 0.61 [†])

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. in zanamivir group	No. in zanamivir group with an event	RR (95% C.I., and p-value if available)
Symptomatic, laboratory-confirmed influenza in subjects with cardiovascular disease	NAI30034	307	1	331	0	Not estimable
Symptomatic, laboratory-confirmed influenza in subjects with diabetes	NAI30034	370	3	359	0	Not estimable

Table 12: Zanamivir for seasonal prophylaxis in the elderly: NAI30034 (LaForce *et al.*, 2007)⁷⁵

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. in zanamivir group	No. in zanamivir group with an event	RR (95% C.I., and p-value if available)
Symptomatic, laboratory-confirmed influenza in subjects aged 65 and above	NAI30034	950	5	946	1	0.20 (0.02 [†] to 1.72 [†])

5.2.2.3.2 Post-exposure prophylaxis with zanamivir

Post-exposure prophylaxis in mixed households

A total of 4 trials of the use of zanamivir in post-exposure prophylaxis in households were included in the review. These were studies published by Hayden *et al.*,⁴⁶ Kaiser *et al.*,⁷⁴ and a report by Monto and co-workers⁴⁷ that was published subsequent to the cut-off date for inclusion of evidence in the original HTA review.¹⁰

Hayden *et al.*⁴⁶ presented evidence from trial NAI30010 that zanamivir, when administered to household contacts (aged 5 years and above) of index cases with ILI for 10 days, conveyed a relative risk of SLCI of 0.18 (95% C.I. 0.08[†] to 0.39[†]). For individual contacts of influenza-positive index cases, the relative risk was 0.20 (95% C.I. 0.09[†] to 0.47[†]). Total adverse events occurred in 50% of the placebo arm and 44% of subjects receiving zanamivir, of which 5% and 6% respectively were possibly drug-related respectively. Withdrawals for any reason were made in 5/423 (1.2%) and 3/414 (0.7%) of the zanamivir groups. One withdrawal due to adverse effects was made in 1/414 zanamivir subjects and no placebo subjects. Study medication was discontinued due to adverse events in 0.2% of the placebo group and 0.5% of the zanamivir arm. In contacts with laboratory-confirmed influenza, the median time to alleviation of symptoms without use of medication was 8.0 days in the placebo and 5.5 days in the zanamivir groups. The percentage of cases with complications requiring antibiotics was 8% in the placebo arm and 5% in the zanamivir arm. Index cases in households randomised to receive zanamivir also received zanamivir as treatment, whilst index cases in the placebo arm received placebo treatment.

Trials NAIA2009 and NAIB2009 performed by Kaiser *et al.*⁷⁴ and reported as a single trial in the literature investigated the use of zanamivir for 5 days in household contacts of index cases with ILI. Index cases received no treatment. During the 5 days of prophylaxis, the relative risk for developing SLCI was 0.33 (95% C.I. 0.09[†] to 1.21[†]), whilst during the 10 days after initiation of medication, the relative risk for SLCI was 0.36 (95% C.I. 0.12[†] to 1.12[†]). Length of illness was shorter in the zanamivir versus placebo groups (mean duration of significant influenza-like symptoms (0.2 vs. 0.6 days, P=0.016). Potentially drug-related adverse effects occurred in 17% (25/144) of the placebo and 19% (27/144) of the zanamivir groups, which were primarily headaches, fatigue, nasal symptoms and throat discomfort.

In trial NAI30031 reported by Monto *et al.* which investigated the efficacy of zanamivir administered for 10 days as post-exposure prophylaxis in household contacts of index cases with

ILI,⁴⁷ protective efficacy for individual contacts was 79%[†] (95% C.I. 62[†] to 89[†], relative risk = 0.21) in the ITT population (when calculated by the Assessment Group) and 81%[†] amongst individual contacts of influenza-positive index cases (95% C.I. 62[†] to 90[†], relative risk = 0.19). Index cases did not receive treatment. For influenza A, the protective efficacy was 79% (95% C.I. 55 to 90, relative risk = 0.21), and for influenza B, the reported protective efficacy was 87% (95% C.I. 64 to 95, relative risk = 0.13). However, when calculated by the Assessment Group, the protective efficacy against influenza B was 79%[†] (95% C.I. 46[†] to 92[†], relative risk = 0.21). The authors observed that, in some cases, there was mismatch between the strains with which the contact cases and index cases were infected, demonstrating infection from an additional source of exposure. Significantly fewer households randomised to zanamivir prophylaxis reported a contact developing a complication of laboratory-confirmed influenza (2% versus 6%, P=0.01). Adverse events (all of which were consistent with ILI) occurred in 52% of the placebo and 42% of the zanamivir groups. Adverse events considered by the investigators to be drug-related were observed in 7% placebo vs. 6% zanamivir subjects. Total withdrawals were made in 1.7% (11/630) of the placebo and 0.9% (6/661) of the zanamivir groups. No withdrawals were due to adverse events.

Additional data relating to trial NAI30031 were identified from the sponsor submissions.⁴⁴ One contact case in the placebo group was hospitalised for more than 5 days. Two zanamivir-treated contact cases were also hospitalised. One contact case was hospitalised for less than a day and another for more than 5 days. The numbers were too low to make a meaningful comparison. For contacts with SLCI from the zanamivir-treated group, the median time to alleviation of symptoms was reduced by 1.5 days compared with the placebo group (6.5 days), demonstrating milder disease. This is supported by evidence that households randomised to zanamivir and with at least one symptomatic ILI contact case spent less time confined to bed/incapacitated, with nearly a one day difference in the mean time confined to bed/incapacitated per household between treatment arms (1.8 vs 2.6 days) (P=0.053). The need for non-prescription medications in households randomised to zanamivir was reduced compared with placebo (13% zanamivir vs. 19% placebo; P=0.076). The number of households requiring prescription medications was also reduced (11% zanamivir vs. 17% placebo subjects; P=0.100). Significantly fewer households receiving zanamivir required additional healthcare contacts (20% zanamivir vs. 32% placebo subjects; P=0.004). Across those households reporting at least one contact case with symptomatic ILI, the zanamivir group required a mean time off work/school of 10.9 hours per household compared with 15.1 hours for those in the placebo group (P=0.693).

When data relating to SLCI were pooled by meta-analysis using a random effects model, the combined protective efficacy was 79% (relative risk = 0.21, 95% C.I. =0.13 to 0.33) (test of heterogeneity: $P=0.72$, $I^2=0$). The trial reported by Kaiser *et al.*⁷⁴ differed from those by Hayden⁴⁶ and Monto⁴⁷ in that all subjects were unvaccinated and prophylaxis was administered for 5 rather than 10 days. When data abstracted from the study reported by Kaiser *et al.*⁷⁴ were removed, the relative risk decreased to 0.20 (95% C.I.=0.12 to 0.32), corresponding to a slightly higher protective efficacy of 80% (test of heterogeneity: $P=0.77$, $I^2=0$).

When data for the incidence of SLCI in contacts of influenza-positive index cases from trials NAI30010⁴⁶ and NAI30031⁴⁷ were pooled, a relative risk of 0.19 (95% C.I. 0.11 to 0.33) was obtained ($P=0.93$, $I^2=0\%$).

Halloran *et al.*⁴⁵ presented a pooled analysis of data from the trials by Hayden *et al.*⁴⁶ and Monto *et al.*,⁴⁷ proposing a prophylactic efficacy against illness of 75% (95% C.I. 54 to 86) and a reduction in infectiousness of 19% (95% C.I. -160 to 75). The secondary analysis by Halloran *et al.* also assessed pathogenicity of influenza in the treatment and control arms of the household post-exposure prophylaxis trials. Pathogenicity was defined as the ability of the virus to cause disease in an infected person and was calculated as the number of contacts with symptomatic laboratory-confirmed influenza (SLCI) divided by the number of contacts with laboratory-confirmed influenza infections (symptomatic or asymptomatic). Pathogenicity was lower amongst subjects treated with zanamivir compared with placebo. In the study reported by Hayden *et al.*,⁴⁶ pathogenicity in the control group was reported as 40/66 (61%) and in the zanamivir group, 7/26 (27%). In the study presented by Monto *et al.*⁴⁷ pathogenicity in the control group was 55/105 (52%) and in the zanamivir group this value was 12/48 (25%). Data from both of these studies included all contacts, whether or not the index case was influenza-positive.

Table 13: Zanamivir for post-exposure prophylaxis in households: NAI30010 (Hayden *et al.*, 2000)⁴⁶, NAIA/B2009 (Kaiser *et al.*, 2000)⁷⁴ and NAI30031 (Monto *et al.*, 2002)⁴⁷

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. in zanamivir group	No. in zanamivir group with an event	RR (95% C.I. and p-values if available)
Symptomatic, laboratory-confirmed influenza in contacts of all index cases	NAI30010	423	40	414	7	0.18 (0.08 [†] , 0.39 [†])
	NAI30031	630	55	661	12	0.21 (0.11 [†] , 0.38 [†])
	NAIA/B2009	144	9	144	3	0.33 (0.09 [†] , 1.21 [†])
	Pooled (random effect)					0.21 (0.13, 0.33) (P=0.72, I ² =0%)
Symptomatic, laboratory-confirmed influenza in contacts of influenza-positive index cases	NAI30010	215	33	195	6	0.20 (0.09 [†] , 0.47 [†])
Symptomatic, laboratory-confirmed influenza in contacts of influenza-positive index cases	NAI30031	398	51	368	9	0.19 (0.10 [†] , 0.38 [†])

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. in zanamivir group	No. in zanamivir group with an event	RR (95% C.I. and p-values if available)
	Pooled (random effect)					0.19 (0.11, 0.33) (P=0.93, I ² =0%)

Outbreak control in the elderly in long-term care

Two trials investigating zanamivir in preventing outbreaks of influenza in the elderly in long-term care settings were included.^{76,77,78} Both of these studies were published since the original assessment was undertaken.¹⁰

Only limited data relating to the prophylactic efficacy of zanamivir could be drawn from the trial by Gravenstein *et al.*⁷⁸ The study compared zanamivir with standard of care (rimantadine for influenza A and placebo for influenza B). As only 25 subjects were randomised during 2 outbreaks of influenza B and no subjects developed influenza, the data relating to influenza B were excluded from further analysis in the published report. Potentially drug-related adverse effects were reported in 38% of placebo and 34% of zanamivir subjects. Withdrawals from study due to adverse events occurred at rates of 0/13 in the placebo and 2/238 (0.8%) zanamivir arms. Early medication discontinuation due to adverse events was necessary in 0/13 of the placebo subjects and 11/238 (4.6%) of the zanamivir group.

The study by Ambrozaitis *et al.*^{76,77} differed from that described above in that the elderly, at-risk subjects living in long-term care had a much lower proportion of vaccination. During influenza A outbreaks, prophylaxis conferred a 32%[†] protective efficacy against SLCI when calculated by the Assessment Group (95% C.I. -27[†] to 67[†]). The authors noted that all cases of SLCI occurred in Lithuania (where none of subjects had been vaccinated). A higher protective efficacy of 70% (95% C.I. 13 to 89) was observed for laboratory-confirmed febrile illness. When subjects becoming ill on days 1-2 were excluded, the protective efficacy against SLCI when calculated by the Assessment Group was 35%[†] (95% C.I. -40[†] to 70[†]).⁴⁴ No differences in SLCI were observed by age group.⁴⁴ Complications of SLCI during the first 28 days following prophylaxis initiation were observed at a lower rate in the zanamivir-treated subjects versus placebo, although this difference was not statistically significant (5% vs 6%, P=0.653). Fewer RTIs occurred in fewer subjects in the zanamivir arm (3% vs 6%), as for complications requiring antibiotics (2% vs 3%, P=0.445). Withdrawals from the study due to adverse events were reported at the following rates: placebo: 1/249 (0.4%), zanamivir: 2/240 (0.8%). Early medication discontinuation due to adverse events was made in 2/249 (0.8%) and 6/240 (2.5%) of the placebo and zanamivir arms respectively. The following additional data were identified in the sponsor submissions.⁴⁴ Drug-related adverse effects were slightly higher in the zanamivir-treated subjects (16/242 (7%), vs. 14/252 (6%) in the placebo arm). Serious adverse events occurred in 6/252 (2.4%) of placebo and 6/242 (2.5%) of zanamivir patients. There were no serious adverse events considered to be related

to the study drug. Adverse events during prophylaxis in high-risk subjects were lower in the zanamivir group (64/202 (32%) in zanamivir and 80/215 (37%) in the placebo arms). Subjects with high-risk respiratory conditions also experienced fewer adverse events when receiving zanamivir rather than placebo (30/83 (36%) vs.32/80 (40%).

Table 14: Zanamivir in outbreak control in elderly subjects in long-term care: NAIA3004 (Ambrozaitis *et al.*, 2005)^{76,77} (9 to 10% vaccinated)

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event	Total no. in zanamivir group	No. in zanamivir group with an event	RR (95% C.I.)
Symptomatic, laboratory-confirmed influenza	NAIA3004	249	23	240	15	0.68 [†] (0.36 [†] , 1.27 [†])

5.2.2.3.3 Prophylaxis with zanamivir against experimentally-induced influenza

No trials in which zanamivir was used in accordance with licensed indications in prophylaxis against experimentally-induced influenza were identified.

5.2.2.3.4 Adherence to zanamivir prophylaxis

Adherence in the zanamivir trials appeared to be high, suggesting the use of the Diskhaler for topical oral inhalation of drug to be acceptable to study participants. In one study, 95% and 97% of placebo and zanamivir-allocated participants took study doses over a 23 to 28 day period.⁷² In another study, 90% of zanamivir and 89% of placebo subjects took at least 24 doses for at least 24 days, with fewer than 1% requiring assistance administering the drug.⁷⁵ In a further study, 97% of placebo group contacts and 99% of zanamivir group contacts took 8-10 doses (80-100%) of study medication.⁴⁷ Compliance in an additional study was high, with 98% of all participants taking 8-10 doses of study drug.⁴⁶ In the studies by Ambrozaitis *et al.*^{76,77} and Gravenstein *et al.*⁷⁸ undertaken in the elderly, subjects missing 2 or more consecutive days of medication were considered noncompliant. These proportions were very low, at 1% of total participants⁷⁶ and 2% or less.⁷⁸

5.2.2.3.5 Viral resistance to zanamivir

Several trials tested viral isolates for their susceptibility to zanamivir.^{75,46,76,78} No evidence of resistance to zanamivir was observed, although rimantadine-resistant variants were reported by Gravenstein *et al.*⁷⁸

5.2.2.3.6 Discussion of zanamivir prophylaxis evidence

Convincing data were obtained for a relatively high protective efficacy of seasonal prophylaxis in healthy adults. The evidence base has been strengthened considerably by the publication of a large-scale trial specifically investigating the efficacy of zanamivir in seasonal prophylaxis in at-risk adolescents and adults, including the elderly. A very high protective efficacy was obtained, which was also high when data were presented by age and risk subgroups. Post-exposure prophylaxis was also shown to be efficacious in preventing transmission of SLCI in households, with shorter and milder disease, fewer complications and a more rapid return to normal activities amongst subjects receiving the intervention. The evidence for outbreak control in the elderly in long-term care was more limited, but a relatively low protective efficacy against SLCI was demonstrated, with all cases occurring in unvaccinated subjects. Adverse events were similar in both treatment arms and across all studies.

5.2.3 *Assessment of effectiveness*

Discussion

The relative efficacies of amantadine, oseltamivir and zanamivir in preventing SLCI are summarised in Table 15. As in the previous HTA review,^{10,88} evidence for effectiveness of amantadine in prophylaxis was limited. However, amantadine was reported to be effective in preventing SLCI in healthy adolescents. The effectiveness of oseltamivir in prophylaxis against SLCI was demonstrated in a number of subgroups, particularly in seasonal prophylaxis in at-risk elderly subjects and in post-exposure prophylaxis within mixed households. Zanamivir was also shown to prevent influenza, most notably in seasonal prophylaxis amongst at-risk adults and adolescents, healthy and at-risk elderly individuals and in post-exposure prophylaxis in mixed households. Variation in the measurement and reporting of adverse events was observed amongst trials. However, no clear trends for the higher incidence of adverse events in treatment than control groups (and vice versa) were observed for amantadine, oseltamivir or zanamivir or across interventions. Interventions appeared to be well tolerated, with few serious drug-related adverse events and drug-related withdrawals. Less evidence was available to demonstrate the effectiveness of the interventions in reducing the impact of influenza in terms of complications, hospitalisations, length of illness and time to return to normal activities. The identified studies suggested that oseltamivir and zanamivir may be effective in preventing influenza-associated complications. Whilst there was no significant difference in numbers of subjects hospitalised between zanamivir and placebo groups, limited evidence was presented suggesting that individuals receiving zanamivir experienced a hospital stay of shorter duration. Limited evidence suggested that amantadine, oseltamivir and zanamivir were effective in shortening the length of influenza illness. The severity of symptoms was also reduced in amantadine-treated subjects. Additional evidence also suggested that fewer subjects receiving oseltamivir or zanamivir were incapacitated due to influenza illness, with a shorter time to return to normal activities. No evidence relating to health-related quality of life or mortality could be identified for inclusion in the clinical effectiveness review. As stated previously, the findings from the included trials in the clinical effectiveness review should be considered in conjunction with evidence for the development of antiviral resistance by influenza strains, particularly against amantadine, and of adverse events associated with amantadine, issues which may not be presented within the trials, but have the potential to have considerable impact upon the use of the interventions in clinical practice.

Table 15: Summary of efficacy of interventions in prophylaxis against symptomatic, laboratory-confirmed influenza (NDA indicates subgroup categories for which no data were available)

Prophylactic strategy	Relative risk of developing symptomatic, laboratory-confirmed influenza (95% C.I.)		
	Amantadine	Oseltamivir	Zanamivir
Seasonal prophylaxis in healthy children	Dosage not established in children	NDA	NDA
Seasonal prophylaxis in at-risk children	Dosage not established in children	NDA	NDA
Seasonal prophylaxis in healthy adults	0.40 (0.08 to 2.03) ⁵⁷ From 1 trial	0.27 (0.09 to 0.83) ⁶⁶ (pooled estimate from 2 trials as reported by Assessment Group)	0.32 (0.17 to 0.63) ⁷² From 1 trial
Seasonal prophylaxis in at-risk adults and adolescents	NDA	NDA	0.17 (0.07 to 0.44) ⁷⁵ From 1 trial
Seasonal prophylaxis in healthy elderly subjects	No data reported ⁵⁵	NDA	0.20 (0.02 to 1.72) ⁷⁵ From 1 trial
Seasonal prophylaxis in at-risk elderly subjects	No data reported ⁵⁵	0.08 (0.01 to 0.63) ⁶⁴ (98% subjects with concomitant disease) From 1 trial	0.20 (0.02 to 1.72) ⁷⁵ From 1 trial
Post-exposure prophylaxis in mixed households	NDA	0.19 (0.08 to 0.45) ^{48,49} From 2 trials	0.21 (0.13 to 0.33) ^{46,74,47} From 3 trials

	Relative risk of developing symptomatic, laboratory-confirmed influenza (95% C.I.)		
Prophylactic strategy	Amantadine	Oseltamivir	Zanamivir
Post-exposure prophylaxis in healthy children	Dosage not established in children	0.36 (0.15 to 0.84) ⁴⁸ From 1 trial	NDA
Post-exposure prophylaxis in at-risk children	Dosage not established in children	NDA (subjects with a number of chronic conditions excluded) ⁴⁸	NDA
Post-exposure prophylaxis in healthy adults and adolescents	0.10 (0.03 to 0.34) ⁵⁹ From 1 trial	NDA	NDA
Post-exposure prophylaxis in at-risk adults and adolescents	NDA	NDA	NDA
Post-exposure prophylaxis in healthy elderly subjects	NDA	NDA	NDA
Post-exposure prophylaxis in at-risk elderly subjects	NDA	NDA	0.68 (0.36 to 1.27) ⁷⁶ (Subjects 85% at-risk of complications)

6. ASSESSMENT OF COST-EFFECTIVENESS

This chapter reports the methods and results of a systematic review of existing economic evaluations of influenza prophylaxis and the development of an independent health economic model to evaluate the cost-effectiveness of amantadine, oseltamivir and zanamivir for the seasonal prophylaxis and post-exposure prophylaxis of influenza. The systematic review of existing economic evaluations is presented in Section 6.1. The methods and results of the Assessment Group model are presented in Sections 6.2 and 6.3 respectively.

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Methods for the systematic review of cost-effectiveness evidence

The methods used to systematically search electronic databases to identify studies relating to the cost-effectiveness of amantadine, oseltamivir and zanamivir for the post-exposure prophylaxis and seasonal prophylaxis of influenza are described in Chapter 5 (see Section 5.1 and Appendix 1). Economic evaluations identified for inclusion in the review were also handsearched to identify other relevant cost-effectiveness studies of influenza prophylaxis not identified by the electronic searches. Alongside published economic evaluations, manufacturers' submissions to NICE were also included in the review of economic evaluations, where available. Appraisal of study quality was undertaken based upon checklists for assessing quality in economic evaluations⁸⁹ and mathematical models.⁹⁰

6.1.2 Results of the systematic review of cost-effectiveness evidence

6.1.2.1 Studies included in the review of cost-effectiveness

The systematic searches identified 580 citations of studies relating to the cost-effectiveness of amantadine, oseltamivir or zanamivir for the prevention of influenza. Titles and abstracts of each citation were screened for possible inclusion in the review. Of the initial 580 citations identified by the searches, full papers of 65 studies were retrieved for further detailed evaluation. Six of these studies met the inclusion criteria for the review described in Chapter 5 (see Section 5.1.2). In addition, one sponsor submission was received from Roche; this report included the details of a mathematical model to assess the cost-effectiveness of oseltamivir for the prophylaxis of influenza. Evidence concerning cost-effectiveness was not submitted by the manufacturers of zanamivir or amantadine. In total, seven economic evaluations were included in the systematic review. A summary of studies included or excluded from the review of cost-effectiveness is presented in Figure 4.

Figure 4: Details of study inclusion and exclusions

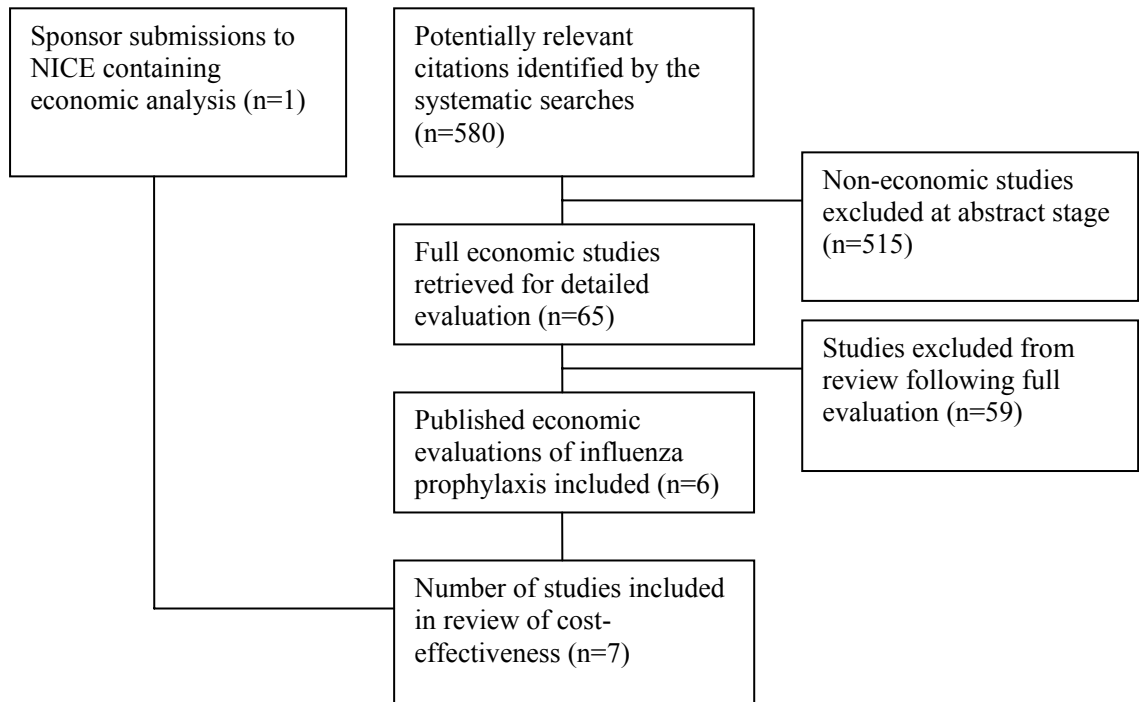


Table 16 details the characteristics of the seven studies included in the review of cost-effectiveness.

Table 16: Characteristics of studies included in the cost-effectiveness review

	Roche submission ²⁰	Sander <i>et al.</i> ⁹¹	Risebrough <i>et al.</i> ⁹²	Turner <i>et al.</i> ¹⁰	Scuffham and West ⁹³	Demicheli <i>et al.</i> ⁹⁴	Patriarca <i>et al.</i> ⁹⁵
Year of publication	2007	2006	2005	2003	2002	2000	1987
Type of economic analysis	Cost-utility analysis	Cost-effectiveness and cost-utility analysis	Cost-effectiveness analysis	Cost-effectiveness analysis and cost-utility analysis	Cost-effectiveness analysis	Cost-effectiveness analysis	Cost-effectiveness analysis
Health economic perspective	NHS	Healthcare payer	Single government-payer	NHS	Health care financier	Ministry of defence	Not reported (direct costs only included in evaluation)
Health economic comparisons	(1) Oseltamivir (2) Zanamivir (3) Amantadine (4) Usual care	(1) Oseltamivir prophylaxis, no treatment (2) No prophylaxis, no treatment (3) No prophylaxis, oseltamivir treatment	(1) Oseltamivir prophylaxis (2) Amantadine prophylaxis (3) No prophylaxis	(1) No intervention (2) Vaccination, no prophylaxis (3) No vaccination, amantadine prophylaxis (4) No vaccination, oseltamivir prophylaxis (5) No vaccination, zanamivir prophylaxis (6) Vaccination plus amantadine prophylaxis (7) Vaccination plus oseltamivir prophylaxis (8) Vaccination plus zanamivir prophylaxis	(1) No intervention (2) Opportunistic vaccination (3) Comprehensive vaccination (4) Oseltamivir chemoprophylaxis (5) Rimantidine chemoprophylaxis, (6) Oseltamivir treatment (7) Rimantidine treatment	(1) Vaccination (2) Amantadine prophylaxis (3) "NI"	(1) No control (2) Vaccination (no chemoprophylaxis) (3) Vaccination plus chemoprophylaxis (4) Outbreak control prophylaxis (no vaccination) (5) Continuous chemoprophylaxis (no vaccination)
Type of prophylaxis	Seasonal prophylaxis (28-42 days depending on drug) and post-exposure prophylaxis (10 days)	Post-exposure prophylaxis. Duration appears to be 7-10 days.	Post-exposure prophylaxis. Median duration of prophylaxis without ILI reported to be 12 days.	Seasonal prophylaxis for 6 weeks (42 days).	Seasonal prophylaxis for 4 weeks (28 days).	Seasonal prophylaxis for 62 days.	Post-exposure (outbreak) prophylaxis for 30 days. Continuous seasonal prophylaxis for 3 months (~91 days)

Population characteristics	Healthy children (1-5 years) At-risk children (1-5 years) Healthy children (1-15 years) At-risk children (1-15 years) Healthy adults (> 15 years) At-risk adults (> 15 years)	Families with members \geq 13yrs of age	Elderly vaccinated patients in long-term care facility	Healthy adults, children, residential care elderly, high-risk adults	Elderly patients (age > 65yrs in UK analysis)	British army effectives	Elderly nursing home residents
Time horizon used in the analysis	Single influenza season. Adjustments for loss in lifetime QALYs due to premature death.	Single influenza season. Adjustments for loss in lifetime QALYs due to premature death.	30 days (intended to reflect a single institutional outbreak).	Single influenza season. Adjustments for loss in lifetime QALYs due to premature death.	Typical (average) influenza season (including years of potential life lost due to premature death)	Single influenza season.	Typical (average) influenza season (including years of potential life lost due to premature death).
Health economic outcomes	Incremental cost per QALY gained (pairwise i.e. oseltamivir versus comparator).	Incremental cost per ILI case avoided; incremental cost per QALY gained.	Incremental costs (or savings) per influenza-like illness case avoided.	Incremental cost per QALY gained; incremental cost per influenza illness day avoided.	Cost per life year gained; cost per hospitalisation averted; cost per death averted; cost per morbidity day averted.	Incremental cost per avoided case.	Incremental cost per illness averted; incremental cost per hospitalisation averted; incremental cost per death averted.
Currency	Pounds sterling (£)	Pounds sterling (£)	Canadian dollars (\$)	Pounds sterling (£)	Euro	Pounds sterling (£)	US dollars (\$)
Modelling approach	Decision tree model	Decision tree model evaluated using Monte Carlo sampling	Decision tree model	Decision tree model	Decision tree model	Decision tree model	Decision tree model
Potential conflicts of interest	Manufacturer of oseltamivir (Roche)	Study funded by Hoffman La Roche	Study funded by Hoffman La Roche	One author is an <i>ad hoc</i> consultant for Hoffman La Roche and has received fees by other influenza prophylaxis sponsor companies.	Study funded by grants from Solvay, Aventis, Chiron, Berna and Medeva.	One author is an <i>ad hoc</i> consultant for Hoffman La Roche	Not reported

6.1.2.2 Review of individual economic evaluation studies

Roche submission to the National Institute for Health and Clinical Excellence²⁰

The Roche submission to the National Institute for Health and Clinical Excellence²⁰ reports the use of a mathematical model to estimate the cost-effectiveness of oseltamivir for the seasonal prophylaxis and post-exposure prophylaxis of influenza. The cost-effectiveness model was submitted to NICE for scrutiny by the Assessment Group. The model presented within Roche's submission is based on the SAVE (Simulating Anti-Influenza Value and Effectiveness) model, and as such the structure and parameter set is similar to the model reported by Sander *et al.*⁹¹ Twenty variations of the SAVE model were made available to the Assessment Group. The model compares oseltamivir prophylaxis against amantadine prophylaxis, zanamivir prophylaxis and no prophylaxis in the seasonal and post-exposure settings for four populations: otherwise healthy adults (including children > 12 years), at-risk adults (including children aged > 12 years), children aged 1-12 and children aged 1-5. The analysis for children aged 1-5 years includes only usual care as a comparator for oseltamivir due to restrictions in the licensed indications of amantadine and zanamivir prophylaxis. It should also be noted that amantadine is only licensed in children aged 10 years or over; this prophylactic option is however included in the analysis for children aged 1-12 years. The base case analysis was undertaken from the perspective of the NHS; secondary analysis was also reported from the societal perspective. The model is reported to use a lifetime horizon, whereby all important events occur within a 1-year time horizon with longer-term adjustments for QALYs lost due to premature death due to influenza-like illness. Cost-effectiveness is expressed in terms of the incremental cost per quality adjusted life year (QALY) gained, although this is based on pairwise comparisons of oseltamivir versus an alternative prophylactic option. In line with current recommendations from NICE,⁹⁶ health outcomes were discounted at a rate of 3.5%; due to the time frame used within the model, costs were not subjected to discounting.

The submission states that for oseltamivir versus amantadine and usual care, a cost-effectiveness analysis was undertaken.²⁰ The model assumes that oseltamivir and zanamivir are equivalent in terms of preventative efficacy and the submission reports a cost minimisation exercise for this comparison. However, the submission does not report the results of any head-to-head trials of zanamivir and oseltamivir prophylaxis (either superiority, non-inferiority or equivalence trials) which provide any evidence to support the assumption of equivalence. Furthermore, the systematic review of clinical effectiveness presented in Chapter 5 did not identify any clinical evidence which could be considered to validate this assumption. Consequently, the use of a cost-

minimisation analysis for oseltamivir and zanamivir appears to be unjustified; even if equivalence trials were available, the comparative prophylactic effects would remain subject to uncertainty and should therefore be considered within the health economic analysis. Importantly, the Roche submission states that the preventative efficacy estimates have a considerable impact upon the cost-effectiveness of oseltamivir prophylaxis.²⁰

Vaccination is not explicitly considered within the model either as an option for influenza prevention, or as a characteristic of the patient cohort. The studies used to estimate the preventative efficacy of zanamivir and oseltamivir included some patients who had been vaccinated and patients who had not been vaccinated.

The model uses a deterministic decision tree approach which is reported to be appropriate as it captures simple ILI pathway and events do not occur more than once.²⁰ The Roche submission argues that the results are conservative as the benefits of a contact case receiving prophylaxis and subsequently not infecting other individuals are not captured (herd immunity effects). The structural assumptions employed in the model are identical for seasonal and post-exposure prophylaxis settings. The model is reported to be based on ILI rather than true influenza alone, as it is intended to capture both the impact of true influenza and other ILI on costs and health outcomes.

The structures of the seasonal prophylaxis and post-exposure prophylaxis models are simple. For the post-exposure model, an individual who has been in contact with an ILI index case in a household may visit their GP to receive prophylaxis or they may do nothing. For the seasonal prophylaxis model, the individual may or may not have been in contact with an index case when they initiate prophylaxis. The model assumes that one household member can obtain prescriptions for 3 contacts in the household. Contact cases may then develop ILI or not. Individuals who develop ILI may be treated using oseltamivir (at-risk populations only) or usual care. Individuals who develop ILI may develop complications or not. ILI complications are treated in an inpatient or outpatient setting depending on the severity of the complication. The model includes three complications: bronchitis, pneumonia and otitis media in children. Patients who develop ILI complications may survive or die.

The model includes different attack rates for the seasonal prophylaxis models and for the post-exposure prophylaxis models; post-exposure attack rates are assumed to be higher than those for

the seasonal prophylaxis models as contacts have by definition had previous exposure to an index case who may have influenza (personal communication: Gavin Lewis, Head of Health Economics, Roche, Welwyn Garden City). The submission states that the attack rates used in the post-exposure prophylaxis model are intended to represent the proportion of patients who after being exposed to ILI go on to develop ILI.²⁰ However, these are sourced from the oseltamivir post-exposure prophylaxis trial reported by Hayden *et al.*⁴⁸ and represent only laboratory-confirmed influenza, rather than all ILI. The attack rate for adults in the seasonal prophylaxis models were taken from Hayden *et al.* (assumed to be 4.8%).⁶⁶ The attack rate for children in the seasonal prophylaxis models was reported to be estimated to “in the region of 10%”,²⁰ although the basis of this assumption is not reported in the submission. The methods used to derive upper and lower C.I.s around these attack rates are unclear from the submission.

The preventative efficacies of oseltamivir and zanamivir prophylaxis were sourced from a meta-analysis reported by Halloran *et al.* (2007).⁴⁵ The effectiveness of amantadine prophylaxis was derived from Monto *et al.*, although it should be noted that within this study patients received amantadine at a dose of 200mg which does not reflect its current licensed indications.⁹⁷ The model assumes that seasonal prophylaxis is effective across the whole influenza season; this is likely to be optimistic as patients may become susceptible to infection after they stop taking prophylaxis (See Chapter 5). Seasonal prophylaxis using zanamivir and oseltamivir are assumed to be equivalent to post-exposure prophylaxis using zanamivir and oseltamivir. The relative difference between amantadine as post-exposure prophylaxis and seasonal prophylaxis was assumed to be the same as the relative difference for oseltamivir in each setting due to a lack of clinical trial evidence. The model does not include the possibility of resistance to amantadine, oseltamivir or zanamivir.

The probability of experiencing specific complications of ILI were sourced from a study reported by Meier *et al.*¹² It should be noted that these complication rates relate to ILI rather than true influenza alone (despite the claim that the model operates in terms of ILI, the Roche model actually appears to be based on true influenza attack rates). Complication rates due to influenza in children are assumed to be the same for both the 1-5 years age group and the 1-12 years age group.²⁰ The incidence of pneumonia and bronchitis were sourced from Meier *et al.*¹² However, the submission states that the incidence of otitis media is likely to be underreported within Meier *et al.* Instead, the Roche model uses estimates sourced from oseltamivir clinical trial data,²⁰

however this estimate is only slightly higher than the estimate reported from Meier *et al.* (28% in Meier *et al.* versus 32.4% in the oseltamivir trials).

The probability of hospitalisation was taken from two US studies;^{98,99} these may not reflect UK practice. The model assumes that the probability of hospitalisation due to bronchitis is the same as that for other ILI. The probability of hospitalisation due to specific complications of ILI is assumed to be the same across the model populations. The model assumes the length of hospital stay to be 4 days for influenza and 7 days for pneumonia irrespective of patient population. The risk of death due to ILI is assumed to be the same as risk of death due to ILI complications; this assumption is unlikely to be reasonable as ILI complications are known to increase the risk of death. It is likely that this assumption would overstate the benefits of avoiding a case of influenza.

The model includes health-related quality of life adjustments for individuals who develop influenza and complications of ILI. Utility estimates for patients experiencing an episode of influenza were derived from Likert valuations of patients with laboratory-confirmed influenza within the oseltamivir treatment trials. These rating scale data were converted to VAS valuations and subsequently converted to Time Trade Off (TTO) utilities using a similar methodology to Turner *et al.*¹⁰ Utility scores for patients with ILI, bronchitis and pneumonia were based on a Dutch person-trade off study reported by Stouthard *et al.*¹⁰⁰ Utility scores are applied for the duration of illness, based on clinical trial data (personal communication: Gavin Lewis, Head of Health Economics, Roche, Welwyn Garden City). In addition, the model includes the number of potential QALYs lost due to premature death resulting from the incidence of ILI complications. Importantly, the model assumes that each potential year of life lost is valued at a state of perfect health; this assumption biases in favour of more effective prophylaxis options. The submission itself notes this assumption as a weakness of the model.²⁰

The model includes costs associated with drug acquisition, GP consultations, diagnostic tests, antibiotics and associated treatments, and hospitalisation for the treatment of ILI complications. Resource use estimates used in the model were derived from a variety of sources. Estimates of drug prescriptions, tests and investigations performed, primary and secondary care resource use for patients with influenza and certain complications were derived from the National Ambulatory Medical Care Survey (NAMCS);¹⁰¹ this is a US database, and may not reflect UK treatment patterns. Assumptions taken from this database were validated by Roche through a structured interview with one clinical expert. Sources for estimates of unit costs included the Personal Social

Services Research Unit (PSSRU),¹⁰² the MIMS database,¹⁰³ the MEDTAP database and the BNF.¹⁴ Rates of antibiotic use were based on expert opinion.

Importantly, the model does not include the costs of drug wastage and the cost of each prophylaxis course is calculated on the basis of the mean cost per tablet. The difference between the cost of oseltamivir with and without wastage is most pronounced in the seasonal prophylaxis indication for adults leading to a cost of £68.88 without wastage, and £81.80 when wastage is included (See Section 6.2.2.3). Consequently, the acquisition cost of oseltamivir as seasonal prophylaxis is underestimated in the Roche submission. However, given the assumption of equivalence between oseltamivir and zanamivir, and the lower cost of a seasonal prophylaxis course using zanamivir, oseltamivir is actually dominated by zanamivir in this indication even when wastage is excluded.

The model assumes a single cost associated with hospitalisation due to ILI or ILI complications; this is quoted as £286 per day. This cost estimate is based on the cost of an inpatient day for mental health services; the justification for using this hospitalisation cost is unclear.¹⁰² The model does not explicitly include the possibility of patients requiring ITU care or mechanical ventilation. A further potential problem with the SAVE model is that it assumes that all patients with ILI will incur GP consultation costs; this is not necessarily true as not all patients with ILI (whether influenza or not) will consult their GP.¹⁰⁴ Further, the model does not consider any costs associated with adverse events of prophylaxis or treatment using amantadine, oseltamivir or zanamivir.

The submission includes the details of 1-way and probabilistic sensitivity analysis to explore uncertainty surrounding model parameters. The probabilistic sensitivity analysis was undertaken using @RISK software alongside Microsoft Excel.

Cost-effectiveness results presented by Roche

It should be noted from the outset that the cost-effectiveness analysis presented within the Roche submission to NICE was not fully incremental; instead 20 incremental cost-effectiveness ratios were presented for pair-wise comparisons of oseltamivir versus amantadine, oseltamivir versus zanamivir and oseltamivir versus usual care for each population group across seasonal and post-exposure prophylaxis settings. The Assessment Group re-analysed the results presented within the Roche submission to generate fully incremental estimates of the cost-effectiveness of each

prophylactic option compared against each other and usual care. The results of the re-analyses of the post-exposure models are presented in Tables 17 to 20.

Table 17: Incremental cost-effectiveness results – post-exposure prophylaxis for children aged 1-5 years

Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	£44.54	109.619	-	-	-
Oseltamivir	£73.54	109.624	£29.00	0.005	£5,800

Table 18: Incremental cost-effectiveness results – post-exposure prophylaxis for children aged 1-12 years

Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	£44.84	108.678	-	-	-
Amantadine	£122.75	108.68			dominated by oseltamivir
Oseltamivir	£84.74	108.683	£39.90	0.005	£7,980
Zanamivir	£139.34	108.683	-	-	dominated by oseltamivir

Table 19: Incremental cost-effectiveness results – post-exposure prophylaxis for otherwise healthy individuals over 12 years of age

Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	£12.61	91.336	-	-	-
Amantadine	£89.65	91.337	£77.04	0.001	extendedly dominated
Oseltamivir	£92.84	91.339	£3.19	0.002	£26,743
Zanamivir	£126.35	91.339			dominated by oseltamivir

Table 20: Incremental cost-effectiveness results – post-exposure prophylaxis for at-risk individuals over 12 years of age

Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	£13.30	85.119	-	-	-
Amantadine	£89.54	85.138	£76.24	0.019	extendedly dominated
Oseltamivir	£91.50	85.159	£78.20	0.04	£1,955
Zanamivir	£123.60	85.159	-	-	dominated by oseltamivir.

The results of the post-exposure models presented in Tables 17 to 20 suggest that the incremental cost-effectiveness of oseltamivir for post-exposure prophylaxis is consistently expected to be below £27,000 across all paediatric and adult populations. The finding that zanamivir is consistently dominated by oseltamivir is unsurprising, as the model assumes oseltamivir and zanamivir have equivalent preventative efficacy, no differential impact on health-related quality of life due to adverse events, yet zanamivir is assumed to be more expensive than oseltamivir over the course of prophylaxis (the submission does not include the proposed price reduction for zanamivir). Uncertainty surrounding the relative efficacies of oseltamivir and zanamivir are not included in the model. The model suggests that amantadine is dominated or extendedly dominated by oseltamivir within each indication.

The results of the re-analyses of the seasonal prophylaxis models are presented in Tables 21 to 24.

Table 21: Incremental cost-effectiveness results – seasonal prophylaxis for children aged 1-5 years

Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	£28.58	109.623	-	-	-
Oseltamivir	£168.25	109.626	£139.67	0.003	£46,556.67

Table 22: Incremental cost-effectiveness results – seasonal prophylaxis for children aged 1-12 years

Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	£20.72	108.681	-	-	-
Amantadine	£95.48	108.683	£74.76	0.002	£37,380
Oseltamivir	£214.04	108.684	£118.56	0.001	£118,560
Zanamivir	£306.32	108.684			dominated by oseltamivir

Table 23: Incremental cost-effectiveness results – seasonal prophylaxis for otherwise healthy individuals over 12 years of age

Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	£8.18	91.337	-	-	-
Amantadine	£87.22	91.338	£79.04	0.001	£79,040
Zanamivir	£302.07	91.339	£214.85	0.001	£214,850
Oseltamivir	£302.48	91.339			dominated by zanamivir

Table 24: Incremental cost-effectiveness results – seasonal prophylaxis for at-risk individuals over 12 years of age

Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICER
Usual care	£8.63	85.134	-	-	-
Amantadine	£86.93	85.146	£78.30	0.012	£6,525.00
Zanamivir	£300.78	85.16	£213.85	0.014	£15,275.00
Oseltamivir	£301.21	85.16			dominated by zanamivir

The re-analysis of the seasonal prophylaxis models presented in Tables 21 to 24 suggests that the incremental cost-effectiveness of oseltamivir is expected to be around £46,000 per QALY gained for children aged 1-5 compared against best supportive care, and around £116,000 per QALY gained for children aged 1-12 compared against amantadine. As noted above, amantadine is only licensed in children aged over 10 years, hence this comparison can only be considered valid for children aged 11 or 12 years of age. Oseltamivir is expected to be dominated by zanamivir for otherwise healthy and at-risk individuals aged over 12 years of age. The Roche models suggest that the prophylaxis using amantadine or zanamivir are likely to have cost-effectiveness ratios below £20,000 per QALY gained in the at-risk population aged 12 years or older.

The Roche submission reported the results of several one-way sensitivity analyses as well as probabilistic sensitivity analysis for each of the pair-wise cost-effectiveness comparisons. The one-way sensitivity analysis was undertaken to explore impact of changing assumptions regarding attack rates, GP visits to receive prophylaxis, health utilities for ILI, bronchitis and pneumonia, preventative efficacy rates and the number of years of life lost. The seasonal prophylaxis models and the post-exposure prophylaxis models were reported to be highly sensitive to changes in assumptions regarding attack rates and the number of GP visits required per household.

In a similar manner to the deterministic health economic analysis, the results of the probabilistic sensitivity analysis were reported using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) only for pair-wise comparisons of oseltamivir versus amantadine and oseltamivir versus usual care. This is inappropriate as all options should be compared incrementally. A fully incremental re-analysis of uncertainty was not possible due to the structural limitations of the model (the model was capable of comparing only 2 prophylaxis options simultaneously). In addition, the submission states that pair-wise comparisons were not undertaken for oseltamivir versus zanamivir due to the assumption of equivalence between these

products; this is inappropriate as there is clearly uncertainty surrounding the relative efficacies of these drugs. Consequently, the correct interpretation of the probabilistic sensitivity analysis is problematic.

Tables 25 and 26 show the probability that oseltamivir has a cost-effectiveness ratio that is better than £20,000 and £30,000 per QALY gained as compared against the next best comparator identified within the incremental re-analysis of the deterministic cost-effectiveness analysis submitted by Roche. These tables have been constructed by the Assessment Group from the simulation outputs used to generate the CEACs within the Roche submission.

Table 25: Probability oseltamivir has a cost-effectiveness ratio better than £20,000 per QALY gained and £30,000 per QALY gained – post-exposure prophylaxis

Population	Comparison (non-dominated)	Probability cost-effective at £20,000 per QALY gained	Probability cost-effective at £30,000 per QALY gained
Children aged 1-5 years	Usual care	0.91	0.97
Children aged 1-12 years	Usual care	0.94	0.99
Otherwise healthy individuals aged > 12 years	Usual care	0.18	0.65
At-risk individuals aged > 12 years	Usual care	1	1

Table 26: Probability oseltamivir has a cost-effectiveness ratio better than £20,000 per QALY gained and £30,000 per QALY gained – seasonal prophylaxis

Population	Comparison (non-dominated)	Probability cost-effective at £20k	Probability cost-effective at £30k
Children aged 1-5 years	Usual care	0.07	0.2
Children aged 1-12 years	Amantadine	0.01	0.04
Otherwise healthy individuals aged > 12 years	Dominated by zanamivir within the deterministic analysis	n/a	n/a
At-risk individuals aged > 12 years	Dominated by zanamivir within the deterministic analysis	n/a	n/a

Tables 25 and 26 suggest that the probability that post-exposure prophylaxis using oseltamivir is optimal at thresholds of £20,000 is in excess of 0.90 in the paediatric and at-risk populations (in

other words, there is a high probability that oseltamivir produces more net benefit than its relevant comparators at a threshold of £20,000 per QALY). The probability that oseltamivir post-exposure prophylaxis has a cost per QALY ratio below £20,000 is around 0.18 for healthy adults; the probability that oseltamivir post-exposure prophylaxis has a cost per QALY ratio below £30,000 is around 0.65 in the healthy adult group. In the seasonal prophylaxis setting, oseltamivir is unlikely to be cost-effective at £30,000 per QALY gained in children aged 1-5 and 1-12 years. Within its adult indications, oseltamivir was dominated by zanamivir within the deterministic analysis; given the assumption of equivalent efficacy between oseltamivir and zanamivir, one would expect zanamivir to be optimal irrespective of the willingness-to-pay threshold assumed.

Sander *et al.* Post-exposure influenza prophylaxis with oseltamivir: Cost effectiveness and cost utility in families in the UK⁹¹

Sander *et al.* present the methods and results of a cost-effectiveness and cost-utility analysis of oseltamivir as post-exposure prophylaxis from the perspective of the UK NHS (health care payer perspective). The model simulates the experience of 100,000 hypothetical family members aged ≥ 13 who receive oseltamivir prophylaxis or no prophylaxis (with or without treatment for symptomatic ILI). The cost-effectiveness and cost-utility of oseltamivir prophylaxis is estimated through comparison with two alternatives: (1) no prophylaxis and no treatment, and (2) no prophylaxis followed by treatment of ILI using oseltamivir. The model does not include options for sequential prophylaxis *and* treatment using antivirals, nor does it include other licensed prophylactic options such as amantadine or zanamivir. The health economic outcomes used within the analysis were the incremental cost per ILI case avoided, and the incremental cost per QALY gained. The analysis uses a time horizon of a single influenza season; the cost-utility analysis also includes adjustments for QALYs lost due to premature death due to secondary complications of influenza.

The model uses a decision tree modelling approach, evaluated using Monte Carlo simulation methods to evaluate first-order uncertainty surrounding costs and health outcomes for each option. The decision tree model includes chance nodes describing the uncertainty surrounding the probability of ILI infection, the treatment of ILI (oseltamivir or no antiviral treatment), the onset of complications due to ILI or influenza, and subsequent outpatient treatment, inpatient treatment and eventual death. The model does not include the impact of herd immunity upon clinical effectiveness or cost-effectiveness outcomes. The model includes two types of influenza-related complications: pneumonia and bronchitis. These are reported to have been included in the model

due to their high incidence within the model population, due to their definite association with influenza, and because oseltamivir reduces the risk of these complications and other hospitalisation.⁹¹ The model assumes that patients cannot develop more than one complication due to ILI.

The base case ILI attack rate in contact cases was assumed to be 8%, based on clinical trials of oseltamivir prophylaxis within households.^{49,48} The diagnostic certainty rate for GP (i.e. sensitivity) was assumed to be 70%, however a reference is not provided for the source of this assumption. The rate of true influenza infection in index cases was taken from clinical trials of oseltamivir as prophylaxis.^{49,48} The model assumes that oseltamivir reduces the number of cases when used prophylactically, and the duration of disease when used as treatment. The model assumes that whilst prophylaxis may reduce the probability of experiencing ILI, and hence the probability of secondary complications, it does not affect the clinical course of complications once they manifest. The probability of avoiding clinically proven influenza using post-exposure prophylaxis using oseltamivir was assumed to be 89%, based on a clinical trial reported by Welliver *et al.*⁴⁹ This estimate of efficacy is noticeably higher than the PEP efficacy rates demonstrated within the trial reported by Hayden *et al.* (62%)⁴⁸ which are not used in the base case health economic analysis.

The model includes health-related quality of life impacts associated with the incidence of ILI, bronchitis, pneumonia and QALY losses due to premature death. The approach to valuing the number of QALYs lost due to premature death from secondary influenza complications is similar to that reported by Turner *et al.*,¹⁰ but certain underlying assumptions differ from the model. Patient health-related quality of life was measured within the clinical trials used to inform the health economic model using Likert visual analogue scales for health, sleep and usual activities (based on studies WV15670, WV15671, WV 15730 and M76001). VAS scores were transformed into Time Trade Off index utilities using an algorithm based on econometric work undertaken by the researchers at the University of York.¹⁰⁵ Time with complications was multiplied by their respective utility scores to estimate QALY losses. Life years lost due to premature death were calculated using UK life tables, based on an assumed age at death. The analysis assumes that premature death due to complications was associated with a loss of 34.24 life years, each of which is valued at a state equivalent to perfect health (1 life year lost is assumed to equal 1 QALY lost). As noted above, this assumption is also applied within the Roche submission to NICE.²⁰ This assumption is highly optimistic, and favours oseltamivir prophylaxis option as this

has the greatest efficacy in terms of avoiding influenza and related complications. The impact of this assumption on the cost-effectiveness of oseltamivir prophylaxis is not addressed within the sensitivity analysis. The majority of events occur within 1 year and were not subjected to discounting which is appropriate. The loss of QALYs due to premature death was discounted at a rate of 1.5% per year.

The cost impact of oseltamivir-related adverse events are not included in the model; the authors state that the adverse events observed in clinical trials of oseltamivir were “*generally mild, self-limiting and did not result in healthcare service utilisation*”⁹¹ The impact of adverse events of treatment using oseltamivir is however included in the QALY estimate, which serves to reduce the number of QALYs gained for the oseltamivir treatment group. Resource use data relating to the prevention and treatment of influenza was derived from the National Ambulatory Medical Care Survey.¹⁰¹ This resource use relates to resource use estimates for drug prescriptions, diagnostic tests and investigations for ILI, bronchitis and pneumonia, and primary and secondary care admissions for patients with influenza and selected complications. Other resource use items included the cost of oseltamivir, GP visits, specialist visits, antibacterials for the treatment of ILI-related complications, bronchitis, pneumonia, over-the-counter medications and hospitalisation. The use of these resource use data may be problematic, as US treatment patterns for influenza-like illness and secondary complications may not reflect those of the UK.

A number of sensitivity analyses were undertaken alongside the underlying probabilistic analysis. This included varying the ILI attack rate for contact cases, varying assumptions regarding healthcare resource utilisation and assumptions regarding the diagnostic accuracy of GPs in identifying influenza, as well as undertaking the analysis from the societal perspective. The sensitivity analysis also considers the impact of a lower efficacy rate of 60%, which reflects the results of the oseltamivir PEP clinical trial reported by Hayden *et al.*⁴⁸ The simulation model uses Monte Carlo sampling to handle both first- and second-order uncertainty surrounding costs and health outcomes.

Under the base case assumptions, the model estimates the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis to be £467 per ILI case avoided, whilst the incremental cost-utility is estimated to be £29,938 per QALY gained. The incremental cost-effectiveness and cost-utility of oseltamivir prophylaxis versus no prophylaxis followed by oseltamivir treatment was estimated to be £451 per ILI case avoided and £52,202 per QALY

gained. The results of the uncertainty analysis suggested that reduced prophylactic effectiveness for oseltamivir results in considerably less favourable estimates of cost-effectiveness and cost-utility. Assumptions concerning higher attack rates and reduced GP utilisation resulted in marked improvements in the cost-effectiveness and cost-utility of oseltamivir. When the economic analysis was undertaken from the societal perspective, oseltamivir was reported to dominate the no prophylaxis options. The probabilistic sensitivity analysis suggests that the probability that post-exposure prophylaxis using oseltamivir has a cost-effectiveness that is better than £30,000 is 50% when compared against no prophylaxis, and 10% when compared against oseltamivir treatment.

Risebrough *et al.* Economic evaluation of oseltamivir phosphate for postexposure prophylaxis of influenza in long-term care facilities⁹²

Risebrough *et al.* report the methods and results of a decision-analytic model to evaluate the cost-effectiveness of post-exposure prophylaxis versus no prophylaxis in long-term care facilities. The model includes three treatment options: post-exposure prophylaxis using oseltamivir, post-exposure prophylaxis using amantadine, and no prophylaxis. The analysis was undertaken from the perspective of the single government-payer in Canada. Zanamivir was excluded from the analysis due to difficulties in drug administration experienced by elderly patients. The primary health economic outcome for the analysis was reported to be the incremental cost per influenza-like illness case avoided as compared against usual care (no prophylaxis), however the model results are presented only in terms of costs and consequences which are not synthesised to produce incremental cost-effectiveness ratios. All patients are assumed to have received prior vaccination for influenza. The model uses a time horizon of 30 days, which is intended to represent the approximate duration of one institutional outbreak.

The model uses a decision tree structure to evaluate the costs and health outcomes associated with each of the three options. The first chance node relates to whether an outbreak occurs within the given care facility. Following an outbreak, patients in the prophylaxis arms begin post-exposure prophylaxis for 12 days using either amantadine or oseltamivir. For patients receiving amantadine, the model includes the possibility of developing amantadine resistance, whilst adverse events may be experienced by individuals receiving either prophylactic option. The model then includes the possibility that the individual develops ILI from which they may experience a complication, recover without complication, or die. If the ILI case is complicated, the patient may be treated in the care facility or alternatively they may be transferred to hospital.

The model does not include the expected effects of herd immunity. The model does not differentiate between specific complications experienced by individuals developing ILI. The incidence of ILI complications has an impact only on the cost side of the model; the impact of ILI and prophylaxis on health-related quality of life is not included in the economic analysis.

The authors assume an ILI attack rate in vaccinated residents of 17%. This estimate was reported to have been derived from a number of case control studies and randomised controlled trials. The precise statistical methods used to derive this baseline attack rate (for example statistical meta-analysis) is unclear. The model does not include the possibility of patients receiving antiviral treatment following the onset of ILI. At the time of the analysis, the authors reported that there were no RCTs evaluating oseltamivir or amantadine as post-exposure prophylaxis in the nursing home setting.⁹² Therefore, the authors assumed that post-exposure prophylaxis using oseltamivir would be at least as effective as seasonal prophylaxis using oseltamivir, and that amantadine would be at least as effective as rimantidine. Relative risk reductions in ILI incidence of 60% and 63% were assumed for amantadine and oseltamivir respectively. The authors assumed prophylaxis using either amantadine or oseltamivir would result in a 50% relative reduction in antibiotic use, serious complications and death; no evidence is provided to support the use of this assumption. The model includes the possibility of patients withdrawing from therapy due to the incidence of adverse events.

The model includes acquisition costs for amantadine and oseltamivir, serum creatinine tests, oral antibiotics, as well as the costs of hospitalisation for the management of influenza or other respiratory infections, and the cost of hospitalisation due to adverse events. A cost is included for death resulting from ILI in an acute hospital. Dose adjustments are included in the cost of amantadine. Acquisition costs for amantadine were taken from the Ontario Drug Benefit Formulary, whilst the cost of oseltamivir was based on the manufacturers wholesale price. Serum creatinine test costs were taken from the Ministry of Health Physician Schedule of Benefits.¹⁰⁶ The costs of hospitalisation due to adverse events were based on authors assumptions. The cost of transfer to an acute care facility for treatment of influenza complications was based on the average of all hospitalisations for influenza or other respiratory procedures per case mix group, derived from the Ontario Case Costing Initiative.¹⁰⁷ Higher costs were assigned to those complications which have potentially life-threatening complexity; the same cost was assumed irrespective of the patient's outcome. Neither costs nor health outcomes were adjusted for time preferences.

The authors undertook one-way sensitivity analysis and best-worse case scenario analysis, varying cost and event probability parameter values to identify the key determinants of cost-effectiveness. The sensitivity analysis explored the impact of changing assumptions concerning the relative efficacy of amantadine and oseltamivir versus placebo, the cost of serum creatinine testing, the incidence of adverse events, the attack rate for ILI, the outbreak rate, and the rate of amantadine resistance. The sensitivity analysis also explored the impact of including the costs of the cost of nurse or pharmacist time to review the patient chart and calculate the creatinine clearance. Finally, the cost-effectiveness of rimantidine was also explored within the sensitivity analysis. Probabilistic sensitivity analysis was not undertaken within this study.

In the base case, the study suggests that post-exposure prophylaxis using oseltamivir or amantadine is expected to reduce the incidence of ILI cases, hospitalisation and death as compared against no prophylaxis. Both options are also expected to produce cost-savings as compared against no prophylaxis. When compared in terms of the incremental cost per ILI case avoided, oseltamivir is expected to dominate both amantadine and no prophylaxis. The sensitivity analysis suggests that the analysis is sensitive to the amantadine dose calculation. The use of alternative assumptions concerning the attack rate for ILI, the outbreak rate, and the rate of amantadine resistance did not affect the base case conclusions. The sensitivity analysis also suggested that if rimantidine were available in Canada, at 32% of the cost of oseltamivir, it would be the least expensive option; however, the authors suggest that oseltamivir would remain the most effective option. The worst-case scenario for amantadine resulted in improvements in ILI cases avoided albeit at a greater cost than no prophylaxis. In the worst-case scenario, oseltamivir remained more effective and less costly as compared with the amantadine and no prophylaxis options.

Turner *et al.* Systematic review and economic decision modelling for the prevention of influenza A and B¹⁰

Turner *et al.* report the methods and results of a mathematical decision model to evaluate the cost-effectiveness of amantadine, zanamivir and oseltamivir in the prevention and treatment of influenza A and B. This study formed the assessment report used to inform the 2003 NICE appraisal of oseltamivir and amantadine for the prevention of influenza.¹⁶ The analysis was undertaken from the perspective of the NHS, although reduced time from work is considered within the sensitivity analysis. The model includes eight preventative options: (1) no prophylaxis, (2) vaccination, (3) amantadine prophylaxis, (4) zanamivir prophylaxis, (5) oseltamivir

prophylaxis, (6) vaccination plus amantadine prophylaxis, (7) vaccination plus zanamivir prophylaxis and (8) vaccination plus oseltamivir prophylaxis. All antiviral strategies relate to seasonal prophylaxis over a period of 6 weeks (42 days). Post-exposure prophylaxis using amantadine, oseltamivir and zanamivir are not included in the economic model; the model has since been adapted to examine the cost-effectiveness of post-exposure prophylaxis, however, the results of this work have not been released into the public domain.¹⁰⁸ The assessment report also evaluated the cost-effectiveness of treatment options for influenza A and B; however these options are considered separately to the antiviral prophylaxis options. Cost-effectiveness is expressed in terms of the incremental cost per QALY gained and the incremental cost per influenza illness day avoided. The model uses a time horizon of a single influenza season, and includes QALY losses resulting from premature death due to influenza. The model estimates the cost-effectiveness of prophylaxis in four discrete subgroups: healthy adults, high-risk adults, children and residential care elderly.

The model uses a decision tree approach to evaluate the costs and health outcomes for each prophylactic option. Chance nodes are used to describe the probability of a patient developing influenza (dependent on the prophylaxis option), and QALY losses and costs are assigned to each branch. Costs and benefits for patients with influenza are modified for strategies including vaccination, on the basis that vaccination may reduce the severity of secondary complications. The model includes two complications: pneumonia and otitis media (the latter is included only in the paediatric model).

The model operates on the basis of true influenza rather than influenza-like illness (ILI). As treatments for influenza are evaluated separately to prophylaxis as vaccination options, the exclusion of ILI may be reasonable as differences in costs and benefits in patients with ILI which is not true influenza are not expected to differ between prophylaxis options (and would therefore cancel out in the cost-effectiveness calculations). Baseline attack rates for true influenza were estimated using random effects meta-analyses of placebo arm outcomes from relevant trials included in the systematic review. The preventative efficacy of each prophylaxis option was estimated by calculating the odds ratio of developing influenza, adjusted for the probability of compliance. The protective benefit of the prophylaxis options was assumed to apply only to the period over which patients are taking prophylaxis. The benefit of prophylaxis in vaccinated patients was assumed to be cumulative, such that the relative benefit of prophylaxis was applied to the baseline influenza attack rate excluding the expected number of cases already protected by

prior vaccination. The probability that an individual presents to the GP with influenza was based on a UK study of excess ILI consultations over a 10-year period reported by the Royal College of General Practitioners⁵ and the baseline influenza attack rate derived from the meta-analysis.¹⁰ The probability of presentation was estimated by dividing the number of excess ARI consultations by the expected number of individuals who are expected to develop influenza within each population group. As the number of patients who present with true influenza is unknown, the numerator for this calculation was based on excess ARI consultations, assuming that all excess consultations are due to influenza. This approach therefore implies that the rate of non-influenza ILI consultations are constant over the year, and is likely to represent the maximum theoretical impact of influenza over a season.⁵

The model includes health-related quality of life impacts associated with the incidence of influenza, adverse events resulting from the use of amantadine, the incidence of pneumonia and otitis media, and a QALY loss resulting from premature death due to complications. QALY losses due to influenza were derived from VAS scores collected within trials of oseltamivir for the treatment of influenza (studies WV15670, WV15671, WV15730, WV15819, WV15876, WV15978, WV15812 and WV15872). QALYs were derived by re-calibrating Likert score data to VAS scores which were then converted into Time Trade Off scores.¹⁰⁵ QALY losses due to premature death were estimated based on mean age of influenza deaths, remaining life expectancy, discount rates and age-specific utility scores. QALY losses due to premature death were estimated based on the mean age of death due to influenza within the model subgroup, remaining life expectancy, age-specific utility scores and the discount rate. QALYs lost due to premature death were discounted at a rate of 1.5% in the base case analysis in line with recommendations from NICE at the time of the assessment. The valuation of serious adverse events due to amantadine was based on an assumed EQ-5D profile. Adverse events resulting from the use of oseltamivir and zanamivir were assumed to have no impact upon health-related quality of life. The valuation of secondary complications of influenza (pneumonia and otitis media) was based on WHO disability weights for lower respiratory conditions.¹⁰⁹

The model includes the costs associated with GP visits, prophylaxis and vaccination acquisition costs, and inpatient hospital stays. The cost of a GP consultation in the surgery or at home was derived from the PSSRU; this cost was weighted by the frequency of home and surgery visits to generate a mean cost per visit for the elderly population and for the healthy adult population. The mean cost of a GP visit for the paediatric model was assumed to be the same as for the healthy

adult model. The cost of antiviral prophylaxis was based on a 6-week course assuming 50% of the recommended dose. Each drug cost was inflated to account for container fees and pharmacy prescribing fees, although these cost adjustments do not form part of NICE's methods guidance.⁹⁶ The cost of vaccination was taken from payments to GPs for vaccination and included an administration cost. Hospitalisation costs were based on Healthcare Resource Groups (HRGs); the HRGs assumed for hospitalisation differed according to the population under consideration. Owing to the short time horizon for the analysis, costs were not subjected to discounting.

Simple uncertainty analysis was undertaken using one-way and two-way sensitivity analysis surrounding the base case model specification. This included varying assumptions surrounding influenza attack rates, the probability of death, and the value of QALY losses due to premature death resulting from influenza complications. Joint uncertainty in model parameters was evaluated using probabilistic sensitivity analysis; parameter uncertainty was propagated through the model using Monte Carlo sampling techniques. However, results are presented as C.I.s surrounding the cost-effectiveness ratio; cost-effectiveness acceptability curves for prophylaxis are not presented within the report.

In the base case, amantadine, oseltamivir and zanamivir were dominated by vaccination. The combined option of amantadine plus vaccination yielded an incremental cost per QALY gained of £28,920 compared with vaccination alone within the residential care population. The incremental cost-effectiveness of amantadine for all other populations was considerably higher, ranging from £124,854 to £909,210. When adverse events were excluded from the model, the results of the probabilistic sensitivity analysis suggested that the probability that amantadine resulted in an incremental cost per QALY gained below £30,000 was around 45% for the elderly residential care population. This is however a conservative assumption which favours amantadine. For the other populations, the probability that amantadine has an incremental cost per QALY gained below £30,000 was below 1%. For the combined option of oseltamivir plus vaccination, the incremental cost per QALY gained for the residential population was £64,841 compared with vaccination alone. For all of the remaining populations, the incremental cost-effectiveness ratios were markedly less favourable, ranging from £251,004 to £1,693,168. The probabilistic sensitivity analysis suggested that the probability that oseltamivir has an incremental cost per QALY gained that is below £30,000 was 3% or lower for all populations. Zanamivir was also dominated by vaccination. For the combined option of zanamivir plus vaccination, the incremental cost per QALY gained for the residential population was £84,682 compared with

vaccination alone. The incremental cost per QALY gained ranged from £324,414 to £2,188,039 for the remaining populations. The uncertainty analysis suggested that the probability that zanamivir has a cost-effectiveness ratio that is below £30,000 per QALY gained was less than 1%.

Scuffham and West – Economic evaluation of strategies for the control and management of influenza in Europe⁹³

Scuffham and West report the use of a decision model to estimate the incremental cost-effectiveness of six influenza control strategies as compared against no intervention in elderly populations in England, France and Germany. The options included in the model are opportunistic vaccination, comprehensive vaccination, chemoprophylaxis using oseltamivir, chemoprophylaxis using rimantidine, treatment using oseltamivir, and treatment using rimantidine. The costs and health effects of zanamivir and amantadine were not included in the model. The analysis was undertaken from the perspective of the health care financier for each country. The analysis reports marginal health economic outcomes in terms of the cost per hospitalisation averted, cost per death averted, cost per life year gained and cost per morbidity day averted. The time horizon used within the model was a typical (average) influenza season.

The modelling approach adopted by the authors was not explicitly stated, however the text indicates that a decision tree modelling methodology was employed. The model estimates the proportion of patients who develop clinical symptoms of ILI, a proportion of whom will visit their GP for treatment and may receive symptomatic treatment or antibiotics for complications of ILI. The model includes the possibility that patients who develop complications may require hospitalisation and the possibility that complications may lead to premature death. The model does not include any herd immunity effects associated with vaccination or prophylaxis.

The model includes the cost of hospitalisation due to complications including influenza and pneumonia, other ARI and congestive heart failure. The model does not include any valuation of the impact of influenza complications upon health-related quality of life, hence complications appear to only be included in the model in terms of costs avoided. The number of premature deaths due to influenza by age group was taken from a study by Fleming *et al.*⁵ Based on UK hospitalisation data, the authors estimated the years of potential life lost for the healthy 80 year-old population to be 7 years; owing to the likely presence of co-morbidities, the authors assumed that premature death due to influenza would result in an mean loss of 3.5 potential years of life.

The authors did not discount costs as almost all relevant events occur within a single influenza season. The potential life years lost due to premature death resulting from secondary influenza complications was discounted at a rate of 1.5%.

The authors assumed an attack rate for ILI of 10%. This estimate was sourced from excess GP consultation rates, current rates of vaccination and expert opinion. Excess GP consultation rates were taken from a study based on national data collected by the Weekly Returns Service (WRS) of the Royal College of General Practitioners and from national data for hospital admissions and deaths.¹¹⁰ These are modelled independently of ILI attack rates. The probability of after-hours GP consultations was derived from expert opinion, whilst the percentage of GP home visits was taken from the UK population-based study of incidence, risk factors, complications and drug treatment of influenza reported by Meier *et al.*¹² The efficacy of chemoprophylaxis was taken from a review reported by Demicheli *et al.*⁹⁴ Based on this review, the authors assumed that neuraminidase inhibitors, specifically oseltamivir, reduce the incidence of influenza by 55%, whilst ion-channel-inhibitors, specifically rimantidine, reduce the incidence of influenza by 35%. The authors assumed that when taken as prophylaxis, these therapies result in the same proportional reductions as vaccination in terms of GP consultation, hospitalisation and death. The model does not appear to include parameters describing the probability that a patient with ILI has true-influenza. However, the estimates of the clinical efficacy of prophylaxis relate specifically to laboratory-confirmed influenza, not ILI. This appears to represent an inconsistency in the parameterisation of the model.

The model includes a number of different resource use items including GP consultations, after-hours visits and home visits, antibiotics, hospitalisations due to influenza and pneumonia, other respiratory illness and congestive health failure, vaccination acquisition and administration costs, and antiviral prophylaxis and treatment. Unit costs were derived from the PSSRU,¹¹¹ national sources of hospitalisation data¹¹² Department of Health publications on prescription costs¹¹³ and national tariff estimates.¹¹⁴ The authors assumed that prophylaxis and treatment did not result in any adverse events. Non-compliance with prophylaxis was included in the model at a weekly rate of 5%.

The authors report the results of a large number of simple sensitivity analyses relevant to each option for the prevention and/or treatment of influenza. This included varying assumptions concerning the years of potential life lost due to premature death due to influenza complications,

the discount rate for health outcomes, ILI attack rates, excess GP consultations, the number of excess hospital admissions for influenza complications and the number of premature deaths due to ILI complications. Specifically with regard to the prophylaxis options, the sensitivity analysis included varying assumptions regarding GP consultations to receive chemoprophylaxis, compliance rates, the dosage of oseltamivir, the percentage of prophylaxis used during the 4-weeks peak of the influenza season, and drug price. Despite the extensive use of simple sensitivity analysis, the authors did not undertake probabilistic sensitivity analysis, and the impact of joint uncertainty in model parameters is not captured within the analysis.

Under the base case assumptions, the authors report the marginal cost per life year gained for oseltamivir to be 197,919 Euro when compared against no intervention. The cost per hospitalisation averted for oseltamivir is reported to be 114,774 Euro, whilst the cost per death averted is reported to be 657,544 Euro. The cost per morbidity day averted, excluding and including deaths, is reported to be 1,198 Euro and 373 Euro respectively. The results of the sensitivity analysis are reported only in terms of the benefit:cost ratio (ratio of the strategy costs minus the costs of hospitalisation averted) and the cost per morbidity day averted. The findings of the sensitivity analysis based on the latter outcome measure are particularly difficult to interpret from a policy context. The analysis is reported to be most sensitive to changes in the timing of the programme, the price and dose of the prophylactic, and the assumed loss in potential life years due to premature death.

Demicheli *et al.* Prevention and early treatment of influenza in health adults⁹⁴

Demicheli and colleagues report the use of model to estimate the cost-effectiveness and cost-utility of influenza prevention in healthy adults from the perspective of the Ministry of Defence (MOD). The health economic analysis was undertaken alongside 3 ongoing Cochrane reviews; the results of these reviews led to marked changes in the scope of proposed economic analysis and the final economic models presented in the paper.⁹⁴ The authors state that potential preventative options to be evaluated within the final model were vaccination, oral amantadine, oral rimantadine, and oral oseltamivir. However, costs and health outcomes are presented for three preventative options: vaccination, amantadine prophylaxis and a third option denoted “NI prophylaxis.” Whilst the authors justify the exclusion of zanamivir from the analysis due to trials apparently only including laboratory-confirmed outcomes, the exclusion of rimantadine is not justified within the paper, and the “NI” option is not directly specified as representing oseltamivir. The primary health economic outcome for the analysis was the incremental cost per

avoided case. The time horizon used within the analysis was not explicitly reported, however the analysis appears to relate to a single influenza season (i.e. 1-year time horizon).

The authors adopted a decision tree approach to evaluate the differences in benefits and costs of the alternative options for the prevention of influenza. The authors report that they simplified an initially complicated decision tree model structure to include only the possibility of developing influenza and the possibility of experiencing adverse events due to prophylaxis. The model does not include the costs and health impacts of complications due to influenza or ILI, and as a consequence, the model does not include the possibility of death. It is reasonable to argue that the specification of this model is poor, as the results of the analysis ignore key costs and benefits associated with influenza prevention.

The model appears to operate in terms of true influenza cases rather than ILI cases, although this is not entirely clear. Influenza attack rates were derived from influenza sickness rates for 1997 obtained from the Defence Analytical Services Agency (DASA). The model assumes an incidence rate for influenza rate of 5.7 per 1,000; whilst this value appears very low, incidence rates of up to 400 per 1,000 were explored within the sensitivity analysis. The model does not include the possibility of a patient with symptomatic influenza presenting to a healthcare professional for treatment. The effectiveness of the amantadine, NIs and vaccination were obtained from three Cochrane reviews of the clinical effectiveness of vaccination and prevention of influenza.

The model includes acquisition costs associated with influenza prevention, which were derived from the Defence Medical Supply Agency and authors' assumptions.⁹⁴ No other cost components appear to be included in the results of the model. The impact of administration costs on overall cost-effectiveness is explored within the sensitivity analysis. A formal price year is not reported. The authors do not mention the use of discounting which appears to be appropriate given the restrictive scope of the model (i.e. the exclusion of complications and death).

The authors undertook simple sensitivity analysis exploring the impact of improved/worsened preventative efficacy of vaccination and prophylaxis, improved adverse event profiles for vaccination and antiviral prophylactics, duration of prophylaxis and the inclusion of administration costs for prevention. Probabilistic sensitivity analysis was not undertaken within this study.

Costs and health outcomes are not reported in a disaggregated form, and it is difficult to establish whether the results are true incremental comparisons between the options, or whether they are compared marginally against a policy of no prevention” The text appears to indicate the latter to be the case. Under the base case assumptions, the marginal cost per case avoided for vaccination, amantadine, and NI (presumably oseltamivir) are reported to be £2,807, £9,458, and £88,193 respectively. The uncertainty analysis suggests that under most conditions, vaccination is likely to be the most cost-effective option. The key determinant of cost-effectiveness appears to be the influenza incidence rate, for which higher rates are expected to result in more favourable cost-effectiveness ratios for vaccination and prophylaxis. The robustness and reliability of the results of this analysis are severely restricted by the limited scope of the model and the limited reporting of the economic evaluation.

Patriarca *et al.* Prevention and control of type A influenza infections in nursing homes⁹⁵

The study reported by Patriarca *et al.*⁹⁵ reports the methods and results of a model of the cost-effectiveness of options for the prevention of influenza A in the elderly nursing home population. The model includes four options for the prevention of influenza A: vaccination without chemoprophylaxis, vaccination with amantadine post-exposure prophylaxis following an outbreak of influenza (30 days duration), amantadine post-exposure prophylaxis following an outbreak of influenza (30 days duration) with no prior vaccination, and amantadine as seasonal prophylaxis (3 months duration) with no prior vaccination. All options are compared against a strategy of no control. Cost-effectiveness is expressed in terms of the incremental cost per illness averted, the incremental cost per hospitalisation averted, and the incremental cost per death averted. The perspective of the analysis is not explicitly reported, however the authors state that only direct costs were included in the analysis. The time horizon for the analysis is unclear, however, the authors state that they did not include future medical costs associated with deaths averted.

The authors used a decision tree model to evaluate the incremental costs and health outcomes for each preventative option. Chance nodes are used to describe the probability that an individual is immune or susceptible to influenza A, the probability of community exposure, the efficacy of vaccination, the possibility of a nursing home outbreak and the possibility that an individual will become ill or not. For patients who become ill, patients experience one of four possible outcomes: infection and survive, infection and die, hospitalisation and survive, or hospitalisation and die.

The model is reported to include the impact of herd immunity although the precise methods for including this factor are unclear. Only respiratory complications are included in the model.

The incidence of disease during the course of an outbreak was based on the experience of 41 separate vaccine efficacy studies conducted in nursing homes during the period 1972-1985. The probability of an outbreak was estimated according to the results of a case-control study;¹¹⁵ this probability was adjusted for the vaccination and chemoprophylaxis options to account for herd immunity effects. The model assumes an overall attack rate of 43% during influenza outbreaks and 16% at other times. The model does not include the possibility of antiviral treatment for patients who develop ILI. The authors assumed that 80% of residents who completed the course of chemoprophylaxis would be fully protected. The probability of recovery/death with or without hospitalisation following influenza infection for patients receiving amantadine prophylaxis was assumed to be the same as for vaccination. More favourable outcomes were assumed for patients who received both vaccination and prophylaxis, although this was reported to be based on only limited clinical evidence. The impact of adverse events is not included on the effectiveness side of the model.

The model includes costs associated with vaccination, acquisition costs for amantadine prophylaxis, and the costs of diagnostic tests, treatments, ambulance and hospitalisation for influenza infections and associated complications. Administrative costs were excluded from the analysis for the chemoprophylaxis options, but were included for vaccination. The authors state that adverse events associated with amantadine are not associated with excess medical care costs, however the authors did include the costs of treating fractures and soft-tissue injuries resulting from dizziness or postural hypotension for patients receiving amantadine. Costs of influenza infections and associated complications were sourced from 1986 prospective payment schedules for appropriate diagnosis-related groups and other sources. Physician charges were based on Medicare Part B payments. The authors do not make any reference to the use of discounting within the analysis.

One-way and multi-way sensitivity analyses were undertaken surrounding the efficacy of influenza vaccination, the efficacy of chemoprophylaxis, and assumptions concerning risk reductions in hospitalisation and death for patients receiving prophylaxis. The authors also undertook a threshold analysis to determine how much amantadine and vaccination would have to cost before these options would no longer result in savings in direct medical costs. Finally the

authors explored the impact of changing the exposure rate to influenza viruses on cost-effectiveness. Probabilistic sensitivity analysis was not undertaken.

The option of outbreak prophylaxis was excluded from the analysis as it was the least effective and most expensive program.⁹⁵ Marginal cost-effectiveness ratios are presented for vaccination plus chemoprophylaxis versus vaccination alone, continuous chemoprophylaxis versus vaccination alone, and continuous chemoprophylaxis versus vaccination plus chemoprophylaxis. The combination of vaccination and chemoprophylaxis during an outbreak was reported to result in demonstrable improvements in outcome at a modest increase in cost. However, the cost-effectiveness calculations only include the program costs, and do not account for expected cost savings in medical care costs. This omission biases against more effective prevention options. The authors report that changing assumptions regarding efficacy and the risk of hospitalisation and death exerted only minor or negligible effects on the clinical and economic outputs of the model. The authors report that varying exposure to influenza led to a proportionate reduction in the number of cases, and a subsequent reduction in the cost-effectiveness of each programme. Increasing the level of coverage of vaccination and chemoprophylaxis led to a progressive decline in morbidity and increases in cost-effectiveness.

6.1.2.3 Summary of existing economic evaluations of amantadine, oseltamivir and zanamivir for the prophylaxis of influenza

The economic models included within this systematic review cover a broad range of prophylaxis options and settings including seasonal, post-exposure and outbreak control prophylaxis using amantadine, oseltamivir and zanamivir. The relevant populations examined within the economic analyses include children, elderly, at-risk adults and healthy adults with or without prior vaccination. However, the majority of studies included in the review do not include all relevant prophylaxis options for the prevention of influenza (i.e. amantadine, oseltamivir and zanamivir). The Roche submission²⁰ and the study reported by Turner *et al.*¹⁰ adopted the broadest scope in terms of prophylaxis options and populations. Included studies consistently adopted a short time horizon (a typical influenza season), however most also accounted for long-term survival or quality-adjusted survival losses resulting from death due to secondary complications of influenza. Only three studies^{10,91,20} presented health economic results in terms of the incremental cost per QALY gained.

The majority of the models included in the review appear to operate on the basis of ILI rather than true influenza alone. However, one study⁹³ appears to inappropriately apply relative reductions of true laboratory-confirmed influenza to the baseline ILI attack rate. The models include a range of secondary complications affecting costs and consequences; these include pneumonia, bronchitis, other ARI and congestive heart failure in adult populations, and otitis media in children. One study did not specify which complications were included in the economic model,⁹² yet costs and consequences of managing these complications were included in the economic analysis. One study did not include the costs and health consequences resulting from secondary complications, nor did it include the possibility of premature death due to influenza.⁹⁴

The review highlights a paucity of good quality evidence relating to many aspects of the decision problem. In particular, many of the models are underpinned by assumptions concerning fundamental parameters such as the underlying ILI or influenza attack rate, the probability that an individual with influenza presents to their GP, and assumptions regarding the treatment of secondary influenza-related complications, each of which have the propensity to considerably influence the resulting cost-effectiveness estimates. A key problem concerns the absence of robust estimates of the effectiveness of prophylaxis in the specific population under consideration, and the need to make assumptions of equivalence for prophylaxis across different population subgroups. In instances whereby the impact of influenza on health-related quality of life has been incorporated into the analysis, this has been consistently drawn from Likert scale data from clinical trials of oseltamivir which are then mapped onto health utilities, or from indirect utility estimates. None of these data are ideal. The limitations of the existing economic models included in the review studies are summarised in Box 1.

Box 1: Key limitations of previous economic models of influenza prophylaxis

1. Failure to include all relevant prophylaxis options in the evaluation;
2. Failure to model secondary complications and death;
3. Failure to account for the impact of disease and prevention on health-related quality of life;
4. Use of unrealistically favourable assumptions regarding the value of avoiding death due to secondary complications (i.e. one life year lost is equal to one QALY lost);
5. Application of laboratory-confirmed influenza preventative efficacy estimates to reduction in ILI baseline attack rate;
6. Failure to incorporate all relevant cost components into cost-effectiveness estimates;
7. Use of US resource use data which may not reflect UK treatment patterns for the management of secondary complications of influenza;
8. Failure to undertake incremental cost-effectiveness analysis (including uncertainty analysis);
9. Failure to account for joint uncertainty in model parameters using probabilistic sensitivity analysis.

6.2 Independent economic assessment

6.2.1 Cost-effectiveness modelling methods

This section details the methods used in the development of the independent Assessment Group model to assess the cost-effectiveness and cost-utility of influenza prophylaxis using amantadine, oseltamivir and zanamivir. The model structure and many of the parameter values draw upon the previous modelling work undertaken by Turner *et al.*¹⁰ within the previous assessment of oseltamivir, amantadine and zanamivir for the seasonal prophylaxis of influenza.¹⁰ Key differences between these models include the incorporation of NICE guidance on the use of neuraminidase inhibitors for the treatment of symptomatic influenza-like illness,¹¹⁶ the inclusion of post-exposure prophylaxis options, an updated systematic review of the effectiveness of influenza prophylaxis (See Chapter 5), and updated estimates of cost and health outcomes associated with influenza and other ILI-related complications.

6.2.1.1 Model scope

Interventions and comparators

The model evaluates the incremental costs and health outcomes of post-exposure prophylaxis and seasonal prophylaxis of influenza using amantadine, oseltamivir and zanamivir in comparison to each other and no prophylaxis.

Model population

Cost-effectiveness estimates for influenza prophylaxis using oseltamivir, amantadine and zanamivir are presented for six discrete subgroups: children aged 1-14 years (with at-risk medical condition or otherwise healthy); adults aged 15-64 years (with at-risk medical condition or otherwise healthy); and elderly adults aged over 65 years (with at-risk medical condition or otherwise healthy). In addition, the analysis considers the impact of prophylaxis for individuals who have been vaccinated against influenza and for individuals who have not been previously vaccinated. Whilst the model structure is identical for all subgroups, the analyses differ in terms of influenza attack rates, prophylaxis dose, prophylactic efficacy and prognosis following influenza onset.

Health economic outcomes

The primary health economic outcome used within the economic model is the incremental cost per quality adjusted life year (QALY) gained. This is calculated for all non-dominated prophylactic options as compared against the next most effective option. Options which are dominated (simple or extended) are ruled out of the analysis.

Time horizon and time preferences

The model assumes that all events of interest occur within a single influenza season, hence the time horizon is effectively one-year in duration. As such, costs and health outcomes arising within this period are not subjected to discounting. However, as secondary complications of influenza and other ILI may result in premature death, the model also accounts for potential years of life lost beyond this time horizon; these are adjusted to account for the expected level of quality of life. Quality adjusted life years (QALYs) lost due to premature death resulting from the incidence of influenza-related complications are discounted at a rate of 3.5%, in line with current recommendations from NICE.⁹⁶ A summary of the scope of the economic comparisons is presented in Table 27 (note the duration of prophylaxis is assumed in line with licensed indications).

Table 27: Description of prophylaxis options included in the health economic model of post-exposure prophylaxis

Prevention strategy	Prophylaxis duration (seasonal)	Prophylaxis duration (post-exposure)	Dosage per day
Amantadine	42 days (21 days for patients who have previously been vaccinated)	10 days	100mg
Oseltamivir*	42 days	10 days	75mg
Zanamivir	28 days	10 days	10mg

* Oseltamivir dosage for children: < 15kg – 30mg, 15-23kg – 45mg, 23-40kg – 60mg, > 40kg – 75mg¹⁴

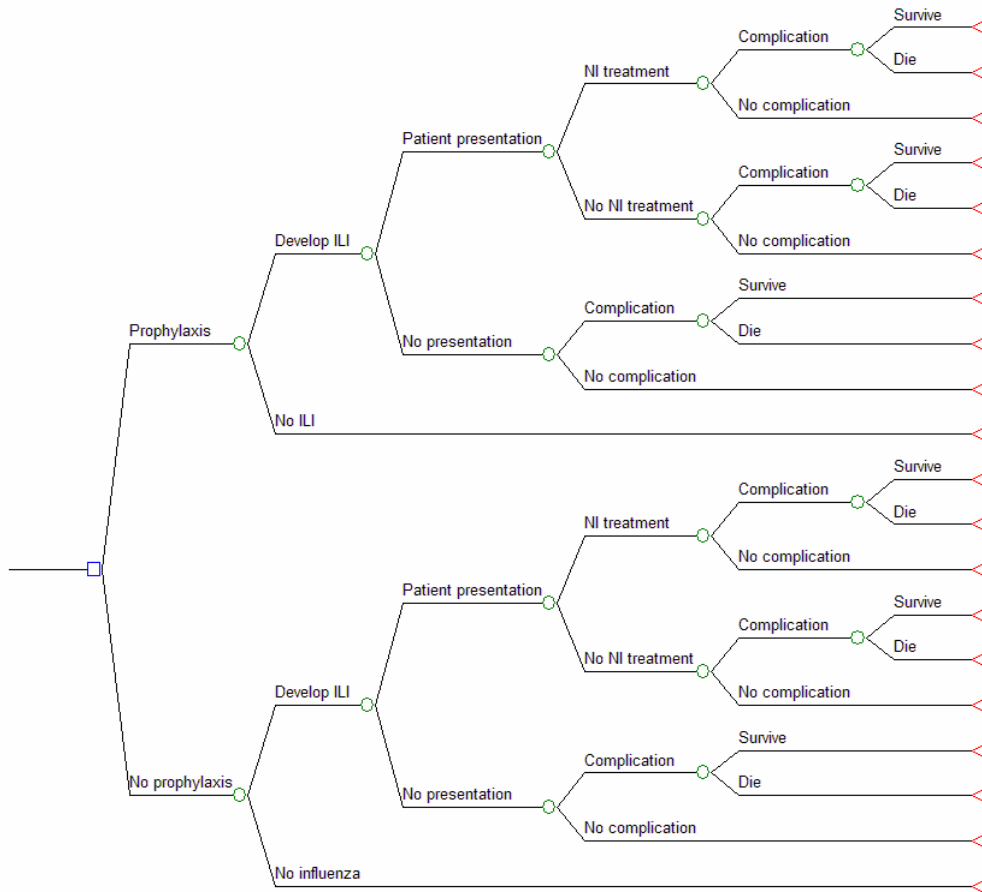
6.2.1.2 Model structure

The model uses a decision-analytic (decision tree) approach to estimate the incremental costs and health outcomes associated with each influenza prophylaxis strategy compared against each other and no prophylaxis. The model operates on the basis of influenza-like illness (ILI) which includes true influenza as well as other illnesses which are clinically similar to influenza, for example Respiratory Syncytial Virus (RSV). The costs and health outcomes of other ILI are included in the model as these are often indistinguishable from true influenza and may result in additional healthcare management costs as well as QALY losses. Furthermore, much of the literature relating to the consequences of influenza infection is actually based on the broader group of ILI including influenza.¹² Costs and health outcomes are estimated for three groups of patients: 1) individuals who develop true influenza; 2) individuals who develop other ILI which is not influenza; and 3) individuals who do not develop influenza or ILI. The prophylactic options evaluated within the model are effective only against the influenza virus, thus effective protection against influenza is assumed to reduce the probability of developing true influenza but will have no impact on other ILI.

A simplified description of the model structure is presented in Figure 5. Patients may receive seasonal or post-exposure prophylaxis using amantadine, oseltamivir or zanamivir, or no prophylaxis. The probability that a contact case develops influenza is dependent on the influenza attack rate, the prophylactic efficacy of the strategy under consideration over the period in which the patient is taking prophylaxis, the probability that influenza is influenza A (amantadine only), the degree of resistance to the prophylactic drug (amantadine only), and whether the patient has been previously vaccinated. In terms of post-exposure prophylaxis, the model assumes that the

patients are prescribed prophylaxis within 48 hours of exposure to an infected index case, in line with licensed indications. Patients receiving vaccination and/or prophylaxis (amantadine only) may experience adverse events which may detract from the patients health-related quality of life and may incur additional medical treatment costs. If patients do not develop ILI, no further costs or health outcomes are considered for these patients in the model. If a patient does develop influenza or other ILI, they may seek medical treatment in either primary care (i.e. GP consultation) or secondary care (i.e. presenting at an Accident and Emergency department). If the patient presents with symptomatic ILI, they may be considered appropriate for treatment using oseltamivir or zanamivir (if the patient presents within 48 hours of developing ILI symptoms and if they are considered to be at risk of developing secondary complications of influenza).¹¹⁶

Figure 5: Simplified decision analytic model structure



A proportion of patients who develop ILI are expected to develop secondary complications, including respiratory complications such as bronchitis, pneumonia, or otitis media, or an

exacerbation of an existing underlying condition (including cardiac, renal and CNS complications).¹² If a patient develops an ILI complication, they are assumed to seek medical attention for treatment. The model assumes that antibiotics may be prescribed for the treatment of uncomplicated ILI cases as well as for the treatment of ILI-related complications.¹² A proportion of patients who develop complications of ILI are assumed to require hospitalisation. The model assumes that a proportion of complications will result in premature death.

The decision model includes the administration and acquisition costs of influenza vaccination and prophylaxis, the costs of treatment of symptomatic ILI using neuraminidase inhibitors in at-risk groups, the costs of consultation in primary and secondary care, the costs of managing secondary complications of influenza and ILI, and the costs of hospitalisation for individuals with severe complications of ILI. QALY losses are included for individuals who develop uncomplicated ILI, adverse events of prophylaxis (amantadine only), complications of ILI, and premature death due to ILI complications.

Key model assumptions

- Other ILI which is not influenza may also result in complications (including RSV and *Mycoplasma pneumoniae*). It should be noted that the complications arising from influenza may in reality differ from those for other ILI such as RSV (this is a limitation in the use of the data from Meier *et al.*¹² – see Section 6.2.2.2). However, since the costs and effects associated with other ILI are the same for each prophylaxis group, these do not affect the resulting estimates of cost-effectiveness.
- Prophylaxis using amantadine, oseltamivir and zanamivir are effective only against true influenza.
- Antiviral prophylaxis is effective in preventing influenza only for the period over which the patient is taking the drug. For seasonal prophylaxis, the model assumes that a patient may be protected over a proportion of the whole influenza season. However, it should be noted that monitoring of influenza activity takes place at a national level and the duration for which activity exceeds the national threshold may not reflect influenza activity at the local level. The importance of this assumption is tested in the sensitivity analysis (See Section 6.3.2). For the sake of simplicity, the model assumes that the risk of infection is constant for the period when influenza is circulating; this is in line with the previous models reviewed in Section 6.1.

- The joint benefit of vaccination followed by prophylaxis is assumed to be cumulative (the effectiveness of prophylaxis is applied to any remaining influenza cases which are not effectively protected by vaccination).
- The model assumes that amantadine, oseltamivir and zanamivir would be used as prophylaxis when influenza is known to be circulating in the community (the threshold is currently set at 30 new ILI GP consultations per 100,000 population).⁸
- The model assumes that the prescription of seasonal prophylaxis and post-exposure prophylaxis of influenza requires a consultation with a GP. The possibility of multiple courses of antiviral prophylaxis being prescribed to an index case on behalf of other household contacts is explored in the sensitivity analysis. The model assumes that prophylaxis is not given at the same time as influenza vaccination, hence a second visit is required.
- If an individual develops a secondary complication of ILI (whether due to influenza or not), the course of the complication is unaffected by the prior use of prophylaxis. Treatment of symptomatic influenza using oseltamivir or zanamivir is assumed to reduce the incidence of complications in at-risk patients. If a patient has already developed a complication whilst receiving prophylaxis, it is unlikely that antiviral treatment will provide any additional benefit. Given the simple structure of the model, the analysis assumes that patients who receive antiviral prophylaxis and subsequent treatment for symptomatic ILI develop complications *after* being prescribed treatment. This assumption is likely favour prophylaxis as it increases the costs of treating symptomatic influenza. Assumptions surrounding the use of antiviral treatment following prophylaxis are explored in the sensitivity analysis.
- Patients who experience adverse events due to prophylaxis are likely to consult their GP for advice.
- Adverse events due to oseltamivir and zanamivir are mild, self-limiting and have no impact upon a patient's health-related quality of life. Adverse events due to amantadine prophylaxis may be more severe and may result in a reduction in the patient's quality of life.
- Antiviral treatment of symptomatic influenza and ILI using zanamivir and oseltamivir is given in line with current NICE recommendations.¹¹⁶ The choice of neuraminidase inhibitor for the treatment of symptomatic ILI is assumed to be independent of the prophylactic strategy under consideration. Antiviral treatment is assumed to incur an additional cost in patients who have previously received prophylaxis. For example, if a

- patient is prescribed oseltamivir prophylaxis, subsequently develops symptomatic ILI and is given oseltamivir treatment, a separate prescription of the drug is required.
- All patients who develop complications due to influenza and other ILI present to a healthcare professional for treatment.
 - Patients who develop either uncomplicated or complicated ILI may be prescribed antibiotics.
 - Patients who stop taking prophylaxis are assumed to do so at the beginning of the course and hence do not gain any additional protection over patients who do not receive prophylaxis (the impact of assumptions regarding withdrawal rates are explored in the sensitivity analysis – see Section 6.3.2).
 - The costs of diagnostic tests (blood test, sputum tests, chest x-ray) for patients presenting with respiratory complications are assumed to be included in the unit costs of GP consultation and A&E consultation.
 - Owing to limitations in the evidence base, the model assumes that only complicated ILI cases may result in hospitalisation and death. These assumptions are explored in the sensitivity analysis (See Section 6.3.2).
 - The model includes only those health benefits accrued by patients receiving influenza prophylaxis; potential benefits accrued through decreased transmission of influenza through the use of prophylaxis are not considered in the health economic model.
 - A proportion of influenza cases are assumed to be resistant to amantadine. Whilst there is some evidence of resistance for the neuraminidase inhibitors, these rates are low and are excluded from the base case analysis. The impact of resistance to oseltamivir is considered within the sensitivity analysis (See Section 6.3.2).

6.2.2 *Model parameters*

Lists of all model parameters for the post-exposure prophylaxis and seasonal prophylaxis models by subgroup are presented in Appendix 7 and Appendix 8 respectively.

6.2.2.1 Event probabilities

Baseline influenza attack rate

The baseline influenza attack rate describes the probability that an individual develops influenza over the influenza season. The model assumes that the probability of developing influenza differs between children, adults and elderly individuals. Different attack rates are also assumed between the seasonal and post-exposure prophylaxis models, as probability of influenza infection is likely

to be higher in an individual who has been in frequent close contact with an index case with symptomatic ILI in the household. In terms of seasonal prophylaxis, the clinical trials included in this review do not represent a good basis for estimating the probability of developing influenza as they include different levels of exposure to influenza vaccination across each subgroup; one would expect that this would result in lower attack rates than in the unvaccinated population. For the seasonal prophylaxis model, influenza attack rates were derived from a large meta-analysis of placebo arm groups of clinical trials of influenza vaccination versus no influenza vaccination reported by Turner *et al.*¹⁰ The model uses the actual patient numbers presented in the summary of each meta-analysis to estimate the mean and distribution of the attack rate. Beta distributions were used to describe the uncertainty surrounding these parameters.

This source does not however provide a useful basis for estimating attack rates for the post-exposure prophylaxis models, as individuals eligible for post-exposure prophylaxis have, by definition, been exposed to an index case with symptomatic influenza or ILI. Consequently, one would expect the attack rate for these individuals to be higher than the attack rate in an individual who has not been exposed to an index case. Attack rates for the post-exposure prophylaxis options were sourced from the trials of post-exposure prophylaxis included in the systematic review (See Chapter 5). For the paediatric subgroup the attack rate was taken directly from the subgroup analysis reported by Hayden *et al.*,⁴⁸ as this was the only study which presented a subgroup analysis for the paediatric population. For the working age adult and elderly populations, the attack rate was taken from a pooled analysis of placebo group attack rates reported in five trials of post-exposure prophylaxis.^{46,48,47,74,49} It should be noted that patient-level data were not available, hence these attack rates relate to populations that are mixed in terms of subject age. Beta distributions were used to characterise the uncertainty surrounding these attack rates. The attack rates are presented in Table 28.

Table 28: Attack rates assumed within the model

Type of prophylaxis	Age group	Number patients with influenza	Number of patients at risk	Attack rate
Seasonal	Children (0-15 years)	256	1469	0.174
Seasonal	Adults (16-64 years)	104	1670	0.062
Seasonal	Elderly (65+ years)	57	1098	0.052
Post-exposure	Children (0-15 years)	21	111	0.189
Post-exposure	Adults (16-64 years)	18	2051	0.088
Post-exposure	Elderly (65+ years)	18	2051	0.088

Probability that an ILI is influenza

The probability of developing influenza-like illness during the influenza season was not available from the literature. Instead, the model uses data provided by the Royal College of General Practitioners (RCGP) concerning the probability that a case of ILI is true influenza. Within the health economic model, this probability is divided by the true influenza attack rate to provide an estimate of the broader ILI attack rate in each subgroup (accounting for true influenza and other influenza-like illnesses). Data relating to the probability that ILI is influenza was based on an analysis of swabs taken from individuals with symptomatic ILI collected during routine surveillance over the influenza seasons 2003/04 to 2006/07 (personal communication, Dr Alex Elliott, RCGP). These data relate to those weeks when influenza was known to be circulating in the community, as defined by the 30/100,000 ILI GP consultation threshold.⁸ These data are shown in Table 29.

Table 29: Influenza and influenza-like illness consultations when ILI consultations are above 30 per 100,000 population threshold

Season	Week	ILI consultation rate	No swabs	Number flu A	Number flu B	Flu 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

Table 29 suggests that one would expect fewer influenza cases among the ILI cases when the consultation rate falls to baseline levels. The model assumes that the probability that ILI is true influenza is 0.50 across all subgroups (622/1256). Uncertainty surrounding this parameter was modelled using a beta distribution.

Probability influenza is influenza A

The probability that a case of influenza is influenza A was based on virological surveillance data provided by the Health Protection Agency (personal communication, Dr Piers Mook, HPA). These data relate to 12 influenza seasons from 1995/6 to 2006/7; these data are shown in Table 30.

Table 30: Surveillance data relating to the probability that an influenza case is influenza A

Season	Influenza A positive	Influenza B positive	Total number of swabs
2006/07	168	2	170
2005/06	28	85	113
2004/05	76	29	105
2003/04	124	0	124
2002/03	20	20	40
2001/02	39	1	40
2000/01	35	93	128
1999/00	77	0	77
1998/99	49	17	66
1997/98	58	1	59
1996/97	74	69	143
1995/96	75	0	75

The probability that influenza A is the dominant influenza strain during a given influenza season was calculated from the data shown in Table 30; this gives a probability of 0.75 (influenza B is assumed to be dominant during the 2002/03 season). The probability that a case of influenza is influenza A was then modelled separately for those years where influenza A is dominant and those where influenza B is dominant. For years in which influenza A is dominant, the probability that an influenza case is influenza A was estimated to be 0.86 (740/859). For years in which influenza B is dominant, the probability that an influenza case is influenza A was estimated to be 0.30 (83/281). The overall mean probability that a case of influenza is influenza A is estimated to be 0.72. Beta distributions were used to characterise the uncertainty surrounding the probability that influenza A is dominant and the probability that an influenza case is influenza A given the

dominant influenza strain during a given influenza season. These data are used to modify the effectiveness of amantadine which is effective only against influenza A.

Duration of the influenza season

The model assumes that individuals who are effectively protected against influenza by vaccination are protected over the entire influenza season. Individuals receiving influenza prophylaxis are assumed to be protected over the period for which they are taking the drug. Assuming the antivirals are prescribed when influenza is known to be circulating, the preventative efficacies of the antivirals were adjusted according to the proportion of the influenza season for which the individual is taking the drug. Data relating to the duration of the influenza season (when the number of new GP ILI consultations is in excess of 30 per 100,000 population at the current threshold or 50 per 100,000 population at the previous threshold)⁸ for influenza seasons 1987/88 to 2006/07 were made available to the assessment team by the RCGP (Personal communication, Dr Alex Elliot, RCGP). These data are shown in Table 31.

Table 31: Duration of influenza epidemic period

Winter	Epidemic weeks	Consultation rate threshold used to estimate duration
1987/88	21	50 per 100,000 population
1988/89	10	50 per 100,000 population
1989/90	9	50 per 100,000 population
1990/91	11	50 per 100,000 population
1991/92	10	50 per 100,000 population
1992/93	10	50 per 100,000 population
1993/94	11	50 per 100,000 population
1994/95	12	50 per 100,000 population
1995/96	11	50 per 100,000 population
1996/97	13	50 per 100,000 population
1997/98	7	50 per 100,000 population
1998/99	8	50 per 100,000 population
1999/00	7	50 per 100,000 population
2000/01	11	30 per 100,000 population
2001/02	7	30 per 100,000 population
2002/03	1	30 per 100,000 population
2003/04	9	30 per 100,000 population
2004/05	6	30 per 100,000 population
2005/06	3	30 per 100,000 population
2006/07	3	30 per 100,000 population

Based on the previously higher influenza threshold of 50 per 100,000 population, the mean duration of the influenza season was estimated to be 10.77 weeks. Using the current threshold of

30 new GP consultations per 100,000 population, the mean duration was estimated to be 5.71 weeks. Data relating to the current threshold are assumed in the base case analysis; the impact of assuming the previous higher threshold is considered within the sensitivity analyses (See Section 6.3.2). Uncertainty surrounding the duration of the influenza season was modelled using a gamma distribution; a standard error of 7 days was assumed within the analysis.

Modelling the preventative efficacy of vaccination, amantadine, oseltamivir and zanamivir

Estimates of the preventative efficacy of amantadine, oseltamivir and zanamivir in reducing symptomatic laboratory confirmed influenza (SCLI) were derived from evidence included in the systematic review of clinical effectiveness presented in Chapter 5. The preventative efficacy of vaccination was sourced from recent systematic reviews of vaccination undertaken by the Cochrane Collaboration.^{117,118,119}

The model assumes that influenza vaccination and prophylaxis are effective against true influenza but not ILI. The model also assumes that amantadine, oseltamivir and zanamivir as seasonal prophylaxis are effective only for the period in which the patient is taking the drug. In the absence of evidence concerning the relationship between the point at which patients withdraw from prophylaxis and the protective benefits of prophylaxis in these patients, the model assumes that patients who withdraw from prophylaxis do so at the beginning of the prophylaxis course and receive no protective benefit over individuals who do not receive prophylaxis. This assumption is in line with the previous modelling work reported by Turner *et al.*¹⁰

Preventative efficacy of influenza vaccination

The preventative efficacy of influenza vaccination for children, adults and the elderly was derived from meta-analyses of RCTs presented within three recent Cochrane reviews of influenza vaccination.^{117,118,119} The model assumes that inactivated parenteral vaccines represent the mainstay of vaccination use in England and Wales. The Cochrane reviews report the relative risk of experiencing influenza for vaccination versus placebo to be 0.36 (95% C.I. 0.28, 0.48) in healthy children, 0.35 (95% C.I. 0.25, 0.49) in healthy adults, and 0.42 (95% C.I. 0.27, 0.66) in elderly populations. These preventative efficacy rates are assumed to be the same for otherwise healthy and at-risk groups within each age band. The propagation of these relative risks leads to a proportionate reduction in the probability of experiencing secondary ILI complications and death within vaccinated patients. It should be noted that the health economic analysis reported by Turner *et al.*¹⁰ assumed that influenza vaccination also had an impact in terms of reducing the

probability of pneumonia, hospitalisation, and mortality in adult and elderly patient groups, based on a meta-analysis of influenza vaccination in the elderly reported by Gross *et al.*¹²⁰ However, the odds ratios for these endpoints appear to relate to pneumonias, hospitalisations and deaths within the intention-to-treat populations within trials of vaccination versus no vaccination; hence, the inclusion of these effects is likely to result in double-counting and an over-estimate of the benefits of vaccination. Additional benefits of vaccination in terms of reducing pneumonias, hospitalisations and mortality are thus *not* included in the Assessment Group model presented here. It should be further noted that vaccination status is included as a characteristic of the subgroups included in the assessment; vaccination is not considered as an option for this assessment.

The benefit of prior influenza vaccination is applied in the model to vaccinated subgroups by reducing the probability of developing influenza without prophylaxis. This is calculated as the probability of developing ILI, minus the probability that ILI is influenza multiplied by one minus the relative risk of influenza for vaccination. The preventative efficacy of prophylaxis is then applied to any remaining cases of influenza which are not effectively protected by vaccination (the probability of developing other ILI is unaffected by vaccination). This approach appears to be the most reasonable, given the inconsistent availability of separate efficacy estimates for amantadine, oseltamivir and zanamivir prophylaxis in vaccinated and unvaccinated subgroups.

Modelling the preventative efficacy of antiviral prophylaxis

Preventative efficacy of prophylaxis using amantadine

The systematic review of clinical effectiveness presented in Chapter 5 highlighted a paucity of evidence relating to the efficacy of amantadine in both the seasonal and post-exposure prophylaxis settings. Two studies were available relating to the seasonal prophylaxis of influenza using amantadine;^{58,57} data relating to the relative protective benefit of amantadine compared to placebo was only available from the study reported by Reuman *et al.*⁵⁷ This study included healthy adults who had not been vaccinated; a mean relative risk of 0.40 (95% C.I. 0.08 to 2.03) was estimated from the event data reported within the clinical trial publication. Owing to the absence of additional or alternative studies, this parameter estimate was applied to all subgroups in the seasonal prophylaxis model, hence the model assumes that the preventative efficacy of amantadine is independent of age and risk status. It should be noted that the systematic searches did not identify any direct evidence of the benefit of amantadine in the paediatric population in

line with licensed indications (See Chapter 5); therefore we have extrapolated efficacy estimates from the adult population.

The systematic review did not identify any clinical trials of the effectiveness of amantadine in the post-exposure prophylaxis setting within households (See Chapter 5). However, one study was identified which examined the efficacy of amantadine in outbreak control in healthy adolescents in a boarding school over a period of 14 days.⁵⁹ The majority of subjects recruited within this study had been previously vaccinated for influenza. Prior vaccination does not necessarily confound the analysis of the efficacy of prophylaxis, however it is likely that the presence of effective vaccination would reduce the statistical power of the trial comparison (due to lower attack rates in both prophylaxis and placebo groups). Efficacy estimates within the outbreak control setting were assumed to be similar to those for amantadine when used as post-exposure prophylaxis, as the duration of prophylaxis is similar (assuming post-exposure prophylaxis using amantadine would be taken for duration of 10-days). Based on the event data reported in the clinical trial publication, the relative risk of amantadine versus placebo was estimated to be 0.10 (95% C.I. 0.03 to 0.34). Owing to a lack of any alternative evidence, this relative risk was applied to all subgroups in the model.

The model assumes that a proportion of patients develop amantadine-resistant disease; these patients are assumed to derive no prophylactic benefit from amantadine. Surveillance data (provided in as academic-in-confidence) were provided by the HPA regarding the proportion of H1N1 and H3N2 isolates that were resistant to amantadine during the years 2004-2007. Resistance may occur in either strain; recent data suggest that amantadine-resistance is considerably higher in the H3N2 strain.

[REDACTED]

Preventative efficacy of prophylaxis using oseltamivir

The systematic review of clinical effectiveness presented in Chapter 5 identified a more substantial evidence base relating to the effectiveness of oseltamivir in the prophylaxis of influenza. Two studies of seasonal prophylaxis using oseltamivir were identified,^{66,64} one study⁶⁶

recruited healthy adults (unvaccinated), whilst the other trial recruited at-risk elderly subjects in a residential home (> 80% subjects vaccinated in intervention and control groups).⁶⁴ The study reported by Hayden *et al.*⁶⁶ was applied to the otherwise healthy and at-risk paediatric and working-age adult populations, whilst preventative efficacy estimates from the study reported by Peters *et al.*⁶⁴ were applied to the otherwise healthy and at-risk elderly populations. Based on event data reported by Hayden *et al.*,⁶⁶ the relative risk of developing influenza was estimated to be 0.24 (95% C.I. 0.10 to 0.58). Analysis of event data reported by Peters *et al.*⁶⁴ suggested a relative risk of developing influenza of 0.08 (95% C.I. 0.01 to 0.63). It is unclear whether the difference between efficacy rates from these two trials is a result of differences in terms of study population, underlying risk or another unknown source of heterogeneity.

Two studies were identified which evaluated the preventative efficacy of oseltamivir in the post-exposure prophylaxis of influenza.^{48,49} The preventative efficacy of oseltamivir for the healthy adult group was based on a random effects meta-analysis of these two studies; the mean relative risk used in the model was estimated to be 0.19 (95% C.I. 0.08 to 0.45). Importantly within the two trials included in the meta-analysis, one trial included paediatric and adult subjects⁴⁸ whilst the other included only adult subjects.⁴⁹ Owing to a paucity of alternative evidence, this relative risk was applied to all otherwise healthy and at-risk adult populations. In the paediatric population, the relative risk of developing influenza following oseltamivir post-exposure prophylaxis was modelled based on the subgroup analysis reported by Hayden *et al.*,⁴⁸ the mean relative risk of developing influenza for children was 0.36 (95% C.I. 0.16 to 0.80). This relative risk was applied to both the otherwise healthy and at-risk paediatric subgroups.

Preventative efficacy of prophylaxis using zanamivir

The systematic review identified two clinical trials relating to the benefit of zanamivir for the seasonal prophylaxis of influenza.^{72,75} The study reported by Monto *et al.*⁷² recruited healthy adults, the majority of whom were unvaccinated. The study reported by La Force⁷⁵ recruited at-risk adults; subjects recruited into this study had a higher level of vaccination. Based on the event data reported in the clinical trial paper, the relative risk of developing influenza in healthy adults was estimated to be 0.32 (95% C.I. 0.17 to 0.63).⁷² This estimate was applied to the otherwise healthy and at-risk children subgroups as well as the healthy adult subgroup. Similarly, the relative risk of developing influenza in at-risk adults was estimated to be 0.17 (95% C.I. 0.06 to 0.50); this relative risk was applied to the at-risk adult working age subgroup.⁷⁵ The relative risk

for the elderly populations was based on a subgroup analysis reported by LaForce *et al.*,⁷⁵ this relative risk was estimated to be 0.20 (95% C.I. 0.02 to 1.72).

The review identified three trials which reported the clinical efficacy of zanamivir versus placebo for the post-exposure prophylaxis of influenza in adults⁷⁴ and children and adults.^{46,47} The relative risk of developing influenza in all subgroups receiving zanamivir was estimated using a random effects meta-analysis of these three trials; the relative risk was estimated to be 0.21 (95% C.I. 0.13 to 0.33). One study did evaluate zanamivir as outbreak control in largely at-risk elderly subjects;⁷⁶ the model does not use efficacy data from this study due to differences in the duration of prophylaxis. The use of the meta-analysis estimate for zanamivir in post-exposure prophylaxis in households represents a bias in favour of zanamivir in this subgroup.

Relative risks and 95% confidence intervals (shown in parentheses) used in the model are summarised in Table 32. The footnotes detail whether each relative risk is based on trial evidence relating exclusively to the model subgroup, trial evidence which includes the subgroup, or whether the efficacy estimate is based on trial evidence relating to other subgroups.

Table 32: Summary of relative risks estimates used in the model

Intervention	1. Healthy children	2. At-risk children	3. Healthy adults	4. At-risk adults	5. Healthy elderly	6. At-risk elderly
Vaccination	0.36 [0.28, 0.48]	0.36 ^c [0.28, 0.48]	0.35 [0.25, 0.49]	0.35 ^c [0.25, 0.49]	0.42 [0.27, 0.66]	0.42 ^c [0.27, 0.66]
Amantadine (seasonal)	0.40 ^c [0.08, 2.03]	0.40 ^c [0.08, 2.03]	0.40 ^a [0.08, 2.03]	0.40 ^a [0.08, 2.03]	0.40 ^c [0.08, 2.03]	0.40 ^c [0.08, 2.03]
Amantadine (post-exposure)	0.10 ^b [0.03, 0.34]	0.10 ^b [0.03, 0.34]	0.10 ^b [0.03, 0.34]	0.10 ^b [0.03, 0.34]	0.10 ^c [0.03, 0.34]	0.10 ^c [0.03, 0.34]
Oseltamivir (seasonal)	0.24 ^c [0.10, 0.58]	0.24 ^c [0.10, 0.58]	0.24 ^a [0.10, 0.58]	0.24 ^a [0.10, 0.58]	0.08 ^b [0.01, 0.63]	0.08 ^b [0.01, 0.63]
Oseltamivir (post-exposure)	0.36 ^a [0.16, 0.80]	0.36 ^a [0.16, 0.80]	0.19 ^b [0.08, 0.45]	0.19 ^b [0.08, 0.45]	0.19 ^b [0.08, 0.45]	0.19 ^b [0.08, 0.45]
Zanamivir (seasonal)	0.32 ^c [0.17, 0.63]	0.32 ^c [0.17, 0.63]	0.32 ^a [0.17, 0.63]	0.17 ^b [0.06, 0.50]	0.20 ^b [0.02, 1.72]	0.20 ^b [0.02, 1.72]
Zanamivir (post-exposure)	0.21 ^b [0.13, 0.33]	0.21 ^b [0.13, 0.33]	0.21 ^b [0.13, 0.33]	0.21 ^b [0.13, 0.33]	0.21 ^{b/c} [0.13, 0.33]	0.21 ^{b/c} [0.13, 0.33]

a – relative risk based on clinical trial evidence relating exclusively to model subgroup

b – relative risk based on clinical trial evidence which includes model subgroup and other subgroups

c – relative risk based on clinical trial evidence from other model subgroups (equal effectiveness assumed)

Note – it is unclear whether elderly individuals were represented within the trials included in the meta-analysis of zanamivir post-exposure prophylaxis

It should be noted that the evidence surrounding the effectiveness of amantadine, oseltamivir and zanamivir within specific subgroups is not ideal, and decisions regarding the appropriate inclusion of specific preventative efficacy estimates are not straightforward. For the most part, preventative efficacy is assumed to be the same across a number of age and risk subgroups (even those where there is no trial evidence relating to the subgroup under consideration e.g. amantadine post-exposure prophylaxis in the elderly). In other instances, where multiple sources exist, there are known heterogeneities between study populations (age, risk status, level of prior vaccination), methods of endpoint measurement and duration of prophylaxis. It is unclear whether differences observed in these preventative efficacy estimates are a result of one or a combination of these known heterogeneities or some other underlying differences between the studies. The uncertainty surrounding all relative risks of developing influenza for vaccination and prophylaxis were modelled using lognormal distributions; estimates of preventative efficacy were sampled from a normal distribution characterised by the log mean relative risk and the standard error of the log of the relative risk. The reader should be aware that there is likely to be a greater level of uncertainty surrounding these effectiveness estimates than the uncertainty reflected in data from the studies included in the systematic review.

Adverse events due to influenza vaccination and prophylaxis

The model includes the possibility of experiencing adverse events for patients receiving vaccination and/or amantadine prophylaxis. The probability of experiencing adverse events due to vaccination was based on data reported by Turner *et al.*,¹⁰ sourced from an observational study of a 2-day work absence per 100 healthy adults from influenza vaccination.¹²¹ Whilst larger surveillance data sources are available (for example the Vaccine Adverse Event Reporting System (VAERS)), these tend to be insensitive in identifying minor adverse events. Adverse events due to vaccination are assumed to be self-limiting, requiring no treatment, and are assumed to have no impact upon health-related quality of life. The model does however assume that patients experiencing adverse events due to vaccination will consult their GP for advice.

Evidence concerning the incidence of adverse events due to influenza prophylaxis is equivocal. In some instances, higher adverse event rates were reported in the placebo groups of the trials than the intervention groups, whilst in other instances, rates were higher in the intervention groups (See Chapter 5). In most cases, it is unclear whether adverse events are related to the prophylaxis or the clinical condition. This is further complicated by the poor reporting of the severity of adverse events within the clinical trials. The evidence does not allow for a robust comparison of

adverse events rates between amantadine, oseltamivir and zanamivir. In the absence of more robust estimates from the trials included in the systematic review (see Chapter 5), assumptions regarding the probability of adverse events for amantadine, oseltamivir and zanamivir were drawn from the previous modelling work reported by Turner *et al.*¹⁰ In line with Turner *et al.*,¹⁰ the model assumes that the adverse events associated with the neuraminidase inhibitors are self-limiting, incur no treatment cost, and have no impact on health-related quality of life. There is however evidence that amantadine can result in severe neuropsychiatric adverse including behavioural changes, delirium, hallucinations, agitations and seizures.^{10,14} In an attempt to capture these health effects, a utility decrement of 0.20 is assumed per day of adverse events for a mean duration of five days, based on the analysis reported by Turner *et al.*¹⁰ The model assumes the probability of experiencing adverse events due to amantadine is 5%. The QALY loss associated with amantadine adverse events was characterised using a beta distribution, whilst the duration of adverse events was modelled using a gamma distribution.

Withdrawal rates for influenza prophylaxis

In the absence of better quality evidence identified from the clinical trials included in the systematic review (see Chapter 5), withdrawal rates from prophylaxis were based on those reported within the previous modelling study reported by Turner *et al.*¹⁰ The probability of withdrawal for amantadine was assumed to be 5.7% in children and healthy adults, and 14.7% in at-risk adults and elderly individuals. The probability of withdrawal was assumed to be 2% for oseltamivir and 1.3% for zanamivir across all model subgroups.¹⁰ Uncertainty surrounding withdrawal rates was modelled using beta distributions.

6.2.2.2 Parameters relating to the onset of influenza and other ILI

Probability that an individual with ILI presents symptomatically

There is considerable uncertainty surrounding the probability that an individual with influenza-like illness consults a healthcare professional in either primary or secondary care. The model reported by Turner *et al.*¹⁰ used evidence from a study of the excess GP consultations reported by Fleming *et al.*¹¹⁰ The use of these data implies the assumption that all excess GP consultations over the influenza season compared to the baseline rate are due to influenza. The validity of this assumption is questionable,¹²² as other influenza-like illnesses such as RSV are often more prevalent during the influenza season, thus accounting for an unknown proportion of excess cases between the influenza season and baseline periods. Instead, the ILI consultation rate was based on a European ILI surveillance study reported by van Noort *et al.*¹⁰⁴ This study used an internet-

based approach to monitoring ILI symptoms and consultations in the general population in the Netherlands, Belgium and Portugal. The study reported highly variable consultation rates for individuals with ILI ranging from 25% to 67%. The model assumes that the true probability that an individual with symptomatic ILI presents is likely to be at the lower end of this range. The model assumes a central estimate of 0.25; uncertainty surrounding this parameter value was modelled using a beta distribution assuming a subjectively large standard error ($\alpha = 5$, $\beta = 15$). The probability of presentation with ILI is assumed to be the same for all subgroups included in the model. The impact of this assumption is explored in the sensitivity analysis (See Section 6.3.2).

Probability an individual presents within 48 hours of symptomatic onset of ILI

Treatment using oseltamivir is currently recommended only for those individuals who are considered to be at high-risk of developing complications who present within 48 hours of symptomatic onset.¹¹⁶ The probability that an individual presents with ILI within 48 hours of onset was derived from a study reported by Ross *et al.*¹²³ The model assumes that half of those presenting on day 2 would be within the 48-hour cut-off; this assumption is in line with the previous model reported by Turner *et al.*¹⁰ In this study, the probability of presentation within 48 hours was reported to be 52%, 16% and 11% in the paediatric, working age adult and elderly populations respectively. These probabilities are assumed to be the same in otherwise healthy and at-risk populations. The uncertainty surrounding these parameters were modelled using beta distributions based on the empirical data reported by Ross *et al.*¹²³

Probability an individual presenting within 48 hours is prescribed a neuraminidase inhibitor for the treatment of ILI

In line with current recommendations from NICE concerning the use of neuraminidase inhibitors for the treatment of influenza and other ILI, the model assumes that oseltamivir and zanamivir are prescribed only for patients who are at-risk of secondary complications of ILI (including elderly patients over 65 years of age). For the paediatric population who are eligible for treatment, the model assumes that patients are treated using oseltamivir. For at-risk adult populations, the model assumes that 89% patients receive oseltamivir, based on data reported within submission to NICE by Roche.²⁰ The remaining 11% of patients are assumed to receive treatment using zanamivir.

Probability of developing complications due to influenza and other ILI

The incidence of complications associated with influenza and ILI are not reported in detail within clinical trials of influenza prophylaxis (See Chapter 5). Instead, the probability of developing a complication of influenza or other ILI was taken directly from a large UK-based observational study reported by Meier *et al.*¹² This study collected and analysed data concerning the incidence, risk factors, clinical complications and drug utilisation associated with influenza and ILI using data collected within the UK General Practice Research Database (GPRD) between the period 1991-1996. A total of 141,293 patients within the database were reported to have one or more diagnoses of influenza or ILI. Data concerning the incidence of specific complications, including exacerbations of underlying diseases and death due to influenza, were reported by age group (1-14 years, 15-49 years, 50-64 years, and > 65 years) and by presence of pre-existing chronic diseases. The rates of specific complications reported by Meier *et al.*¹² are shown in Table 33.

Table 33: ILI complications by subgroup based on Meier *et al.*¹²

Type of complication	1-14 years		15-49 years		50-64 years		65+ years	
	Healthy	Predisposed	Healthy	Predisposed	Healthy	Predisposed	Healthy	Predisposed
Respiratory tract	1,697	520	4,530	1,337	1,106	604	819	754
Bronchitis	113	21	748	203	309	167	273	256
Pneumonia	29	9	185	35	52	27	106	97
URTI	1,470	302	3,502	684	722	300	457	346
Cardiac	0	0	4	9	7	20	9	59
CNS	17	0	85	10	16	5	21	23
Renal	2	0	5	3	4	2	5	12
Other	701	156	646	143	141	49	195	171
Otitis media	684	153	454	94	46	16	21	11
GI bleeding	17	2	171	44	81	22	67	49
Death	0	1	21	5	12	11	110	114
Total patients	2,311	650	5,185	1,472	1,252	670	981	936
Total complications	2,417	676	5,270	1,502	1,274	680	1,049	1,019
Complications per patient	1.05	1.04	1.02	1.02	1.02	1.01	1.07	1.09
Number in group	17,201	3,695	69,231	12,195	16,017	5,402	10,145	7,407
Total cases in age group	20,896		81,426		21,419		17,552	

Data concerning complication rates for the “predisposed” group were assumed to represent the “at-risk” populations within the model. Complication rates within the 15-49 year age group and the 50-64 year age group were combined to represent the working age adult model populations. Uncertainty surrounding the probability of experiencing a complication of influenza within each population group was modelled using beta distributions, whilst the multinomial probabilities of experiencing specific complications were modelled using Dirichlet distributions with minimally informative priors based on the methods reported by Briggs *et al.*¹²⁴ The model assumes that the risk of developing complications is the same for influenza and other ILI.

It should be noted that the use of this study is flawed in that many of the ILIs reported by Meier *et al.* will be caused by viruses other than influenza. This problem is further compounded as the study reported ILI complications over the whole year rather than the influenza season, hence the proportion of episodes caused by other ILIs is likely to be higher than that for the period when influenza is known to be circulating. A limitation of these data, and their use in the model, is that the rates of complications resulting from other ILIs which are not influenza may not reflect complication rates due to influenza infection.

Effectiveness of neuraminidase inhibitors for the treatment of symptomatic influenza

The efficacy and safety of oseltamivir and zanamivir for the treatment of influenza and other ILI is beyond the scope of this assessment and is scheduled for re-appraisal in 2008. However, both zanamivir and oseltamivir are currently recommended for treatment of symptomatic influenza and ILI in at-risk individuals.¹¹⁶ Evidence concerning the safety and efficacy of the neuraminidase inhibitors for the treatment of ILI was derived from the earlier HTA report by Turner *et al.*¹⁰ The model assumes that oseltamivir and zanamivir reduce the probability of experiencing complications due to influenza, and also lead to a modest reduction in the impact of influenza on quality of life as compared against best symptomatic care alone. The model assumes an odds ratio for all complications for zanamivir versus no treatment is 0.49 (95% C.I. 0.23, 1.04) in all at-risk populations, whilst the odds ratio for complications for oseltamivir versus no treatment is assumed to be 0.65 (95% C.I. 0.43, 0.97) in the at-risk paediatric population and 0.40 (95% C.I. 0.16, 0.93) in at-risk adult and elderly populations.¹⁰ The model assumes that the NIs are not effective in reducing complications due to other ILIs which are not influenza. The odds ratios derived from Turner *et al.*¹⁰ relate to reductions in complications requiring antibiotics; due to the high rates of antibiotic use for the treatment of ILI-related complications,¹² and the absence of alternative evidence, the model assumes that these efficacy rates are applied to all ILI-related

complications. It is possible that this may overstate the benefit of zanamivir and oseltamivir in terms of reducing complications due to influenza and other ILI. A summary of treatment efficacy values assumed within the model are shown in Table 34; 95% C.I.s are shown in parentheses.

Table 34: Effectiveness of oseltamivir and zanamivir treatment in reducing complications (based on Turner *et al.*¹⁰)

Population	Odds ratio for reduction in complications	
	Odds ratio for zanamivir	Odds ratio for oseltamivir
1. Healthy children	0.70 (0.52, 0.96)	0.65 (0.43, 0.97)
2. At-risk children	0.49 (0.23, 1.04)	0.65 (0.43, 0.97)
3. Healthy adults	0.70 (0.52, 0.96)	0.40 (0.16, 0.93)
4. At-risk adults	0.49 (0.23, 1.04)	0.40 (0.16, 0.93)
5. Healthy elderly	0.70 (0.52, 0.96)	0.40 (0.16, 0.93)
6. At-risk elderly	0.49 (0.23, 1.04)	0.40 (0.16, 0.93)

As noted in Section 6.2.1.2, the model assumes that the use of neuraminidase inhibitors for the treatment of symptomatic influenza is independent of the prophylactic strategy and requires a further prescription (any remaining NI prophylaxis at the point of infection cannot be used as treatment at a higher dose). The impact of this assumption is explored in the sensitivity analysis by excluding the possibility of NI treatment for patients who develop symptomatic ILI.

Probability of receiving antibiotics

The model assumes that antibiotics may be prescribed both for patients who present with uncomplicated ILI and those who present with complicated ILI. The probability that an individual with or without complications is prescribed antibiotics was derived from the study reported by Meier *et al.*¹² The probability that a patient with uncomplicated influenza or ILI receives antibiotics was estimated to be 0.28, 42 and 0.55 in the paediatric, adult and elderly populations respectively. The probability that a patient with complicated influenza or ILI receives antibiotics was estimated to be 0.71, 0.80 and 0.74 in the paediatric, adult and elderly populations respectively. Owing to a lack of evidence to the contrary, these values are assumed to be the same for both the otherwise health and the “at-risk” populations. Uncertainty surrounding these probabilities was modelled using beta distributions based on the empirical data reported by Meier *et al.*,¹² as shown in Table 35.

Table 35: Probability of antibiotic use for ILI-related complications¹²

Age group	Patients without complications		Patients with complications	
	Number receiving antibiotics	Number in group	Number receiving antibiotics	Number in group
1-14 years	2,183	3,093	4,997	17,910
15-64 years	6,983	8,726	39,622	94,338
> 65 years	1,527	2,068	8,544	15,620

Probability of hospitalisation due to ILI-related complications

The model assumes that patients who experience ILI-related complications may require hospitalisation. As noted above, the clinical trials of influenza prophylaxis do not consistently report the incidence of complications and as such do not provide any information regarding the probability that an individual requires hospitalisation. Furthermore, data relating to hospitalisation rates were not available from the study by Meier *et al.*¹² Instead, the probability of hospitalisation was derived from hospitalisation rates for lower respiratory tract infections reported within a meta-analysis of ten trials of oseltamivir for the treatment of symptomatic influenza reported by Kaiser *et al.*⁹⁹ The probability of hospitalisation for individuals with influenza-related complications was estimated from the placebo arm data across the ten included studies; this probability was estimated to be 0.11 (5/46) in the otherwise healthy children and working age adult subgroups and 0.16 (15/95) in the at-risk subgroups (including otherwise healthy elderly).⁹⁹ The data presented in the study publication did not allow for these estimates to be further subdivided according to age group; this is unfortunate as age is likely to affect the risk of hospitalisation. Uncertainty surrounding the probability of hospitalisation was modelled using beta distributions based on the empirical data reported by Kaiser *et al.*⁹⁹

A proportion of patients who are hospitalised may require ITU care with or without mechanical ventilation. The previous model reported by Turner *et al.*¹⁰ assumed that 4.9% (22/453) of patients undergo mechanical ventilation. No alternative evidence could be identified, hence the model uses these same parameter values. A beta distribution was used to characterise the uncertainty surrounding this parameter.

Probability of death due to ILI-related complications

The probability of death due to ILI-related complications was taken from the population-based study reported by Meier *et al.*¹² The probability of death due to influenza complications was

observed to be very low in the paediatric and adult populations (< 1%); this probability was observed to be considerably higher in the elderly patients represented within the database (10-11%). The risk of death due to complications of ILI was observed to be slightly elevated in the predisposed populations compared against the otherwise healthy patients. As complications may be a result of true influenza or other ILI, the model assumes that the probability of death is the same for those patients who develop complications due to influenza and for those patients who develop complications due to other ILI. Uncertainty surrounding this parameter was modelled using beta distributions based on the empirical data reported by Meier *et al.*,¹² as shown in Table 36.

Table 36: Probability of death due to influenza and ILI-related complications¹²

Population	Number of deaths	Number of complications	Probability of death
1. Healthy children	0	2417	0.00
2. At-risk children	1	676	0.00
3. Healthy adults	33	6544	0.005
4. At-risk adults	16	2182	0.007
5. Healthy elderly	110	1049	0.1049
6. At-risk elderly	114	1019	0.112

6.2.2.3 Modelling resource use and costs associated with influenza and other ILI

The model includes the acquisition and administration costs for vaccination, antiviral prophylaxis and treatment, costs associated with the management of adverse events, consultation costs, antibiotics, and hospitalisation costs for managing severe ILI-related complications. As the time horizon for the model is effectively 1-year in duration, costs were not subjected to discounting.

Costs of prophylaxis and treatment using amantadine, oseltamivir and zanamivir

Prophylaxis and treatment were costed according to BNF list prices at the time of the assessment. The number of doses of prophylaxis required using amantadine, oseltamivir and zanamivir was calculated based on the dosages and durations in line with licensed indications (See Table 27). The model assumes that seasonal prophylaxis using amantadine is given for a period of 6 weeks (42 days) for patients who have not been previously vaccinated, and 3 weeks (21 days) for patients who have been previously vaccinated. The model assumes that seasonal prophylaxis using oseltamivir is given for a period of 6-weeks (42 days). Seasonal prophylaxis using zanamivir is assumed to be given for a period of 4-weeks (28 days). The model assumes that post-exposure prophylaxis using amantadine, oseltamivir and zanamivir is given for a period of 10 days. The duration of treatment of symptomatic ILI using oseltamivir and zanamivir is assumed

to be 5 days. In line with licensed indications, the daily dosage of amantadine prophylaxis and zanamivir prophylaxis are assumed to be 100mg and 10mg respectively for all populations. The cost of prophylaxis and treatment using oseltamivir for children assumes a mean body mass of between 23kg and 40kg. Unit costs for amantadine, oseltamivir and zanamivir were taken from the BNF No. 54.¹⁴ Amantadine is available in both capsule and syrup form, and oseltamivir is available as capsules and as a suspension for reconstitution with water. The model assumes that prophylaxis for adults is administered using capsules rather than syrup or suspension, as this allows for more reliable dosing (personal communication: Dr Andrew Ross, RCGP). The cost of each prophylaxis course and treatment course includes the possibility of wastage. Where multiple products were available, the least expensive is assumed. The costs of prophylaxis used in the model are presented in Table 37.

Table 37: Acquisition cost per course of antiviral prophylaxis and treatment

Drug	Seasonal prophylaxis		Post-exposure prophylaxis		Treatment	
	Adults	Children	Adults	Children	Adults	Children
Amantadine prophylaxis (unvaccinated)	£14.40	£14.40	£4.80	£4.80	n/a	n/a
Amantadine prophylaxis (previously vaccinated)	£9.60	£9.60	£4.80	£4.80	n/a	n/a
Oseltamivir prophylaxis	£81.80	£73.65	£16.36	£16.36	£16.36	£16.36
Zanamivir prophylaxis	£73.65	£73.65	£24.55	£24.55	£24.55	£24.55

In the base case analysis, the model assumes that each prescription of prophylaxis requires a GP consultation. The model assumes that the administration of vaccination and the prescription of antiviral prophylaxis require separate consultations. The impact of prescribing multiple courses of prophylaxis for contact cases is explored in the sensitivity analysis (See Section 6.3.2).

Cost of vaccination

The cost of influenza vaccination was estimated from list prices derived from BNF 54.¹⁴ Current unit costs for influenza vaccine products range from £4.98 to £6.59, including both proprietary and non-proprietary products (See Table 38). Recommended influenza vaccines vary between influenza seasons; the mean vaccine price was assumed within the model (£5.63). The model assumes that influenza vaccination is administered by a GP; the cost of vaccination is assumed to include the cost of a GP consultation based on costs reported by Netten and Curtis.¹⁰² A GP visit is assumed to cost £25. As these costs are common to all patients receiving vaccination, these parameters have no impact upon the incremental cost-effectiveness of influenza prophylaxis.

Table 38: Unit costs of inactivated influenza vaccines¹⁴

Product name	Type of vaccine	Unit cost
Inactivated Influenza Vaccine*	suspension of formaldehyde-inactivated influenza virus (split virion)	£6.29
Inactivated Influenza Vaccine*	suspension of propiolactone-inactivated influenza virus (surface antigen)	£3.98
Agrippal®	suspension of formaldehyde-inactivated influenza virus (surface antigen)	£5.03
Begrivac®	suspension of formaldehyde-inactivated influenza virus (split virion)	£5.03
Enzira®	suspension of inactivated influenza virus (split virion)	£6.59
Fluarix®	suspension of formaldehyde-inactivated influenza virus (split virion)	£4.49
Imuvac®	suspension of formaldehyde-inactivated influenza virus (surface antigen)	£6.59
Influvac Sub-unit®	suspension of formaldehyde-inactivated influenza virus (surface antigen)	£5.22
Mastaflu®	suspension of formaldehyde-inactivated influenza virus (surface antigen)	£6.50
Viroflu®	suspension of inactivated influenza virus (surface antigen, virosome)	£6.59

* *Non-proprietary vaccine products*

Cost of ILI presentation

The model assumes that patients present with symptomatic ILI either to their GP (either in the surgery or at home) or at an Accident and Emergency department. The probability that a patient with influenza or other ILI requires a home visit was derived from the study reported by Ross *et al.*¹²³ Counts of patients with ILI who had home visits were reported in aggregate form for those patients aged under 75 and patients aged over 75. Further data regarding the proportion of consultations which took place at home within each age group were provided by the lead author of this study (personal communication: Dr Andrew Ross, RCGP). The proportion of home visits was low in the paediatric and adult populations (5% and 8% respectively); this proportion was considerably higher in the elderly population (38%). Beta distributions were used to characterise the uncertainty surrounding this parameter based on the empirical data provided by Dr Ross of the RCGP. The proportion of all ILI presentations that take place in Accident and Emergency departments was based on clinical opinion (personal communication: Professor Robert Read, University of Sheffield); the model assumes that 3% of patients present to A&E departments (range 1% to 5%). A beta distribution was used to capture the uncertainty surrounding this

quantity. This parameter was assumed to be the same for otherwise healthy and at-risk paediatric, adult and elderly populations.

Unit costs for GP surgery consultations and home visits were derived from the PSSRU¹⁰² whilst the cost of an Accident and Emergency consultation was derived from the NHS Reference Costs.¹²⁵ The model assumes that a GP surgery consultation costs £25,¹⁰² a home visit costs £69¹⁰² and an A&E attendance costs £95.56 (First attendance data code 180F).¹²⁵ The unit costs for A&E attendances are assumed to include the costs of diagnostic tests (e.g. blood and sputum tests, lung function tests etc.). Based on the information reported above, the model assumes a mean cost of presentation with symptomatic ILI of £29.52 for children, £30.73 for working age adults, and £43.20 for elderly individuals.

Cost of antibiotics for the treatment of ILI-related complications

The model assumes that antibiotics are prescribed for individuals presenting with uncomplicated ILI as well as those presenting with influenza and ILI-related complications. The precise antibiotic prescribed depends on the type of complication; for simplicity, the model assumes that the preferred antibiotic for the treatment of symptomatic ILI and related complications is co-amoxiclav. In its non-proprietary tablet form, the unit cost for co-amoxiclav is £6.80 for a 21-tablet course.¹⁴

Costs of managing adverse events resulting from vaccination and prophylaxis

The model assumes that adverse events resulting from vaccination and prophylaxis (amantadine only) incur additional costs due to additional GP attendances. As noted above, the cost of a GP attendance was assumed to be £25.¹⁰² It should be noted that not all patients who experience adverse events will consult their GP, hence it is possible that the costs of managing adverse events is overestimated in the model, although the impact of this bias on cost-effectiveness outcomes is minor. The model assumes that adverse events due to oseltamivir and zanamivir are mild, self-limiting and incur no additional medical costs.

Costs of hospitalisation due to serious complications of influenza and other ILI

The cost of hospitalisation for was taken from the NHS Reference Costs 2005-2006.¹²⁵ The unit cost for lobar, atypical or viral pneumonia (D14) without complications was assumed; this was divided by the mean length of stay to derive an estimate of the daily cost of hospitalisation. The standard error for this parameter was estimated by dividing the inter-quartile range by 1.349 and

dividing this by the square root of the number of submissions. This cost was then multiplied by the assumed duration of inpatient stay within each population group reported by Turner *et al.*¹⁰

Mean length of hospitalisation stay due to ILI-related complications were taken from Turner *et al.*¹⁰ these are assumed to differ substantially between the paediatric, adult and elderly population subgroups. Turner *et al.*¹⁰ did not include any uncertainty surrounding these estimates, hence the degree of uncertainty surrounding these mean values has been subjectively modelled using gamma distributions. These data are shown in Table 39.

Table 39: Mean length of hospital stay assumed for patients experiencing ILI-related complications

Population	Mean length of stay (days)	Assumed standard error
1. Healthy children	2.3	3
2. At-risk children	2.3	3
3. Healthy adults	11.9	3
4. At-risk adults	11.9	3
5. Healthy elderly	15	3
6. At-risk elderly	15	3

A proportion of patients with particularly severe complications may require ITU care and mechanical ventilation; Turner *et al.*¹⁰ note that the proportion of cases requiring mechanical ventilation is not known. The model uses the same value reported by Turner *et al.*¹⁰ (probability of ITU care = 0.05). The typical duration of intensive care required for severely complicated cases was derived from a descriptive study of pneumonia management in the US reported by Oliveira *et al.*¹²⁶ Oliveira *et al.* report a mean duration of ICU stay of 28 days +/- 26 days (10 patients). It should be noted however that this study may not reflect UK treatment patterns. Uncertainty surrounding this parameter was modelled using a lognormal distribution. The cost per intensive care day was taken from the NHS Reference Costs 2005-2006.¹²⁵ The cost per critical care day was assumed to be £1,345.39 (Critical care Level 2 Code TCCS CC1L2).

6.2.2.4 Modelling the impact of influenza and ILI on health-related quality of life

The model estimates the number of QALYs lost due to adverse events of prophylaxis (amantadine only), influenza and ILI episodes, complications resulting from influenza and other ILI, and premature death as a result of secondary complications of ILI. In contrast to conventional methods for deriving the number of QALYs gained by the typical patient receiving a given health

intervention, the model operates in terms of the number of QALYs *lost* over the influenza season including an estimate of the impact of premature death due to ILI complications. The difference in QALYs lost between one prophylactic option and its next best comparator gives an estimate of the number of QALYs saved, *ceteris paribus*. It should be noted from the outset, that the clinical trials of influenza prophylaxis did not include the direct evaluation of the impact of the prophylaxis or disease upon health utility using a preference-based valuation method. This problem is compounded by the paucity of reliable health utility estimates indirectly available within the literature. As such, the estimates of health-related quality of life employed within the model should be approached with caution.

QALYs lost due to influenza and ILI episodes

Previous evaluations of influenza and its prevention and treatment have used health utility scores derived using the EQ-5D¹²⁷ or the HUI3¹²⁸ based on general population valuations or retrospective valuations from individuals with a history of virologically confirmed influenza. These studies were based on small numbers of subjects ($n < 25$). The study reported by Griffin *et al.*¹²⁷ reported an extreme value for the utility associated with influenza infection which is valued as a state worse than death (utility = -0.066).¹²⁷ It is likely that the impact of influenza on quality of life will be greatest when the illness is at its peak, and that it will have a lesser impact in the first and last days of illness.

The methodology reported by Turner *et al.*¹⁰ was used to generate QALY loss estimates for cases of influenza and other ILI (See Section 6.1.2.2). The expected QALY loss due to an episode of influenza was estimated using data collected within five clinical trials of oseltamivir for the treatment of influenza in healthy adults, and at-risk and elderly populations. Within these studies, a 10-point Likert scale was completed daily for up to 21 days by patients receiving oseltamivir treatment and patients receiving placebo. The scale used was similar to a visual analogue scale (VAS), using a lower anchor which had a score of zero describing “worst possible health” and an upper anchor which had a score of ten describing “normal health for someone your age.” As the upper anchor on the rating scale did not describe a notional state of “best possible health”, Turner *et al.*¹⁰ recalibrated the upper anchor to represent mean utility scores for each age group using data from the MVH study. The VAS equivalent data were then converted Time Trade Off (TTO) utility scores based on a VAS-TTO transformation algorithm reported by the MVH group.¹⁰⁵ Turner *et al.*¹⁰ assumed that missing values were due to the respondent having returned to normal health; missing values were therefore imputed as “normal health” utility scores. The number of

QALYs gained over the 21-day period was estimated for the healthy adult, and at-risk and elderly populations for oseltamivir and placebo. The number of QALYs lost due to an influenza episode was calculated as the expected QALYs gained in the non-influenza population over 21 days minus the QALYs lost due to influenza over 21 days. For example, assuming a baseline utility of 0.90 without influenza, and a mean 21-day QALY gain of 0.041 with influenza, the number of QALYs lost due to influenza is calculated as $(0.90 \times 21 - 0.041 \times 365)/365$.

As equivalent data were not available from the zanamivir trials, the model assumes that the impact of zanamivir treatment on health-related quality of life is equivalent to that for oseltamivir. Data were not available for the paediatric population, therefore the model assumes the same QALY loss as the healthy adult population. The model also assumes that the QALY loss for an uncomplicated influenza episode is the same as that for an uncomplicated ILI episode. Mean QALY gains over 21 days used in the model are presented in Table 40. In their earlier report, Turner *et al.*¹⁰ modelled the uncertainty in the data, but did not account for additional uncertainty resulting from the process of mapping from Likert data collected in the trials to a VAS and subsequently to TTO utilities. In order to better reflect this uncertainty, the model uses the mean QALY scores and an assumed level of additional uncertainty (subjectively assigned). These parameters were modelled using beta distributions.

Table 40: Mean QALY gains over 21-day period

Population	Oseltamivir	Placebo
	Mean QALY	Mean QALY
1. Healthy children	0.042	0.041
2. At-risk children	0.030	0.028
3. Healthy adults	0.042	0.041
4. At-risk adults	0.030	0.028
5. Healthy elderly	0.030	0.028
6. At-risk elderly	0.030	0.028

QALYs lost due to adverse events due to prophylaxis

The model assumes that adverse events due to amantadine impact upon a patient's health-related quality of life. The model assumes a utility decrement of 0.20 for a mean duration of 5 days based on the previous work reported by Turner *et al.*¹⁰ Uncertainty surrounding the disutility of adverse events was modelled using a beta distribution, whilst uncertainty surrounding the duration of adverse events was modelled using a gamma distribution, assuming a standard error of 1 day.

QALYs lost due to ILI-related complications

In principle, the Likert scale data collected within the oseltamivir trials should have included quality of life valuations for individuals who experienced serious complications of influenza (or at least those occurring within the 21-day evaluation period). However, it should be noted that beyond the first seven days, the number of respondents in the treatment and placebo groups declined considerably. The model assumes that serious complications such as respiratory illness and the exacerbation of underlying health problems are not captured within these valuations, and that such complications result in a further reduction in a patient's health-related quality of life.

Systematic searches were undertaken to identify studies reporting preference-based valuations of the impact of influenza, influenza-like illness and related complications on health-related quality of life (See Appendix 1). The searches did not identify any published studies which reported preference-based valuations of the impact of the range of ILI complications associated with influenza and influenza-like illness (bronchitis, pneumonia, otitis media, exacerbation of an underlying condition e.g asthma). Instead, health utility decrements for secondary complications were derived from a modelling study of vaccination against a variety of diseases.¹²⁹ Within this study, committee Health Utility Index (Mark II) scores were derived for a number of health states associated with influenza and ILI (See Table 41). These utility estimates represent the consensus of the Committee who undertook the valuation exercise and as such do not include any estimates of uncertainty. Wide standard errors were assumed within the probabilistic sensitivity analysis based on lognormal distributions.

Table 41: Utility scores associated with ILI-related complications

Parameter	Committee HUI values	Mean decrement from baseline	Assumed lower 95% C.I.	Assumed upper 95% C.I.
Baseline utility score	0.90	-	-	-
Utility - moderate to severe respiratory illness	0.75	0.15	0.05	0.25
Utility - exacerbation of cardiac/asthma complication	0.53	0.37	0.27	0.47
Utility - other complications	0.53	0.37	0.27	0.47

The duration over which these utility decrements are applied was based on clinical trial data presented within the Roche submission,²⁰ sourced from clinical trials of oseltamivir. The duration of each illness was derived by simply calculating the number of days between the onset of the complication and its resolution (personal communication: Gavin Lewis, Roche). The submission

contained data relating to the duration of pneumonia, bronchitis and otitis media in children, healthy adults and at-risk groups. The mean duration of disutility for *any* respiratory complication was estimated by weighting the durations observed in the clinical trials by the ratio of pneumonia:bronchitis in each age group, as reported by Meier *et al.*¹² In the absence of any alternative evidence, the duration of other respiratory complications were assumed to follow this same pattern. The uncertainty analysis assumes a large standard error of 3 days for each subgroup; uncertainty surrounding these quantities was modelled using gamma distributions. Owing to a lack of alternative evidence, the duration of other non-respiratory complications are assumed to be the same as those for respiratory complications. Table 42 shows the assumed durations for these reductions in health-related quality of life.

Table 42: Assumed duration of utility reductions

Population	Respiratory and other complications		Otitis media	
	Mean duration (days)	Assumed standard error	Mean duration (days)	Assumed standard error
1. Healthy children	7.89	3.00	9.36	3.00
2. At-risk children	8.07	3.00	9.36	3.00
3. Healthy adults	9.23	3.00	9.36	3.00
4. At-risk adults	10.65	3.00	9.36	3.00
5. Healthy elderly	10.88	3.00	9.36	3.00
6. At-risk elderly	10.87	3.00	9.36	3.00

QALYs lost due to premature death resulting from ILI complications

The expected number of QALYs lost due to premature death due to secondary complications of ILI were also based on the methods reported by Turner *et al.*¹⁰ Crude estimates of the mean age of death due to influenza for the paediatric, adult and elderly populations were derived from data reported by the Office for National Statistics (DH2).¹³⁰ Interim life tables for England and Wales were then used to calculate the expected number of life years lost due to premature death for each age group based on the mean age of death. Life years lost were weighted by general population utility scores derived from Kind *et al.*¹³¹ to generate estimates of the number of QALYs lost within each age group. Expected QALYs losses were discounted at a rate of 3.5%. It should be noted that whilst the risk of death due to ILI complications is higher in the at-risk groups, the estimate of the number of QALYs lost is assumed to be the same for the healthy and at-risk populations; this assumption may bias in favour of prophylaxis within the at-risk population subgroups. Table 43 shows the modelled estimates of the expected discounted QALYs for each population group.⁹⁶

Table 43: Expected QALYs potentially lost resulting from death due to influenza

Population subgroup	Expected QALYs (discounted at 3.5%)
Children	24.74
Adults	13.37
Elderly	2.95

6.2.3 Calculation of cost-effectiveness

The central estimates of cost-effectiveness are based on the expected costs and QALYs lost for each option, as calculated from the results of the stochastic model. This approach is intended to capture any non-linearities in the model parameter distributions. The calculation of cost-effectiveness is fully incremental whereby each prophylactic strategy is compared against its next best comparator. Prophylactic strategies which are dominated (simple or extended) are ruled out of the analysis.

6.2.4 Uncertainty analysis

6.2.4.1 One-way sensitivity analysis and scenario analysis

Simple one-way sensitivity analysis and scenario analysis were undertaken to examine the impact of changing model assumptions on the incremental cost-effectiveness of alternative prophylaxis options (the results of these analyses are presented in Section 6.3.2). Details of these sensitivity analyses are detailed below.

Sensitivity analysis 1 Proposed price reduction for zanamivir

In November 2007, the manufacturer of zanamivir (GSK) applied to the Department of Health for a price modulation of two of their drugs, one of which was zanamivir. The current list price for zanamivir is £24.55 (5 disks, 4 blisters per disk); the new proposed price for zanamivir is £16.55 (Personal communication: Toni Maslen, Health Outcomes Programme Leader, GSK). This proposed price reduction for zanamivir was approved by the Department of Health with effect from the 1st February 2008 but was not listed in the BNF (No. 54)¹⁴ at the time of submission. This scenario analysis presents the central estimates of cost-effectiveness of influenza prophylaxis including this proposed price reduction for zanamivir. All other parameter values and assumptions within this analysis are held the same as per the base case analysis presented in Section 6.3.1. The reader should note that where zanamivir remains dominated by another prophylaxis option despite the price change, the slight differences in the cost-effectiveness of the

remaining prophylactic options from the base case results are due to sampling errors in the stochastic model.

Sensitivity analysis 2 Deterministic estimates of cost-effectiveness

The base case health economic analysis is based upon the expected (mean) costs and health outcomes for each prophylactic option, drawn from the stochastic model. The second scenario presents the cost-effectiveness results based upon the deterministic model.

Sensitivity analysis 3. Cost-effectiveness of oseltamivir given in suspension form

The base case analysis assumes that seasonal prophylaxis using oseltamivir is prescribed in capsule form to all adult populations, as this is likely to ensure more accurate dosing. However, in principle, oseltamivir given as suspension may allow for less wastage than in capsule form, thus leading to a reduction in the cost of the drug. A 56-cap pack of oseltamivir provides 10 x 75mg tablets providing 750 mg of the drug (10 doses) whilst a 75mL bottle (60mg/5mL) of oseltamivir in suspension form provides a total of 900mg of the drug (12 doses of 75mg). Whilst both products cost £16.36 per unit, the use of suspension could in principle offer savings over oseltamivir capsules.

Sensitivity analysis 4 Multiple prescriptions

The base case model assumes that each prescription of prophylaxis requires a GP consultation; for vaccinated patients, the model assumes that prophylaxis can be given during the same consultation as the influenza vaccine. The Roche model assumed that four prescriptions of prophylaxis could be obtained per GP attendance. This scenario analysis assumes that 4 prescriptions may be obtained per individual, thus resulting in a reduction in the cost of GP attendances for unvaccinated patients.²⁰

Sensitivity analyses 5 and 6 Reduced vaccine efficacy

Sensitivity analysis was undertaken assuming a lower efficacy rate for vaccination to capture the potential impact of a mismatch between vaccine and circulating strains of influenza. Scenario 5 assumes a relative risk for vaccination of 0.50, whilst Scenario 6 assumes a relative risk of 0.75.

Sensitivity analysis 7 Protection over entire influenza season

The base case analysis assumes that patients receiving seasonal prophylaxis are at risk of infection when they stop taking the drug. This scenario assumes that the patient is protected over the entire influenza season.

Sensitivity analysis 8 No antiviral treatment for symptomatic influenza

This sensitivity analysis assumes that patients who develop symptomatic ILI do not receive antiviral treatment using oseltamivir or zanamivir.

Sensitivity analysis 9 Equivalent efficacy for oseltamivir and zanamivir prophylaxis

There is uncertainty surrounding the relative efficacy of oseltamivir and zanamivir for the prophylaxis of influenza. The Roche model assumed that oseltamivir and zanamivir had equivalent efficacy. This scenario assumes that oseltamivir and zanamivir are equivalent, and uses the most favourable efficacy estimate for NIs within the model subgroup under evaluation.

Sensitivity analysis 10 No adverse events

There is uncertainty regarding the cost and health impact of adverse events associated with influenza prophylaxis. The base case model assumes that individuals receiving prophylaxis may experience adverse events that may lead to additional medical care costs and a further loss of quality of life for amantadine. This scenario explores the impact of assuming no costs or health impacts associated with adverse events.

Sensitivity analysis 11 No withdrawals from prophylaxis

The model assumes a proportion of patients withdraw from prophylaxis, and that patients who withdraw gain no protective benefit against influenza. This scenario assumes a withdrawal probability of zero.

Sensitivity analyses 12 to 16 Resistance against oseltamivir

The base case model assumes that resistance to oseltamivir is zero. These scenarios explore the impact of oseltamivir resistance on resulting cost-effectiveness estimates. Levels of resistance against amantadine are assumed to be the same as the base case value for each scenario.

Sensitivity analysis 17 Lower attack rates

Previous models of influenza prophylaxis have reported that cost-effectiveness estimates are highly sensitive to the true influenza attack rate. This scenario assumes that the attack rate is half that of the base case rate in each model subgroup.

Sensitivity analysis 18 Higher attack rates

This scenario assumes that the attack rate is double that of the base case rate in each model subgroup.

Sensitivity analysis 19 Use of a higher threshold for influenza activity

The base case analysis assumes that seasonal prophylaxis will be used when the GP consultation rate for ILI is in excess of 30 per 100,000 population.⁸ This scenario analysis examines the potential impact of using the previous influenza threshold of 50 consultations per 100,000 population on the cost-effectiveness of prophylaxis. This analysis draws on parameter values reported by Turner *et al.*¹⁰ which was undertaken when the previous influenza threshold was implemented.

Sensitivity analysis 20 Lower GP consultation rate

The base case model assumes that the probability that an individual with symptomatic influenza-like illness consults a healthcare professional is 0.25, however, this is based on a single survey and is associated with considerable uncertainty. This sensitivity analysis assumes that the probability that an individual with symptomatic ILI consults their GP is half the base case value.

Sensitivity analysis 21 Higher GP consultation rate

This sensitivity analysis assumes that the probability that an individual with symptomatic ILI consults their GP is double the base case value.

Sensitivity analysis 22 Alternative mapping function for influenza QALY loss

The base case model uses rating scale data from clinical trials, mapped to a VAS, and subsequently mapped to TTO to generate QALY gains for the period in which an individual has influenza. This sensitivity analysis uses an alternative mapping function, converting VAS data into EQ-5D utilities.

Sensitivity analysis 23 Lower QALY losses for at-risk groups

The base case model assumes that the likely reduction in expected QALYs lost due to premature death as a result of influenza complications is the same in healthy and at-risk populations. This analysis assumes that the expected QALY loss in the at-risk group is half the value used in the base case.

Sensitivity analysis 24 Complication utility decrements halved

The evidence concerning the impact of ILI complications on health outcomes is scarce and subject to considerable uncertainty (See Section 6.2). This analysis assumes a 50% reduction in utility decrements associated with ILI complications.

Sensitivity analysis 25 Impact of assumptions regarding hospitalisation in uncomplicated cases

The base case model assumes that uncomplicated ILI cases do not result in hospitalisation or death. Scenario 25 assumes that 10% of uncomplicated cases result in hospitalisation.

Sensitivity analysis 26 Undiscounted cost-effectiveness estimates

Within the base case model analysis, health outcomes were discounted at a rate of 3.5%. This analysis presents cost-effectiveness estimates without discounting.

6.2.4.2 Probabilistic sensitivity analysis

Comprehensive probabilistic sensitivity analysis was undertaken to explore the joint uncertainty in model parameters on the cost-effectiveness of each prophylaxis option. Uncertainty in model parameters was propagated through the model using Monte Carlo sampling techniques (5,000 samples) to generate information on the probability that each prophylactic option is optimal (i.e. that it produces the greatest amount of net benefit). The results of the probabilistic sensitivity analysis are presented as incremental cost-effectiveness acceptability curves (See Section Section 6.3.3, Appendix 10 and Appendix 11).

6.2.4 Model validation

The validity of the model was tested extensively. The model structure was reviewed throughout the model development process; the validity of key model assumptions were reviewed by clinical experts and compared against assumptions used within previous health economic models of influenza prophylaxis. At the end of the model development process, the logical consistency of

the model structure and the handling of model parameters were checked by the lead modeller and also by a second modeller who was not involved in the assessment. In addition, every model parameter and its distributional characteristics were checked against the source data that were used to inform it. Finally, the expectation of probabilistic samples of each model parameter was checked against its parameter mean to identify any programming errors and any areas of non-linearity introduced through the model structure.

6.3 Cost-effectiveness results

This section presents the results of the cost-effectiveness analysis of amantadine, oseltamivir and zanamivir for the prevention of influenza. Section 6.3.1 presents the central estimates of cost-effectiveness for each of the six model subgroups with and without previous influenza vaccination. As noted in Section 6.2.3, all central estimates of cost-effectiveness are based on expected costs and health outcomes generated by the stochastic model. Section 6.3.2 presents the results of the simple sensitivity analysis and scenario analysis to identify key determinants of the cost-effectiveness of amantadine, oseltamivir and zanamivir for the prevention of influenza. Section 6.3.3 presents the results of the probabilistic sensitivity analysis using cost-effectiveness acceptability curves (CEACs).

6.3.1 Central estimates of cost-effectiveness

6.3.1.1 Seasonal prophylaxis model results

Tables 44 to 49 present the central estimates of cost-effectiveness for seasonal prophylaxis using amantadine, oseltamivir and zanamivir for the six model subgroups. The reader should note that these central estimates are based on the BNF prices of amantadine, oseltamivir and zanamivir at the time of the assessment.

Group 1: *Healthy children - seasonal prophylaxis model results*

Table 44: Cost-effectiveness of seasonal prophylaxis - Healthy children

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£17.72	0.0043	-	-	-
Amantadine SP	£56.23	0.0040	-	-	ext dominated
Zanamivir SP	£112.15	0.0033	-	-	dominated
Oseltamivir SP	£85.51	0.0028	£67.79	0.0015	£44,007
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Amantadine SP	£78.64	0.0030	-	-	dominated
No prophylaxis	£43.23	0.0030	-	-	dominates
Zanamivir SP	£140.36	0.0026	-	-	dominated
Oseltamivir SP	£115.05	0.0024	£71.81	0.0006	£129,357

The model results presented in Table 44 suggests that the most effective seasonal prophylaxis option for healthy children is oseltamivir irrespective of vaccination status. Oseltamivir is expected to produce a small improvement in terms of QALYs losses avoided as compared against the other prophylactic strategies; however this is not the most expensive prophylactic option. Zanamivir is less effective and more expensive than oseltamivir irrespective of vaccination status, hence it is ruled out by simple dominance and is not included in this analysis. For healthy children who have not been previously vaccinated against influenza, amantadine is expected to be ruled out through extended dominance, as oseltamivir has a more favourable incremental cost-effectiveness ratio. For healthy children who have been previously vaccinated, amantadine is expected to be dominated by no prophylaxis. For unvaccinated children, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £44,000 per QALY gained. For healthy children who have received prior vaccination, the incremental cost-effectiveness of oseltamivir as compared against no prophylaxis is estimated to be approximately £129,000 per QALY gained.

Group 2: *At-risk children - seasonal prophylaxis model results*

Table 45: Cost-effectiveness of seasonal prophylaxis - At-risk children

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£29.89	0.0109	-	-	-
Amantadine SP	£66.92	0.0097	-	-	ext dominated
Zanamivir SP	£121.56	0.0083	-	-	dominated
Oseltamivir SP	£93.57	0.0071	£63.68	0.0038	£16,630
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£51.71	0.0075	-	-	-
Amantadine SP	£86.84	0.0073	-	-	ext dominated
Zanamivir SP	£147.86	0.0065	-	-	dominated
Oseltamivir SP	£122.06	0.0061	£70.34	0.0014	£51,069

The model results presented in Table 45 suggests that the most effective seasonal prophylaxis option for at-risk children is oseltamivir irrespective of whether they have been previously vaccinated or not. Again, zanamivir is expected to be less effective and more expensive than oseltamivir, hence it is ruled out of the analysis through simple dominance. Amantadine is expected to be ruled out of the analysis through extended dominance (again oseltamivir has a more favourable cost-effectiveness ratio). The incremental cost-effectiveness of oseltamivir as compared against no prophylaxis is estimated to be approximately £17,000 per QALY gained in unvaccinated at-risk children and £51,000 per QALY gained in at-risk children who have previously been vaccinated against influenza.

Group 3: *Healthy adults - seasonal prophylaxis model results*

Table 46: Cost-effectiveness of seasonal prophylaxis - Healthy adults

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£6.63	0.0020	-	-	-
Amantadine SP	£46.49	0.0019	-	-	ext dominated
Zanamivir SP	£103.70	0.0015	-	-	ext dominated
Oseltamivir SP	£111.09	0.0013	£104.45	0.0007	£147,505
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Amantadine SP	£71.34	0.0014	-	-	dominated
No prophylaxis	£35.64	0.0014	-	-	dominates
Zanamivir SP	£133.74	0.0012	-	-	ext dominated
Oseltamivir SP	£141.62	0.0011	£105.98	0.0002	£427,184

The results presented in Table 46 suggest that oseltamivir is expected to be the most effective option for seasonal prophylaxis of influenza in healthy adults. This analysis suggests that zanamivir is expected to be slightly less expensive than oseltamivir, but is ruled out by extended dominance. For unvaccinated healthy adults amantadine is ruled out of the analysis through extended dominance, whilst for vaccinated healthy adults amantadine is expected to be dominated by no prophylaxis. The incremental cost-effectiveness of oseltamivir as compared against no prophylaxis is estimated to be approximately £148,000 per QALY gained in unvaccinated healthy adults and £427,000 per QALY gained in healthy adults who have previously been vaccinated.

Group 4: *At-risk adults - seasonal prophylaxis model results*

Table 47: Cost-effectiveness of seasonal prophylaxis - At-risk adults

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£13.57	0.0046	-	-	-
Amantadine SP	£52.74	0.0042	-	-	ext dominated
Zanamivir SP	£108.33	0.0033	-	-	ext dominated
Oseltamivir SP	£115.63	0.0030	£102.06	0.0016	£63,552
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Amantadine SP	£75.94	0.0032	-	-	dominated
No prophylaxis	£40.39	0.0031			dominates
Zanamivir SP	£137.67	0.0027	-	-	ext dominated
Oseltamivir SP	£145.53	0.0025	£105.14	0.0006	£186,651

Table 47 suggests that oseltamivir is expected to be the most effective option for seasonal prophylaxis in at-risk adults. As with the healthy adult model, zanamivir is expected to be ruled out by extended dominance as oseltamivir has a lower incremental cost-effectiveness ratio. For unvaccinated at-risk adults, amantadine is expected to be ruled out through extended dominance, whilst for vaccinated individuals amantadine is expected to be less effective and more expensive than a policy of no prophylaxis. The incremental cost-effectiveness of oseltamivir as compared against no prophylaxis is estimated to be approximately £64,000 per QALY gained in unvaccinated individuals and £187,000 per QALY gained in at-risk adults who have previously been vaccinated against influenza.

Group 5: *Healthy elderly - seasonal prophylaxis model results*

Table 48: Cost-effectiveness of seasonal prophylaxis - Healthy elderly

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£10.43	0.0048	-	-	-
Amantadine SP	£49.93	0.0044	-	-	ext dominated
Zanamivir SP	£106.16	0.0035	-	-	ext dominated
Oseltamivir SP	£112.80	0.0028	£102.38	0.0021	£49,742
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Amantadine SP	£74.16	0.0035	-	-	dominated
No prophylaxis	£38.59	0.0035			dominates
Zanamivir SP	£136.02	0.0029	-	-	ext dominated
Oseltamivir SP	£143.54	0.0026	£104.95	0.0009	£121,728

The cost-effectiveness results presented in Table 48 suggest that oseltamivir is expected to be the most effective seasonal prophylaxis option for elderly adults who are otherwise healthy. As with the working age adult models, zanamivir is expected to be ruled out by extended dominance. Amantadine is expected to be ruled out through extended dominance for unvaccinated individuals, and is dominated by no prophylaxis in vaccinated populations. The incremental cost-effectiveness of oseltamivir as compared against no prophylaxis is estimated to be around £50,000 per QALY gained in unvaccinated healthy elderly adults, and around £122,000 per QALY gained in healthy elderly adults who have previously been vaccinated.

Group 6: *At-risk elderly - seasonal prophylaxis model results*

Table 49: Cost-effectiveness of seasonal prophylaxis - At-risk elderly

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£13.45	0.0062	-	-	-
Amantadine SP	£52.63	0.0057	-	-	ext dominated
Zanamivir SP	£108.39	0.0045	-	-	ext dominated
Oseltamivir SP	£114.54	0.0036	£101.09	0.0027	£38,098
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£40.75	0.0045	-	-	-
Amantadine SP	£76.25	0.0044	-	-	ext dominated
Zanamivir SP	£137.84	0.0037	-	-	ext dominated
Oseltamivir SP	£145.15	0.0033	£104.40	0.0011	£93,763

The results presented in Table 49 suggest that oseltamivir is expected to be the most effective seasonal prophylaxis option for at-risk elderly adults. Zanamivir and amantadine are both ruled out of the analysis by extended dominance. The incremental cost-effectiveness of oseltamivir compared against amantadine is estimated to be around £38,000 per QALY gained in unvaccinated at-risk elderly individuals and £94,000 per QALY gained in at-risk elderly adults who have previously been vaccinated.

6.3.1.2 Post-exposure prophylaxis model results

Tables 50 to 55 present the central estimates of cost-effectiveness for post-exposure prophylaxis of influenza using amantadine, oseltamivir and zanamivir for the six model subgroups.

Group 1: *Healthy children – post-exposure prophylaxis model results*

Table 50: Cost-effectiveness of post-exposure prophylaxis - Healthy children

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£18.96	0.0047	-	-	-
Amantadine PEP	£46.40	0.0039	-	-	ext dominated
Oseltamivir PEP	£54.35	0.0032	-	-	ext dominated
Zanamivir PEP	£61.18	0.0029	£42.22	0.0018	£23,225
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£44.09	0.0032	-	-	-
Amantadine PEP	£73.84	0.0030	-	-	ext dominated
Oseltamivir PEP	£83.30	0.0027	-	-	ext dominated
Zanamivir PEP	£91.00	0.0026	£46.91	0.0007	£71,648

The model results presented in Table 50 suggest that zanamivir is expected to be the most effective option for the post-exposure prophylaxis of influenza in otherwise healthy children. In this instance, oseltamivir and amantadine are ruled out of the analysis by extended dominance. The incremental cost-effectiveness of zanamivir versus no prophylaxis is estimated to be £23,000 per QALY gained for unvaccinated healthy children and around £72,000 in vaccinated healthy children.

The reader should note that oseltamivir is the only licensed prophylactic in children under the age of 5 years; the incremental cost-effectiveness ratio for oseltamivir versus no prophylaxis is expected to be around £24,000 per QALY gained and £74,000 per QALY gained in unvaccinated and vaccinated groups respectively.

Group 2: *At-risk children – post-exposure prophylaxis model results*

Table 51: Cost-effectiveness of post-exposure prophylaxis - At-risk children

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£32.56	0.0118	-	-	-
Amantadine PEP	£57.55	0.0097	-	-	ext dominated
Oseltamivir PEP	£63.97	0.0082	-	-	ext dominated
Zanamivir PEP	£69.76	0.0073	£37.20	0.0045	£8,233
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£53.57	0.0081	-	-	-
Amantadine PEP	£82.44	0.0074	-	-	ext dominated
Oseltamivir PEP	£91.35	0.0068	-	-	ext dominated
Zanamivir PEP	£98.67	0.0065	£45.10	0.0016	£27,684

The cost-effectiveness results presented in Table 51 suggest that zanamivir is expected to be the most effective option for the post-exposure prophylaxis of influenza in at-risk children. Oseltamivir and amantadine are expected to be ruled out of the analysis through extended dominance for unvaccinated and vaccinated subgroups. The incremental cost-effectiveness of zanamivir versus no prophylaxis is estimated to be around £8,000 per QALY gained in unvaccinated at-risk children and approximately £28,000 per QALY gained in vaccinated at-risk children.

For at-risk children under the age of 5 years, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £9,000 per QALY gained for unvaccinated at-risk children and around £29,000 per QALY gained for vaccinated at-risk children.

Group 3: *Healthy adults – post-exposure prophylaxis model results*

Table 52: Cost-effectiveness of post-exposure prophylaxis – Healthy adults

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£9.17	0.0028	-	-	-
Amantadine PEP	£38.48	0.0024	-	-	ext dominated
Zanamivir PEP	£55.19	0.0017	-	-	dominated
Oseltamivir PEP	£46.94	0.0017	£37.77	0.0011	£34,181
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£37.36	0.0019	-	-	-
Amantadine PEP	£67.80	0.0019	-	-	ext dominated
Zanamivir PEP	£85.67	0.0015	-	-	dominated
Oseltamivir PEP	£77.46	0.0015	£40.10	0.0004	£103,706

The cost-effectiveness estimates presented in Table 52 suggest that oseltamivir is expected to be the most effective option for the post-exposure prophylaxis of influenza in healthy adults. Within this subgroup, zanamivir is expected to be dominated by oseltamivir irrespective of vaccination status. Amantadine is expected to be ruled out through extended dominance. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is estimated to be £34,000 per QALY gained for vaccinated healthy adults and around £104,000 per QALY gained for unvaccinated healthy adults.

Group 4: *At-risk adults – post-exposure prophylaxis model results*

Table 53: Cost-effectiveness of post-exposure prophylaxis – At-risk adults

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£19.34	0.0064	-	-	-
Amantadine PEP	£47.10	0.0055	-	-	ext dominated
Zanamivir PEP	£61.49	0.0040	-	-	dominated
Oseltamivir PEP	£53.18	0.0039	£33.85	0.0025	£13,459
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£44.32	0.0044	-	-	-
Amantadine PEP	£74.21	0.0041	-	-	ext dominated
Zanamivir PEP	£91.27	0.0035	-	-	dominated
Oseltamivir PEP	£83.04	0.0035	£38.73	0.0009	£43,970

Table 53 suggests that oseltamivir is expected to be the most effective option for the post-exposure prophylaxis of influenza in at-risk adults. Again, zanamivir is expected to be dominated by oseltamivir irrespective of vaccination status. Amantadine is again expected to be ruled out through extended dominance. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is estimated to be around £13,000 per QALY gained for unvaccinated at-risk adults and £44,000 per QALY gained for previously vaccinated at-risk adults.

Group 5: *Healthy elderly – post-exposure prophylaxis model results*

Table 54: Cost-effectiveness of post-exposure prophylaxis – Healthy elderly

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£17.75	0.0082	-	-	-
Amantadine PEP	£45.76	0.0069	-	-	ext dominated
Zanamivir PEP	£60.50	0.0051	-	-	dominated
Oseltamivir PEP	£52.17	0.0050	£34.42	0.0032	£10,716
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£43.82	0.0059	-	-	-
Amantadine PEP	£73.59	0.0054	-	-	ext dominated
Zanamivir PEP	£90.52	0.0045	-	-	dominated
Oseltamivir PEP	£82.27	0.0045	£38.45	0.0014	£28,473

Table 54 suggest that oseltamivir is expected to be the most effective option for the post-exposure prophylaxis of influenza in otherwise healthy elderly adults. Zanamivir is again expected to be dominated by oseltamivir and is hence ruled out of the analysis. Amantadine is expected to be ruled out of the analysis through extended dominance. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is estimated to be around £11,000 per QALY gained for unvaccinated healthy elderly individuals and around £28,000 per QALY gained for at-risk elderly who have previously been vaccinated against influenza.

Group 6: *At-risk elderly – post-exposure prophylaxis model results*

Table 55: Cost-effectiveness of post-exposure prophylaxis – At-risk elderly

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£22.88	0.0106	-	-	-
Amantadine PEP	£50.05	0.0089	-	-	ext dominated
Zanamivir PEP	£63.68	0.0065	-	-	dominated
Oseltamivir PEP	£55.33	0.0065	£32.45	0.0041	£7,866
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£47.50	0.0076	-	-	-
Amantadine PEP	£76.92	0.0070	-	-	ext dominated
Zanamivir PEP	£93.37	0.0059	-	-	dominated
Oseltamivir PEP	£85.11	0.0058	£37.60	0.0017	£21,608

The model results presented in Table 55 suggest that oseltamivir is expected to be the most effective option for the post-exposure prophylaxis of influenza in at-risk elderly individuals. Zanamivir is expected to be dominated by oseltamivir and is ruled out of the analysis. Amantadine is expected to be ruled out through extended dominance. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is estimated to be around £8,000 per QALY for vaccinated at-risk elderly individuals and around £22,000 per QALY gained for at-risk elderly individuals who have previously been vaccinated.

6.3.2 *One-way/multi-way sensitivity analysis and scenario analysis*

This section presents one-way and multi-way sensitivity analysis to explore the impact of changing parameter assumptions on the incremental cost-effectiveness of amantadine, oseltamivir and zanamivir for the prevention of influenza. Descriptions of these scenarios are presented in Section 6.2.4.1.

6.3.2.1 Sensitivity analysis – cost-effectiveness results including proposed reduction in the price of zanamivir

Tables 56 to 67 present the results of the model incorporating the proposed price reduction for zanamivir. The reader should note that as these results are based on the stochastic model, they are subject to a small degree of Monte Carlo sampling error.

Seasonal prophylaxis

Table 56: Cost-effectiveness of seasonal prophylaxis – Healthy children

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£17.71	0.0043	-	-	-
Amantadine SP	£56.20	0.0040	-	-	ext dominated
Zanamivir SP	£87.59	0.0033	-	-	dominated
Oseltamivir SP	£85.49	0.0028	£67.78	0.0015	£43,870
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Amantadine SP	£78.64	0.0030	-	-	dominated
No prophylaxis	£43.22	0.0030	-	-	dominates
Zanamivir SP	£115.80	0.0026	-	-	dominated
Oseltamivir SP	£115.05	0.0024	£71.82	0.0006	£129,888

Table 57: Cost-effectiveness of seasonal prophylaxis – At-risk children

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£29.62	0.0109	-	-	-
Amantadine SP	£66.68	0.0097	-	-	ext dominated
Zanamivir SP	£96.83	0.0084	-	-	dominated
Oseltamivir SP	£93.38	0.0071	£63.76	0.0038	£16,598
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£51.53	0.0075	-	-	-
Amantadine SP	£86.66	0.0074	-	-	ext dominated
Zanamivir SP	£123.14	0.0066	-	-	dominated
Oseltamivir SP	£121.90	0.0061	£70.37	0.0014	£50,902

Table 58: Cost-effectiveness of seasonal prophylaxis – Healthy adults

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£6.57	0.0020	-	-	-
Amantadine SP	£46.40	0.0019	-	-	ext dominated
Zanamivir SP	£79.09	0.0015	-	-	ext dominated
Oseltamivir SP	£111.04	0.0013	£104.46	0.0007	£147,083
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Amantadine SP	£71.26	0.0014	-	-	dominated
No prophylaxis	£35.58	0.0014	-	-	dominates
Zanamivir SP	£109.11	0.0012	-	-	ext dominated
Oseltamivir SP	£141.56	0.0011	£105.98	0.0002	£427,802

Table 59: Cost-effectiveness of seasonal prophylaxis – At-risk adults

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£13.70	0.0046	-	-	-
Amantadine SP	£52.83	0.0042	-	-	ext dominated
Zanamivir SP	£83.85	0.0033	£70.15	0.0013	£53,159
Oseltamivir SP	£115.69	0.0030	£31.84	0.0003	£108,379
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Amantadine SP	£76.03	0.0031	-	-	dominated
No prophylaxis	£40.47	0.0031	-	-	dominates
Zanamivir SP	£113.17	0.0026	£72.70	0.0005	£157,216
Oseltamivir SP	£145.58	0.0025	£32.41	0.0001	£313,592

Table 60: Cost-effectiveness of seasonal prophylaxis – Healthy elderly

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£10.48	0.0048	-	-	-
Amantadine SP	£49.98	0.0044	-	-	ext dominated
Zanamivir SP	£81.63	0.0035	-	-	ext dominated
Oseltamivir SP	£112.82	0.0028	£102.34	0.0021	£49,590
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Amantadine SP	£74.21	0.0035	-	-	dominated
No prophylaxis	£38.63	0.0035	-	-	dominates
Zanamivir SP	£111.48	0.0029	-	-	ext dominated
Oseltamivir SP	£143.55	0.0026	£104.92	0.0009	£120,292

Table 61: Cost-effectiveness of seasonal prophylaxis – At-risk elderly

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£13.46	0.0062	-	-	-
Amantadine SP	£52.64	0.0057	-	-	ext dominated
Zanamivir SP	£83.81	0.0045	-	-	ext dominated
Oseltamivir SP	£114.53	0.0036	£101.07	0.0027	£37,968
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£40.75	0.0045	-	-	-
Amantadine SP	£76.26	0.0044	-	-	ext dominated
Zanamivir SP	£113.26	0.0037	-	-	ext dominated
Oseltamivir SP	£145.15	0.0033	£104.40	0.0011	£93,581

Post-exposure prophylaxis

Table 62: Cost-effectiveness of post-exposure prophylaxis – Healthy children

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£18.92	0.0047	-	-	-
Amantadine PEP	£46.38	0.0040	-	-	ext dominated
Oseltamivir PEP	£54.34	0.0032	-	-	dominated
Zanamivir PEP	£52.98	0.0029	£34.06	0.0018	£18,717
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£44.04	0.0032	-	-	-
Amantadine PEP	£73.81	0.0030	-	-	ext dominated
Oseltamivir PEP	£83.28	0.0027	-	-	dominated
Zanamivir PEP	£82.79	0.0026	£38.75	0.0007	£59,412

Table 63: Cost-effectiveness of post-exposure prophylaxis – At-risk children

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£32.38	0.0119	-	-	-
Amantadine PEP	£57.38	0.0098	-	-	ext dominated
Oseltamivir PEP	£63.82	0.0082	-	-	dominated
Zanamivir PEP	£61.45	0.0073	£29.07	0.0045	£6,390
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£53.42	0.0081	-	-	-
Amantadine PEP	£82.29	0.0075	-	-	ext dominated
Oseltamivir PEP	£91.22	0.0068	-	-	dominated
Zanamivir PEP	£90.37	0.0065	£36.96	0.0016	£22,663

Table 64: Cost-effectiveness of post-exposure prophylaxis – Healthy adults

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£9.23	0.0028	-	-	-
Amantadine PEP	£38.54	0.0024	-	-	ext dominated
Zanamivir PEP	£47.03	0.0017	-	-	dominated
Oseltamivir PEP	£46.96	0.0017	£37.73	0.0011	£34,099
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£37.40	0.0019	-	-	-
Amantadine PEP	£67.84	0.0019	-	-	ext dominated
Zanamivir PEP	£77.51	0.0015	-	-	dominated
Oseltamivir PEP	£77.49	0.0015	£40.09	0.0004	£103,573

Table 65: Cost-effectiveness of post-exposure prophylaxis – At-risk adults

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£19.18	0.0064	-	-	-
Amantadine PEP	£46.94	0.0055	-	-	ext dominated
Zanamivir PEP	£53.20	0.0040	-	-	dominated
Oseltamivir PEP	£53.09	0.0039	£33.92	0.0025	£13,539
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£44.20	0.0044	-	-	-
Amantadine PEP	£74.10	0.0041	-	-	ext dominated
Zanamivir PEP	£82.99	0.0035	-	-	dominated
Oseltamivir PEP	£82.96	0.0035	£38.75	0.0009	£44,163

Table 66: Cost-effectiveness of post-exposure prophylaxis – Healthy elderly

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£17.70	0.0082	-	-	-
Amantadine PEP	£45.74	0.0069	-	-	ext dominated
Zanamivir PEP	£52.28	0.0051	-	-	dominated
Oseltamivir PEP	£52.14	0.0050	£34.44	0.0032	£10,734
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£43.78	0.0059	-	-	-
Amantadine PEP	£73.56	0.0054	-	-	ext dominated
Zanamivir PEP	£82.30	0.0045	-	-	dominated
Oseltamivir PEP	£82.24	0.0045	£38.46	0.0013	£28,608

Table 67: Cost-effectiveness of post-exposure prophylaxis – At-risk elderly

Unvaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£22.75	0.0106	-	-	-
Amantadine PEP	£49.95	0.0089	-	-	ext dominated
Zanamivir PEP	£55.39	0.0065	-	-	dominated
Oseltamivir PEP	£55.24	0.0064	£32.49	0.0041	£7,892
Previously vaccinated individuals					
Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
No prophylaxis	£47.41	0.0075	-	-	-
Amantadine PEP	£76.84	0.0069	-	-	ext dominated
Zanamivir PEP	£85.10	0.0058	-	-	dominated
Oseltamivir PEP	£85.04	0.0058	£37.63	0.0017	£21,749

Table 68 summarises the incremental cost-effectiveness ratios presented in the base case analysis and the incremental cost-effectiveness ratios including the proposed reduction in the price of zanamivir.

Table 68: Summary of incremental cost-effectiveness ratios for influenza prophylaxis (base case and secondary analysis including proposed price reduction for zanamivir)

Population	Base case (incremental cost per QALY gained)			Price reduction for zanamivir (incremental cost per QALY gained)		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Seasonal prophylaxis						
1. Healthy children (no vacc)	ext dom	dom	£44,007	ext dom	dom	£43,870
1. Healthy children (vacc)	dom	dom	£129,357	dom	dom	£129,888
2. At-risk children (no vacc)	ext dom	dom	£16,630	ext dom	dom	£16,598
2. At-risk children (vacc)	ext dom	dom	£51,069	ext dom	dom	£50,902
3. Healthy adults (no vacc)	ext dom	ext dom	£147,505	ext dom	ext dom	£147,083
3. Healthy adults (vacc)	dom	ext dom	£427,184	dom	ext dom	£427,802
4. At-risk adults (no vacc)	ext dom	ext dom	£63,552	ext dom	£53,159	£108,379
4. At-risk adults (vacc)	dom	ext dom	£186,651	dom	£157,216	£313,592
5. Healthy elderly (no vacc)	ext dom	ext dom	£49,742	ext dom	ext dom	£49,590
5. Healthy elderly (vacc)	dom	ext dom	£121,728	dom	ext dom	£120,292
6. At-risk elderly (no vacc)	ext dom	ext dom	£38,098	ext dom	ext dom	£37,968
6. At-risk elderly (vacc)	ext dom	ext dom	£93,763	ext dom	ext dom	£93,581
Post-exposure prophylaxis						
1. Healthy children (no vacc)	ext dom	£23,225	ext dom	ext dom	£18,717	dom
1. Healthy children (vacc)	ext dom	£71,648	ext dom	ext dom	£59,412	dom
2. At-risk children (no vacc)	ext dom	£8,233	ext dom	ext dom	£6,390	dom
2. At-risk children (vacc)	ext dom	£27,684	ext dom	ext dom	£22,663	dom
3. Healthy adults (no vacc)	ext dom	dom	£34,181	ext dom	dom	£34,099
3. Healthy adults (vacc)	ext dom	dom	£103,706	ext dom	dom	£103,573
4. At-risk adults (no vacc)	ext dom	dom	£13,459	ext dom	dom	£13,539
4. At-risk adults (vacc)	ext dom	dom	£43,970	ext dom	dom	£44,163
5. Healthy elderly (no vacc)	ext dom	dom	£10,716	ext dom	dom	£10,734
5. Healthy elderly (vacc)	ext dom	dom	£28,473	ext dom	dom	£28,608
6. At-risk elderly (no vacc)	ext dom	dom	£7,866	ext dom	dom	£7,892
6. At-risk elderly (vacc)	ext dom	dom	£21,608	ext dom	dom	£21,749

Dom = dominated, ext dom = extendedly dominated

The summary of cost-effectiveness results presented in Table 68 shows that the proposed price reduction has no impact on the majority of economic comparisons presented in the base case analysis. In terms of seasonal prophylaxis, the cost-effectiveness of zanamivir is no longer ruled out through extended dominance in at-risk adults, however the incremental cost-effectiveness ratio for zanamivir versus no prophylaxis remains in excess of £50,000 per QALY gained for these comparisons. In terms of the post-exposure prophylaxis of influenza, the price reduction has no impact on the adult and elderly subgroup analyses, as zanamivir consistently remains dominated by oseltamivir. The proposed price reduction is however expected to lead to an improvement in the cost-effectiveness of zanamivir for otherwise healthy and at-risk children. For unvaccinated healthy children, the reduction in the price of zanamivir is expected to result in a reduction in the cost-effectiveness of zanamivir versus no prophylaxis from £23,000 per QALY gained to £19,000 per QALY gained. The cost-effectiveness of zanamivir in vaccinated otherwise healthy children is expected to be in excess of £59,000 per QALY gained. For unvaccinated at-risk children, the lower price for zanamivir is expected to lead to an improvement in the cost-effectiveness of zanamivir versus no prophylaxis from £8,000 per QALY gained to £6,000 per QALY gained. For vaccinated at-risk children, the cost-effectiveness of zanamivir is improved from £28,000 per QALY gained to £23,000 per QALY gained.

6.3.2 *One-way sensitivity analysis and scenario analysis results*

6.3.2.1 One-way sensitivity analysis and scenario analysis results – healthy children

The results of the simple sensitivity analysis for the healthy children subgroup are presented in Table 69.

Table 69: Sensitivity analysis - healthy children

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Seasonal prophylaxis						
Base case (stochastic model)	ext dom	dom	£44,007	dom	dom	£129,357
1. Price reduction zanamivir	ext dom	dom	£43,870	dom	dom	£129,888
2. Base case deterministic model	ext dom	dom	£42,244	dom	dom	£124,523
3. Oseltamivir as suspension	ext dom	dom	£42,244	dom	dom	£124,523
4. Multiple prescriptions	ext dom	dom	£42,244	dom	dom	£124,523
5. Vaccine efficacy = 50%	ext dom	dom	£42,244	dom	dom	£88,526
6. Vaccine efficacy = 25%	ext dom	dom	£42,244	ext dom	dom	£57,672
7. 100% protection over flu season	ext dom	dom	£42,244	ext dom	dom	£124,523
8. No antiviral treatment	ext dom	dom	£42,244	dom	dom	£124,523
9. Best case efficacy for NIs	ext dom	dom	£42,244	dom	dom	£124,523
10. No adverse events	ext dom	dom	£42,244	ext dom	dom	£124,523
11. No withdrawals	ext dom	dom	£41,319	dom	dom	£121,952
12. 10% resistance for oseltamivir	ext dom	dom	£47,387	dom	dom	£138,807
13. 20% resistance for oseltamivir	ext dom	dom	£53,815	dom	dom	£156,663
14. 30% resistance for oseltamivir	ext dom	dom	£62,079	dom	dom	£179,620
15. 40% resistance for oseltamivir	ext dom	£573,163	£73,099	dom	£1,599,296	£210,229
16. 50% resistance for oseltamivir	ext dom	£117,218	£88,526	dom	£332,782	£253,083
17. Attack rates halved	ext dom	dom	£88,526	dom	dom	£253,083
18. Attack rates doubled	ext dom	dom	£19,104	ext dom	dom	£60,243
19. Higher influenza threshold	ext dom	dom	£70,476	dom	dom	£202,944
20. GP consultation rates halved	ext dom	dom	£42,560	dom	dom	£124,839
21. GP consultation rates doubled	ext dom	dom	£41,613	dom	dom	£123,891
22. VAS to EQ-5D mapping function	ext dom	dom	£38,980	dom	dom	£114,902
23. QALY loss for at-risk halved	ext dom	dom	£42,244	dom	dom	£124,523
24. Complication disutilities halved	ext dom	dom	£43,102	dom	dom	£127,052
25. 10% uncomplicated hospitalised	ext dom	dom	£22,513	dom	dom	£104,791
26. Undiscounted	ext dom	dom	£35,111	dom	dom	£103,495

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Post-exposure prophylaxis						
Base case (stochastic model)	ext dom	£23,225	ext dom	ext dom	£71,648	ext dom
1. Price reduction zanamivir	ext dom	£18,717	dom	ext dom	£59,412	dom
2. Base case deterministic model	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
3. Oseltamivir as suspension	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
4. Multiple prescriptions	ext dom	£19,634	£11,322	ext dom	£61,717	£38,627
5. Vaccine efficacy = 50%	ext dom	£23,217	ext dom	ext dom	£50,471	ext dom
6. Vaccine efficacy = 25%	ext dom	£23,217	ext dom	ext dom	£32,302	ext dom
7. 100% protection over flu season	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
8. No antiviral treatment	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
9. Best case efficacy for NIs	ext dom	£630,864	£18,875	ext dom	£1,759,576	£59,607
10. No adverse events	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
11. No withdrawals	ext dom	£22,863	ext dom	ext dom	£70,684	ext dom
12. 10% resistance for oseltamivir	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
13. 20% resistance for oseltamivir	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
14. 30% resistance for oseltamivir	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
15. 40% resistance for oseltamivir	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
16. 50% resistance for oseltamivir	ext dom	£23,217	dom	ext dom	£71,668	ext dom
17. Attack rates halved	ext dom	£50,471	ext dom	ext dom	£147,374	ext dom
18. Attack rates doubled	ext dom	£9,590	ext dom	ext dom	£33,816	ext dom
19. Higher influenza threshold	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
20. GP consultation rates halved	ext dom	£23,533	ext dom	ext dom	£71,984	ext dom
21. GP consultation rates doubled	ext dom	£22,585	ext dom	ext dom	£71,037	ext dom
22. VAS to EQ-5D mapping function	ext dom	£21,423	ext dom	ext dom	£66,131	ext dom
23. QALY loss for at-risk halved	ext dom	£23,217	ext dom	ext dom	£71,668	ext dom
24. Complication disutilities halved	ext dom	£23,688	ext dom	ext dom	£73,124	ext dom
25. 10% uncomplicated hospitalised	dom	£3,485	dom	ext dom	£51,937	ext dom
26. Undiscounted	ext dom	£19,296	ext dom	ext dom	£59,566	ext dom

Dom = dominated, ext dom = extendedly dominated

The simple sensitivity analysis results presented in Table 69 suggest that the base case seasonal prophylaxis cost-effectiveness estimates are sensitive to assumptions regarding influenza attack rates, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community (particularly the duration of the influenza season), the risk of hospitalisation in uncomplicated cases, and the discount rate. Amantadine and zanamivir as seasonal prophylaxis remain dominated across almost all scenarios. The cost-effectiveness estimates for post-exposure prophylaxis are sensitive to the influenza attack rate, the use of multiple prescriptions of prophylaxis at a single GP visit, vaccine efficacy, assumptions regarding the relative effectiveness of oseltamivir and zanamivir, and the risk of hospitalisation in uncomplicated cases. Amantadine and oseltamivir as post-exposure prophylaxis remain dominated or extendedly dominated by zanamivir within the majority of the scenarios presented for healthy children.

6.3.2.2 One-way sensitivity analysis and scenario analysis results – at-risk children

The results of the simple sensitivity analysis for the at-risk children subgroup are presented in Table 70.

Table70: Sensitivity analysis – at-risk children

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Seasonal prophylaxis						
Base case (stochastic model)	ext dom	dom	£16,630	ext dom	dom	£51,069
1. Price reduction zanamivir	ext dom	dom	£16,598	ext dom	dom	£50,902
2. Base case deterministic model	ext dom	dom	£15,882	ext dom	dom	£48,943
3. Oseltamivir as suspension	ext dom	dom	£15,882	ext dom	dom	£48,943
4. Multiple prescriptions	ext dom	dom	£15,882	ext dom	dom	£48,943
5. Vaccine efficacy = 50%	ext dom	dom	£15,882	ext dom	dom	£34,479
6. Vaccine efficacy = 25%	ext dom	dom	£15,882	ext dom	dom	£22,081
7. 100% protection over flu season	ext dom	dom	£15,882	ext dom	dom	£48,943
8. No antiviral treatment	ext dom	dom	£15,595	ext dom	dom	£48,118
9. Best case efficacy for NIs	ext dom	dom	£15,882	ext dom	dom	£48,943
10. No adverse events	ext dom	dom	£15,882	ext dom	dom	£48,943
11. No withdrawals	ext dom	dom	£15,510	ext dom	dom	£47,910
12. 10% resistance for oseltamivir	ext dom	dom	£17,948	ext dom	dom	£54,683
13. 20% resistance for oseltamivir	ext dom	dom	£20,531	ext dom	dom	£61,857
14. 30% resistance for oseltamivir	ext dom	dom	£23,852	ext dom	dom	£71,082
15. 40% resistance for oseltamivir	ext dom	£229,215	£28,280	ext dom	£641,536	£83,381
16. 50% resistance for oseltamivir	£29,840	£46,007	£42,085	ext dom	£132,625	£100,601
17. Attack rates halved	ext dom	dom	£34,479	dom	dom	£100,601
18. Attack rates doubled	ext dom	dom	£6,583	ext dom	dom	£23,114
19. Higher influenza threshold	ext dom	dom	£27,226	ext dom	dom	£80,454
20. GP consultation rates halved	ext dom	dom	£15,863	ext dom	dom	£48,653
21. GP consultation rates doubled	ext dom	dom	£15,921	ext dom	dom	£49,538
22. VAS to EQ-5D mapping function	ext dom	dom	£16,932	ext dom	dom	£52,179
23. QALY loss for at-risk halved	ext dom	dom	£17,821	ext dom	dom	£54,920
24. Complication disutilities halved	ext dom	dom	£16,041	ext dom	dom	£49,435
25. 10% uncomplicated hospitalised	ext dom	dom	£8,341	ext dom	dom	£41,402
26. Undiscounted	ext dom	dom	£11,658	ext dom	dom	£35,925

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Post-exposure prophylaxis						
Base case (stochastic model)	ext dom	£8,233	ext dom	ext dom	£27,684	ext dom
1. Price reduction zanamivir	ext dom	£6,390	dom	ext dom	£22,663	dom
2. Base case deterministic model	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
3. Oseltamivir as suspension	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
4. Multiple prescriptions	£2,991	£6,797	£4,075	ext dom	£23,706	£14,428
5. Vaccine efficacy = 50%	ext dom	£8,236	ext dom	ext dom	£19,187	ext dom
6. Vaccine efficacy = 25%	ext dom	£8,236	ext dom	ext dom	£11,887	ext dom
7. 100% protection over flu season	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
8. No antiviral treatment	ext dom	£8,073	ext dom	ext dom	£27,226	ext dom
9. Best case efficacy for NIs	ext dom	£252,401	£6,491	ext dom	£705,940	£22,858
10. No adverse events	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
11. No withdrawals	ext dom	£8,094	ext dom	ext dom	£27,310	ext dom
12. 10% resistance for oseltamivir	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
13. 20% resistance for oseltamivir	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
14. 30% resistance for oseltamivir	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
15. 40% resistance for oseltamivir	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
16. 50% resistance for oseltamivir	ext dom	£8,236	dom	ext dom	£27,705	dom
17. Attack rates halved	ext dom	£19,187	ext dom	ext dom	£58,125	ext dom
18. Attack rates doubled	ext dom	£2,761	ext dom	ext dom	£12,495	ext dom
19. Higher influenza threshold	ext dom	£8,236	ext dom	ext dom	£27,705	ext dom
20. GP consultation rates halved	ext dom	£8,280	ext dom	ext dom	£27,589	ext dom
21. GP consultation rates doubled	ext dom	£8,147	ext dom	ext dom	£27,943	ext dom
22. VAS to EQ-5D mapping function	ext dom	£8,781	ext dom	ext dom	£29,537	ext dom
23. QALY loss for at-risk halved	ext dom	£9,242	ext dom	ext dom	£31,088	ext dom
24. Complication disutilities halved	ext dom	£8,319	ext dom	ext dom	£27,983	ext dom
25. 10% uncomplicated hospitalised	dom	£696	dom	ext dom	£20,165	ext dom
26. Undiscounted	ext dom	£6,045	ext dom	ext dom	£20,336	ext dom

Dom = dominated, ext dom = extendedly dominated

The simple sensitivity analysis results presented in Table 70 suggest that the base case seasonal prophylaxis cost-effectiveness estimates for at-risk children are again sensitive to influenza attack rates, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community, the risk of hospitalisation in uncomplicated cases, and the discount rate. Amantadine and zanamivir remain dominated by oseltamivir in almost every scenario within this subgroup. The cost-effectiveness estimates for post-exposure prophylaxis are also sensitive to the influenza attack rate, the use of multiple prescriptions of prophylaxis at a single GP visit, vaccine efficacy, assumptions regarding the relative effectiveness of oseltamivir and zanamivir, and the risk of hospitalisation in uncomplicated cases. Amantadine and oseltamivir post-exposure prophylaxis are generally dominated or extendedly dominated by zanamivir within the at-risk children subgroup.

6.3.2.3 One-way sensitivity analysis and scenario analysis results – healthy adults

The results of the simple sensitivity analysis for the healthy adult subgroup are presented in Table 71.

Table 71: Sensitivity analysis - healthy adults

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Seasonal prophylaxis						
Base case (stochastic model)	ext dom	ext dom	£147,505	dom	ext dom	£427,184
1. Price reduction zanamivir	ext dom	ext dom	£147,083	dom	ext dom	£427,802
2. Base case deterministic model	ext dom	ext dom	£141,659	dom	ext dom	£410,832
3. Oseltamivir as suspension	ext dom	dom	£119,456	dom	dom	£347,397
4. Multiple prescriptions	ext dom	ext dom	£141,659	dom	ext dom	£410,832
5. Vaccine efficacy = 50%	ext dom	ext dom	£141,659	dom	ext dom	£286,598
6. Vaccine efficacy = 25%	ext dom	ext dom	£141,659	dom	ext dom	£189,972
7. 100% protection over flu season	ext dom	ext dom	£141,659	dom	ext dom	£410,832
8. No antiviral treatment	ext dom	ext dom	£141,659	dom	ext dom	£410,832
9. Best case efficacy for NIs	ext dom	ext dom	£141,659	dom	ext dom	£410,832
10. No adverse events	ext dom	ext dom	£141,659	ext dom	ext dom	£410,832
11. No withdrawals	ext dom	ext dom	£138,760	dom	ext dom	£402,550
12. 10% resistance for oseltamivir	ext dom	ext dom	£157,763	dom	ext dom	£456,845
13. 20% resistance for oseltamivir	ext dom	ext dom	£177,894	dom	ext dom	£514,360
14. 30% resistance for oseltamivir	ext dom	ext dom	£203,776	dom	ext dom	£588,309
15. 40% resistance for oseltamivir	ext dom	£210,381	dom	dom	£607,181	dom
16. 50% resistance for oseltamivir	ext dom	£210,381	dom	dom	£607,181	dom
17. Attack rates halved	dom	ext dom	£286,598	dom	ext dom	£824,945
18. Attack rates doubled	ext dom	ext dom	£69,189	dom	ext dom	£203,776
19. Higher influenza threshold	ext dom	ext dom	£230,072	dom	ext dom	£663,441
20. GP consultation rates halved	ext dom	ext dom	£141,921	dom	ext dom	£411,095
21. GP consultation rates doubled	ext dom	ext dom	£141,133	dom	ext dom	£410,307
22. VAS to EQ-5D mapping function	ext dom	ext dom	£133,013	dom	ext dom	£385,758
23. QALY loss for at-risk halved	ext dom	ext dom	£141,659	dom	ext dom	£410,832
24. Complication disutilities halved	ext dom	ext dom	£143,075	dom	ext dom	£414,940
25. 10% uncomplicated hospitalised	ext dom	dom	£110,466	dom	ext dom	£379,639
26. Undiscounted	ext dom	ext dom	£119,801	dom	ext dom	£347,440

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Post-exposure prophylaxis						
Base case (stochastic model)	ext dom	dom	£34,181	ext dom	dom	£103,706
1. Price reduction zanamivir	ext dom	dom	£34,099	ext dom	dom	£103,573
2. Base case deterministic model	ext dom	dom	£34,113	ext dom	dom	£103,558
3. Oseltamivir as suspension	ext dom	dom	£34,113	ext dom	dom	£103,558
4. Multiple prescriptions	ext dom	dom	£17,161	ext dom	dom	£55,124
5. Vaccine efficacy = 50%	ext dom	dom	£34,113	ext dom	dom	£71,507
6. Vaccine efficacy = 25%	ext dom	dom	£34,113	ext dom	dom	£46,578
7. 100% protection over flu season	ext dom	dom	£34,113	ext dom	dom	£103,558
8. No antiviral treatment	ext dom	dom	£34,113	ext dom	dom	£103,558
9. Best case efficacy for NIs	ext dom	£1,032,921	£34,113	ext dom	£2,957,296	£103,558
10. No adverse events	ext dom	dom	£34,113	ext dom	dom	£103,558
11. No withdrawals	ext dom	dom	£33,365	ext dom	dom	£101,422
12. 10% resistance for oseltamivir	ext dom	£86,714	£38,268	ext dom	£253,847	£115,429
13. 20% resistance for oseltamivir	ext dom	£42,326	ext dom	ext dom	£127,024	ext dom
14. 30% resistance for oseltamivir	ext dom	£42,326	ext dom	ext dom	£127,024	ext dom
15. 40% resistance for oseltamivir	ext dom	£42,326	ext dom	ext dom	£127,024	ext dom
16. 50% resistance for oseltamivir	ext dom	£42,326	ext dom	ext dom	£127,024	ext dom
17. Attack rates halved	ext dom	dom	£71,507	dom	dom	£210,397
18. Attack rates doubled	ext dom	dom	£15,416	ext dom	dom	£50,139
19. Higher influenza threshold	ext dom	dom	£34,113	ext dom	dom	£103,558
20. GP consultation rates halved	ext dom	dom	£34,376	ext dom	dom	£103,821
21. GP consultation rates doubled	ext dom	dom	£33,588	ext dom	dom	£103,033
22. VAS to EQ-5D mapping function	ext dom	dom	£32,031	ext dom	dom	£97,238
23. QALY loss for at-risk halved	ext dom	dom	£34,113	ext dom	dom	£103,558
24. Complication disutilities halved	ext dom	dom	£34,454	ext dom	dom	£104,594
25. 10% uncomplicated hospitalised	dom	dom	£2,920	ext dom	dom	£72,366
26. Undiscounted	ext dom	dom	£28,849	ext dom	dom	£87,579

Dom = dominated, ext dom = extendedly dominated

The results presented in Table 71 suggest that the cost-effectiveness estimates for seasonal prophylaxis in healthy adults are sensitive to assumptions regarding influenza attack rates, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community, the risk of hospitalisation in uncomplicated cases, and the discount rate. The post-exposure prophylaxis healthy adult model is sensitive to the influenza attack rate, the use of multiple prescriptions of prophylaxis at a single GP visit, vaccine efficacy, and the risk of hospitalisation in uncomplicated cases.

6.3.2.4 One-way sensitivity analysis and scenario analysis results – at-risk adults

The results of the simple sensitivity analysis for the at-risk adult subgroup are presented in Table 72.

Table 72: Sensitivity analysis – at-risk adults

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Seasonal prophylaxis						
Base case (stochastic model)	ext dom	ext dom	£63,552	dom	ext dom	£186,651
1. Price reduction zanamivir	ext dom	£53,159	£108,379	dom	£157,216	£313,592
2. Base case deterministic model	ext dom	ext dom	£60,742	dom	ext dom	£179,061
3. Oseltamivir as suspension	ext dom	dom	£50,982	dom	dom	£151,177
4. Multiple prescriptions	ext dom	ext dom	£60,742	dom	ext dom	£179,061
5. Vaccine efficacy = 50%	ext dom	ext dom	£60,742	ext dom	ext dom	£124,452
6. Vaccine efficacy = 25%	ext dom	ext dom	£60,742	ext dom	ext dom	£81,979
7. 100% protection over flu season	ext dom	£50,868	dom	ext dom	£150,850	dom
8. No antiviral treatment	ext dom	ext dom	£60,133	dom	ext dom	£177,346
9. Best case efficacy for NIs	ext dom	ext dom	£55,732	dom	ext dom	£164,748
10. No adverse events	ext dom	ext dom	£60,742	ext dom	ext dom	£179,061
11. No withdrawals	ext dom	ext dom	£59,468	dom	ext dom	£175,421
12. 10% resistance for oseltamivir	ext dom	ext dom	£67,821	dom	ext dom	£199,287
13. 20% resistance for oseltamivir	ext dom	£73,941	£136,614	dom	£216,773	£395,839
14. 30% resistance for oseltamivir	ext dom	£73,941	dom	dom	£216,773	dom
15. 40% resistance for oseltamivir	ext dom	£73,941	dom	dom	£216,773	dom
16. 50% resistance for oseltamivir	ext dom	£73,941	dom	dom	£216,773	dom
17. Attack rates halved	ext dom	ext dom	£124,452	dom	ext dom	£361,091
18. Attack rates doubled	ext dom	ext dom	£28,887	ext dom	ext dom	£88,046
19. Higher influenza threshold	ext dom	ext dom	£99,605	dom	ext dom	£290,100
20. GP consultation rates halved	ext dom	ext dom	£60,550	dom	ext dom	£178,314
21. GP consultation rates doubled	ext dom	ext dom	£61,130	dom	ext dom	£180,578
22. VAS to EQ-5D mapping function	ext dom	ext dom	£64,220	dom	ext dom	£189,314
23. QALY loss for at-risk halved	ext dom	ext dom	£72,871	dom	ext dom	£214,817
24. Complication disutilities halved	ext dom	ext dom	£61,222	dom	ext dom	£180,476
25. 10% uncomplicated hospitalised	ext dom	ext dom	£47,704	dom	ext dom	£166,024
26. Undiscounted	ext dom	ext dom	£51,290	dom	ext dom	£151,197

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Post-exposure prophylaxis						
Base case (stochastic model)	ext dom	dom	£13,459	ext dom	dom	£43,970
1. Price reduction zanamivir	ext dom	dom	£13,539	ext dom	dom	£44,163
2. Base case deterministic model	ext dom	dom	£13,468	ext dom	dom	£43,994
3. Oseltamivir as suspension	ext dom	dom	£13,468	ext dom	dom	£43,994
4. Multiple prescriptions	ext dom	dom	£6,017	ext dom	dom	£22,704
5. Vaccine efficacy = 50%	ext dom	dom	£13,468	ext dom	dom	£29,905
6. Vaccine efficacy = 25%	ext dom	dom	£13,468	ext dom	dom	£18,947
7. 100% protection over flu season	ext dom	dom	£13,468	ext dom	dom	£43,994
8. No antiviral treatment	ext dom	dom	£13,301	ext dom	dom	£43,542
9. Best case efficacy for NIs	ext dom	£452,511	£13,468	ext dom	£1,298,402	£43,994
10. No adverse events	ext dom	dom	£13,468	ext dom	dom	£43,994
11. No withdrawals	ext dom	dom	£13,140	ext dom	dom	£43,055
12. 10% resistance for oseltamivir	ext dom	£36,590	£15,295	ext dom	£110,056	£49,212
13. 20% resistance for oseltamivir	ext dom	£17,078	ext dom	ext dom	£54,309	ext dom
14. 30% resistance for oseltamivir	ext dom	£17,078	ext dom	ext dom	£54,309	ext dom
15. 40% resistance for oseltamivir	ext dom	£17,078	ext dom	ext dom	£54,309	ext dom
16. 50% resistance for oseltamivir	ext dom	£17,078	ext dom	ext dom	£54,309	ext dom
17. Attack rates halved	ext dom	dom	£29,905	ext dom	dom	£90,957
18. Attack rates doubled	ext dom	dom	£5,250	ext dom	dom	£20,513
19. Higher influenza threshold	ext dom	dom	£13,468	ext dom	dom	£43,994
20. GP consultation rates halved	ext dom	dom	£13,499	ext dom	dom	£43,881
21. GP consultation rates doubled	ext dom	dom	£13,406	ext dom	dom	£44,223
22. VAS to EQ-5D mapping function	ext dom	dom	£14,239	ext dom	dom	£46,513
23. QALY loss for at-risk halved	ext dom	dom	£16,158	ext dom	dom	£52,779
24. Complication disutilities halved	ext dom	dom	£13,575	ext dom	dom	£44,342
25. 10% uncomplicated hospitalised	dom	dom	£430	ext dom	dom	£30,956
26. Undiscounted	ext dom	dom	£11,372	ext dom	dom	£37,148

Dom = dominated, ext dom = extendedly dominated

The results presented in Table 72 suggest that the cost-effectiveness estimates for seasonal prophylaxis in at-risk adults are again sensitive to assumptions regarding influenza attack rates, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community, the relative effectiveness of oseltamivir and zanamivir, the risk of hospitalisation in uncomplicated cases, and the discount rate. The post-exposure prophylaxis healthy adult model is sensitive to the influenza attack rate, the use of multiple prescriptions of prophylaxis at a single GP visit, vaccine efficacy, and the risk of hospitalisation in uncomplicated cases.

6.3.2.5 One-way sensitivity analysis and scenario analysis results – healthy elderly

The results of the simple sensitivity analysis for the healthy elderly subgroup are presented in Table 73.

Table 73: Sensitivity analysis – healthy elderly

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Seasonal prophylaxis						
Base case (stochastic model)	ext dom	ext dom	£49,742	dom	ext dom	£121,728
1. Price reduction zanamivir	ext dom	ext dom	£49,590	dom	ext dom	£120,292
2. Base case deterministic model	ext dom	ext dom	£47,609	dom	ext dom	£116,346
3. Oseltamivir as suspension	ext dom	dom	£39,984	dom	dom	£98,192
4. Multiple prescriptions	ext dom	ext dom	£47,609	dom	ext dom	£116,346
5. Vaccine efficacy = 50%	ext dom	ext dom	£47,609	ext dom	ext dom	£97,384
6. Vaccine efficacy = 25%	ext dom	ext dom	£47,609	ext dom	ext dom	£64,201
7. 100% protection over flu season	ext dom	ext dom	£47,609	ext dom	ext dom	£116,346
8. No antiviral treatment	ext dom	ext dom	£47,055	dom	ext dom	£115,020
9. Best case efficacy for NIs	ext dom	ext dom	£47,609	dom	ext dom	£116,346
10. No adverse events	ext dom	ext dom	£47,609	ext dom	ext dom	£116,346
11. No withdrawals	ext dom	ext dom	£46,613	ext dom	ext dom	£113,976
12. 10% resistance for oseltamivir	ext dom	ext dom	£53,140	dom	ext dom	£129,515
13. 20% resistance for oseltamivir	ext dom	ext dom	£60,053	dom	ext dom	£145,975
14. 30% resistance for oseltamivir	ext dom	ext dom	£68,941	dom	ext dom	£167,138
15. 40% resistance for oseltamivir	ext dom	£72,737	dom	dom	£176,176	dom
16. 50% resistance for oseltamivir	ext dom	£72,737	dom	dom	£176,176	dom
17. Attack rates halved	ext dom	ext dom	£97,384	dom	ext dom	£234,859
18. Attack rates doubled	ext dom	ext dom	£22,721	ext dom	ext dom	£57,090
19. Higher influenza threshold	ext dom	ext dom	£77,972	dom	ext dom	£188,639
20. GP consultation rates halved	ext dom	ext dom	£47,456	dom	ext dom	£115,805
21. GP consultation rates doubled	ext dom	ext dom	£47,919	dom	ext dom	£117,447
22. VAS to EQ-5D mapping function	ext dom	ext dom	£49,733	dom	ext dom	£121,537
23. QALY loss for at-risk halved	ext dom	ext dom	£47,609	dom	ext dom	£116,346
24. Complication disutilities halved	ext dom	ext dom	£47,856	dom	ext dom	£116,950
25. 10% uncomplicated hospitalised	ext dom	dom	£35,219	dom	ext dom	£103,957
26. Undiscounted	ext dom	ext dom	£44,358	dom	ext dom	£108,402

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Post-exposure prophylaxis						
Base case (stochastic model)	ext dom	dom	£10,716	ext dom	dom	£28,473
1. Price reduction zanamivir	ext dom	dom	£10,734	ext dom	dom	£28,608
2. Base case deterministic model	ext dom	dom	£10,754	ext dom	dom	£28,597
3. Oseltamivir as suspension	ext dom	dom	£10,754	ext dom	dom	£28,597
4. Multiple prescriptions	ext dom	dom	£4,897	ext dom	dom	£14,651
5. Vaccine efficacy = 50%	ext dom	dom	£10,754	ext dom	dom	£23,675
6. Vaccine efficacy = 25%	ext dom	dom	£10,754	ext dom	dom	£15,061
7. 100% protection over flu season	ext dom	dom	£10,754	ext dom	dom	£28,597
8. No antiviral treatment	ext dom	dom	£10,615	ext dom	dom	£28,257
9. Best case efficacy for NIs	ext dom	£355,876	£10,754	ext dom	£850,316	£28,597
10. No adverse events	ext dom	dom	£10,754	ext dom	dom	£28,597
11. No withdrawals	ext dom	dom	£10,496	ext dom	dom	£27,982
12. 10% resistance for oseltamivir	ext dom	£28,930	£12,190	ext dom	£71,872	£32,015
13. 20% resistance for oseltamivir	ext dom	£13,592	ext dom	ext dom	£35,354	ext dom
14. 30% resistance for oseltamivir	ext dom	£13,592	ext dom	ext dom	£35,354	ext dom
15. 40% resistance for oseltamivir	ext dom	£13,592	ext dom	ext dom	£35,354	ext dom
16. 50% resistance for oseltamivir	ext dom	£13,592	ext dom	ext dom	£35,354	ext dom
17. Attack rates halved	ext dom	dom	£23,675	ext dom	dom	£59,361
18. Attack rates doubled	ext dom	dom	£4,294	ext dom	dom	£13,215
19. Higher influenza threshold	ext dom	dom	£10,754	ext dom	dom	£28,597
20. GP consultation rates halved	ext dom	dom	£10,810	ext dom	dom	£28,552
21. GP consultation rates doubled	ext dom	dom	£10,641	ext dom	dom	£28,689
22. VAS to EQ-5D mapping function	ext dom	dom	£11,234	ext dom	dom	£29,873
23. QALY loss for at-risk halved	ext dom	dom	£10,754	ext dom	dom	£28,597
24. Complication disutilities halved	ext dom	dom	£10,810	ext dom	dom	£28,746
25. 10% uncomplicated hospitalised	dom	dom	dominates	dom	dom	£16,207
26. Undiscounted	ext dom	dom	£10,020	ext dom	dom	£26,645

Dom = dominated, ext dom = extendedly dominated

Table 73 suggests that the cost-effectiveness estimates are sensitive to assumptions regarding influenza attack rates, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community, the risk of hospitalisation in uncomplicated cases, and the discount rate. The post-exposure prophylaxis healthy elderly model is sensitive to the influenza attack rate, the use of multiple prescriptions of prophylaxis at a single GP visit, vaccine efficacy, and the risk of hospitalisation in uncomplicated cases.

6.3.2.5 One-way sensitivity analysis and scenario analysis results – healthy elderly

Table 74 presents the results of the simple sensitivity analysis for the at-risk elderly subgroup.

Table 74: Sensitivity analysis – at-risk elderly

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Seasonal prophylaxis						
Base case (stochastic model)	ext dom	ext dom	£38,098	ext dom	ext dom	£93,763
1. Price reduction zanamivir	ext dom	ext dom	£37,968	ext dom	ext dom	£93,581
2. Base case deterministic model	ext dom	ext dom	£36,460	ext dom	ext dom	£89,781
3. Oseltamivir as suspension	ext dom	dom	£30,545	ext dom	dom	£75,699
4. Multiple prescriptions	ext dom	ext dom	£36,460	ext dom	ext dom	£89,781
5. Vaccine efficacy = 50%	ext dom	ext dom	£36,460	ext dom	ext dom	£75,072
6. Vaccine efficacy = 25%	ext dom	ext dom	£36,460	ext dom	ext dom	£49,331
7. 100% protection over flu season	ext dom	ext dom	£36,460	ext dom	ext dom	£89,781
8. No antiviral treatment	ext dom	ext dom	£35,983	ext dom	ext dom	£88,639
9. Best case efficacy for NIs	ext dom	ext dom	£36,460	ext dom	ext dom	£89,781
10. No adverse events	ext dom	ext dom	£36,460	ext dom	ext dom	£89,781
11. No withdrawals	ext dom	ext dom	£35,688	ext dom	ext dom	£87,942
12. 10% resistance for oseltamivir	ext dom	ext dom	£40,750	ext dom	ext dom	£99,996
13. 20% resistance for oseltamivir	ext dom	ext dom	£46,113	ext dom	ext dom	£112,764
14. 30% resistance for oseltamivir	ext dom	ext dom	£53,008	ext dom	ext dom	£129,181
15. 40% resistance for oseltamivir	ext dom	£55,953	dom	ext dom	£136,192	dom
16. 50% resistance for oseltamivir	ext dom	£55,953	dom	ext dom	£136,192	dom
17. Attack rates halved	ext dom	ext dom	£75,072	dom	ext dom	£181,714
18. Attack rates doubled	ext dom	ext dom	£17,154	ext dom	ext dom	£43,815
19. Higher influenza threshold	ext dom	ext dom	£60,013	dom	ext dom	£145,860
20. GP consultation rates halved	ext dom	ext dom	£36,317	ext dom	ext dom	£89,304
21. GP consultation rates doubled	ext dom	ext dom	£36,751	ext dom	ext dom	£90,754
22. VAS to EQ-5D mapping function	ext dom	ext dom	£37,709	ext dom	ext dom	£92,858
23. QALY loss for at-risk halved	ext dom	ext dom	£57,467	dom	ext dom	£141,511
24. Complication disutilities halved	ext dom	ext dom	£36,666	ext dom	ext dom	£90,288
25. 10% uncomplicated hospitalised	ext dom	dom	£27,159	ext dom	ext dom	£80,480
26. Undiscounted	ext dom	ext dom	£33,713	ext dom	ext dom	£83,016

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
Post-exposure prophylaxis						
Base case (stochastic model)	ext dom	dom	£7,866	ext dom	dom	£21,608
1. Price reduction zanamivir	ext dom	dom	£7,892	ext dom	dom	£21,749
2. Base case deterministic model	ext dom	dom	£7,871	ext dom	dom	£21,712
3. Oseltamivir as suspension	ext dom	dom	£7,871	ext dom	dom	£21,712
4. Multiple prescriptions	ext dom	dom	£3,327	ext dom	dom	£10,894
5. Vaccine efficacy = 50%	ext dom	dom	£7,871	ext dom	dom	£17,894
6. Vaccine efficacy = 25%	ext dom	dom	£7,871	ext dom	dom	£11,212
7. 100% protection over flu season	ext dom	dom	£7,871	ext dom	dom	£21,712
8. No antiviral treatment	ext dom	dom	£7,750	ext dom	dom	£21,419
9. Best case efficacy for NIs	ext dom	£275,589	£7,871	ext dom	£659,137	£21,712
10. No adverse events	ext dom	dom	£7,871	ext dom	dom	£21,712
11. No withdrawals	ext dom	dom	£7,671	ext dom	dom	£21,235
12. 10% resistance for oseltamivir	ext dom	£21,970	£8,985	ext dom	£55,281	£24,364
13. 20% resistance for oseltamivir	ext dom	£10,072	ext dom	ext dom	£26,954	ext dom
14. 30% resistance for oseltamivir	ext dom	£10,072	ext dom	ext dom	£26,954	ext dom
15. 40% resistance for oseltamivir	ext dom	£10,072	ext dom	ext dom	£26,954	ext dom
16. 50% resistance for oseltamivir	ext dom	£10,072	ext dom	ext dom	£26,954	ext dom
17. Attack rates halved	ext dom	dom	£17,894	ext dom	dom	£45,576
18. Attack rates doubled	ext dom	dom	£2,860	ext dom	dom	£9,780
19. Higher influenza threshold	ext dom	dom	£7,871	ext dom	dom	£21,712
20. GP consultation rates halved	ext dom	dom	£7,908	ext dom	dom	£21,662
21. GP consultation rates doubled	ext dom	dom	£7,796	ext dom	dom	£21,814
22. VAS to EQ-5D mapping function	ext dom	dom	£8,141	ext dom	dom	£22,456
23. QALY loss for at-risk halved	ext dom	dom	£12,406	ext dom	dom	£34,222
24. Complication disutilities halved	ext dom	dom	£7,915	ext dom	dom	£21,835
25. 10% uncomplicated hospitalised	dom	dom	dominates	dom	dom	£12,411
26. Undiscounted	ext dom	dom	£7,278	ext dom	dom	£20,076

Dom = dominated, ext dom = extendedly dominated

Table 74 suggests that the cost-effectiveness estimates are sensitive to assumptions regarding influenza attack rates, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community, the risk of hospitalisation in uncomplicated cases, and the discount rate. The post-exposure prophylaxis at-risk elderly model is sensitive to the influenza attack rate, the use of multiple prescriptions of prophylaxis at a single GP visit, vaccine efficacy, and the risk of hospitalisation in uncomplicated cases.

6.3.3 Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis was undertaken for the use of seasonal prophylaxis and post-exposure prophylaxis using amantadine, oseltamivir and zanamivir in each of the six subgroups, for vaccinated and unvaccinated patients. Cost-effectiveness acceptability curves for these 24 base case health economic comparisons are presented in Appendix 8. Probability sensitivity analysis was also undertaken for all health economic comparisons incorporating the proposed reduction in the price of zanamivir. CEACs for these comparisons are presented in Appendix 9. For clarity of reporting, the results of the probabilistic sensitivity analysis are presented in tabular form in Tables 75 and 76. These tables show the probability that each prophylactic option produces the greatest incremental net benefit assuming cost-effectiveness thresholds of £20,000 per QALY gained and £30,000 per QALY gained.

6.3.3.1 Uncertainty analysis results - base case scenario

Table 75 presents the probability that each prophylactic option produces the greatest level of net benefit at thresholds of £20,000 per QALY gained and £30,000 per QALY gained for the base case analysis. The option which is most likely to produce the greatest level of expected net benefit is highlighted in bold for each comparison.

Table 75: Uncertainty analysis results: Probability optimal at willingness to pay thresholds (base case scenario)

Population	Probability optimal at £20,000/QALY				Probability optimal at £30,000/QALY			
	No Px	Ama	Ose	Zan	No Px	Ama	Ose	Zan
Seasonal prophylaxis								
Healthy children (no vacc)	1.00	0.00	0.00	0.00	0.97	0.00	0.03	0.00
Healthy children (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk children (no vacc)	0.27	0.03	0.70	0.00	0.02	0.03	0.94	0.01
At-risk children (vacc)	1.00	0.00	0.00	0.00	0.97	0.00	0.03	0.00
Healthy adults (no vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Healthy adults (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults (no vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Healthy elderly (no vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Healthy elderly (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk elderly (no vacc)	1.00	0.00	0.00	0.00	0.89	0.02	0.08	0.01
At-risk elderly (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Post-exposure prophylaxis								
Healthy children (no vacc)	0.63	0.00	0.22	0.15	0.15	0.00	0.40	0.45
Healthy children (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk children (no vacc)	0.00	0.00	0.33	0.67	0.00	0.00	0.27	0.73
At-risk children (vacc)	0.81	0.00	0.11	0.08	0.39	0.00	0.29	0.31
Healthy adults (no vacc)	1.00	0.00	0.00	0.00	0.81	0.00	0.19	0.00
Healthy adults (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults (no vacc)	0.02	0.00	0.89	0.10	0.00	0.00	0.84	0.16
At-risk adults (vacc)	1.00	0.00	0.00	0.00	0.96	0.00	0.04	0.00
Healthy elderly (no vacc)	0.00	0.00	0.87	0.13	0.00	0.00	0.82	0.18
Healthy elderly (vacc)	0.91	0.00	0.09	0.00	0.47	0.00	0.50	0.03
At-risk elderly (no vacc)	0.00	0.00	0.83	0.17	0.00	0.00	0.77	0.23
At-risk elderly (vacc)	0.64	0.00	0.35	0.01	0.15	0.00	0.78	0.07

6.3.3.2 Uncertainty analysis results – proposed price reduction for zanamivir

Table 76 presents the probability that each prophylactic option produces the greatest level of net benefit at thresholds of £20,000 per QALY gained and £30,000 per QALY gained, incorporating the proposed reduction in the price of zanamivir. The option which is most likely to produce the greatest level of expected net benefit is highlighted in bold for each comparison.

Table 76: Uncertainty analysis results: Probability optimal at willingness to pay thresholds (incorporating proposed reduction in price of zanamivir)

Population	Probability optimal at £20,000/QALY				Probability optimal at £30,000/QALY			
	No Px	Ama	Ose	Zan	No Px	Ama	Ose	Zan
Seasonal prophylaxis								
Healthy children (no vacc)	1.00	0.00	0.00	0.00	0.97	0.00	0.03	0.00
Healthy children (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk children (no vacc)	0.25	0.03	0.70	0.03	0.01	0.02	0.91	0.05
At-risk children (vacc)	1.00	0.00	0.00	0.00	0.97	0.00	0.03	0.00
Healthy adults (no vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Healthy adults (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults (no vacc)	1.00	0.00	0.00	0.00	0.99	0.00	0.00	0.01
At-risk adults (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Healthy elderly (no vacc)	1.00	0.00	0.00	0.00	0.97	0.00	0.00	0.03
Healthy elderly (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk elderly (no vacc)	0.99	0.00	0.00	0.00	0.77	0.02	0.05	0.16
At-risk elderly (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Post-exposure prophylaxis								
Healthy children (no vacc)	0.44	0.00	0.09	0.47	0.06	0.00	0.15	0.79
Healthy children (vacc)	1.00	0.00	0.00	0.00	0.99	0.00	0.00	0.01
At-risk children (no vacc)	0.00	0.00	0.15	0.85	0.00	0.00	0.15	0.85
At-risk children (vacc)	0.70	0.00	0.04	0.26	0.24	0.00	0.12	0.65
Healthy adults (no vacc)	1.00	0.00	0.00	0.00	0.76	0.00	0.18	0.06
Healthy adults (vacc)	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults (no vacc)	0.00	0.00	0.59	0.40	0.00	0.00	0.59	0.41
At-risk adults (vacc)	1.00	0.00	0.00	0.00	0.95	0.00	0.04	0.01
Healthy elderly (no vacc)	0.00	0.00	0.62	0.38	0.00	0.00	0.62	0.38
Healthy elderly (vacc)	0.90	0.00	0.07	0.03	0.42	0.00	0.38	0.20
At-risk elderly (no vacc)	0.00	0.00	0.60	0.40	0.00	0.00	0.60	0.40
At-risk elderly (vacc)	0.60	0.00	0.25	0.15	0.11	0.00	0.54	0.34

6.4 Budget impact analysis

This section presents estimates of the budget impact of a positive recommendation for each prophylactic option within each model subgroup as compared against current NICE recommendations. The analysis is based upon the expected cost of each prophylaxis strategy, including potential cost savings associated with the avoidance of influenza and other influenza-like illnesses. Separate budget impact analyses are presented for seasonal prophylaxis and for post-exposure prophylaxis. NICE currently recommends the use of oseltamivir as post-exposure prophylaxis in at-risk individuals aged over 13 years of age; this is taken to be the baseline cost, against which the incremental cost of each prophylactic option is compared.

The population of England and Wales is currently estimated to be around 53,728,600, based on data from the Office for National Statistics. Of these, approximately 11,295,800 are aged under 16, 33,822,300 are working age adults, and 8,610,500 are elderly. The previous assessment by Turner *et al.*¹⁰ suggested that approximately 12%, 25% and 42% of children, adults and elderly individuals would be considered high risk. Recent evidence suggests that uptake of influenza vaccination is approximately 79% in individuals over the age of 65 years, and around 42% in high risk individuals who are under the age of 65. Data from the Department of Health suggests that the residential care home population in England and Wales is around 545,000 persons. These data were synthesised to crudely estimate the number of individuals who fall into each of the model subgroups (See Table 77).

Table 77: Number of individuals in each model subgroup

Population group	No. individuals	Community dwelling	Residential care home
Healthy children (no vacc)	9,940,304	9,940,304	0
Healthy children (vacc)	0	0	0
At-risk children (no vacc)	784832	784,832	0
At-risk children (vacc)	570664	570,664	0
Healthy adults (no vacc)	25,366,725	25,366,725	0
Healthy adults (vacc)	0	0	0
At-risk adults (no vacc)	4,895,778	4,895,778	0
At-risk adults (vacc)	3,559,797	3,559,797	0
Healthy elderly (no vacc)	1,033,777	968,344	65,433
Healthy elderly (vacc)	3,960,313	3,709,646	250,667
At-risk elderly (no vacc)	748,597	701,215	47,382
At-risk elderly (vacc)	2,867,813	2,686,295	181,518

For the seasonal prophylaxis budget impact model, *any* individual within each subgroup could be potentially eligible to receive prophylaxis provided they are over the age specified within the licensed indications for each prophylaxis drug. The proportion of children who would be eligible for prophylaxis using amantadine, oseltamivir and zanamivir was estimated using data from the ONS. The estimated budget impact for seasonal prophylaxis options are presented in Table 78.

For the post-exposure prophylaxis budget impact model, the population of interest relates to individuals who have come into contact with an index ILI case. The number of potentially eligible contact cases is crudely estimated by multiplying the number of individuals within each model subgroup by an estimated overall household ILI attack rate (the estimated household influenza attack rate multiplied by the probability that ILI is influenza).²⁰ The budget impact

model assumes that if a household is infected, all contact cases will be eligible for prophylaxis if they present within 48 hours of contact with the index case. The model estimates the additional cost of each policy to the existing NICE guidance (the “current cost” column details the expected per patient cost of prophylaxis according to current NICE guidance). The budget impact for residential care home population was based on an assumed ILI attack rate of 41%.¹³² The estimated budget impact for post-exposure prophylaxis options are presented in Tables 79 and 80.

Table 78: Seasonal prophylaxis budget impact estimates

Population group	Number individuals	Current policy	Expected cost per patient				Current policy cost	Additional budget impact over eligible population		
			no px	ama	zan	ose		ama	zan	ose
Healthy children (no vacc)	10,240,912	np	£17.72	£56.23	£112.15	£85.51	£17.72	£183,952,396	£343,735,708	£655,247,656
Healthy children (vacc)	-	np	£43.23	£78.64	£140.36	£115.05	£43.23	£0	£0	£0
At-risk children (no vacc)	808,567	np	£29.89	£66.92	£121.56	£93.57	£29.89	£13,970,266	£26,347,333	£48,599,333
At-risk children (vacc)	587,921	np	£51.71	£86.84	£147.86	£122.06	£51.71	£9,632,657	£20,090,863	£39,033,738
Healthy adults (no vacc)	25,110,750	np	£6.63	£46.49	£103.70	£111.09	£6.63	£1,000,937,591	£2,437,345,426	£2,622,899,442
Healthy adults (vacc)	-	np	£35.64	£71.34	£133.74	£141.62	£35.64	£0	£0	£0
At-risk adults (no vacc)	4,846,375	np	£13.57	£52.74	£108.33	£115.63	£13.57	£189,831,470	£459,262,856	£494,635,028
At-risk adults (vacc)	3,523,875	np	£40.39	£75.94	£137.67	£145.53	£40.39	£125,278,544	£342,831,299	£370,497,449
Healthy elderly (no vacc)	1,033,813	np	£10.43	£49.93	£106.16	£112.80	£10.43	£40,836,559	£98,974,490	£105,837,889
Healthy elderly (vacc)	3,960,451	np	£38.59	£74.16	£136.02	£143.54	£38.59	£140,896,254	£385,872,027	£415,636,663
At-risk elderly (no vacc)	748,623	np	£13.45	£52.63	£108.39	£114.54	£13.45	£29,333,408	£71,075,149	£75,678,598
At-risk elderly (vacc)	2,867,913	np	£40.75	£76.25	£137.84	£145.15	£40.75	£101,827,060	£278,453,842	£299,415,220

no px = no prophylaxis

ama = amantadine

ose = oseltamivir

zan = zanamivir

Table 79: Post-exposure prophylaxis budget impact estimates (including community dwelling elderly)

Population group	Number individuals	Current policy	Expected cost per patient				Current cost	Additional budget impact over eligible population		
			no px	ama	zan	ose		ama	zan	ose
Healthy children (no vacc)	2,067,940	np	£18.96	£46.40	£61.18	£54.35	£19.0	£31,971,071	£16,526,348	£35,963,481
Healthy children (vacc)	-	np	£44.09	£73.84	£91.00	£83.30	£44.1	£0	£0	£0
At-risk children (no vacc)	163,273	ose/np	£32.56	£57.55	£69.76	£63.97	£48.0	-£254,503	-£1,873,897	£0
At-risk children (vacc)	118,719	ose/np	£53.57	£82.44	£98.67	£91.35	£72.1	-£256,859	-£1,966,380	£0
Healthy adults (no vacc)	5,070,595	np	£9.17	£38.48	£55.19	£46.94	£9.2	£23,136,834	£36,323,410	£29,814,690
Healthy adults (vacc)	-	np	£37.36	£67.80	£85.67	£77.46	£37.4	£0	£0	£0
At-risk adults (no vacc)	978,625	ose	£19.34	£47.10	£61.49	£53.18	£24.6	-£927,521	£1,265,252	£0
At-risk adults (vacc)	711,574	ose	£44.32	£74.21	£91.27	£83.04	£50.3	-£978,796	£911,673	£0
Healthy elderly (no vacc)	195,544	ose	£17.75	£45.76	£60.50	£52.17	£21.6	-£141,505	£183,604	£0
Healthy elderly (vacc)	749,114	ose	£43.82	£73.59	£90.52	£82.27	£48.2	-£733,300	£696,777	£0
At-risk elderly (no vacc)	141,601	ose	£22.88	£50.05	£63.68	£55.33	£26.5	-£84,394	£133,358	£0
At-risk elderly (vacc)	542,462	ose	£47.50	£76.92	£93.37	£85.11	£51.7	-£500,882	£505,397	£0

no px = no prophylaxis
ama = amantadine
ose = oseltamivir
zan = zanamivir

Table 80: Post-exposure prophylaxis budget impact estimates – residential care elderly

Population group	Number individuals	Current policy	Expected cost per patient				Current cost	Additional budget impact over eligible population		
			no px	ama	zan	ose		ama	zan	ose
Healthy elderly (no vacc)	26,827	ose	£17.75	£45.76	£60.50	£52.17	£21.63	-£19,413.59	£25,189	£0.00
Healthy elderly (vacc)	102,774	ose	£43.82	£73.59	£90.52	£82.27	£48.16	-£100,603.99	£4,352,991	£0.00
At-risk elderly (no vacc)	19,427	ose	£22.88	£50.05	£63.68	£55.33	£26.54	-£11,578.37	£721,445	£0.00
At-risk elderly (vacc)	74,422	ose	£47.50	£76.92	£93.37	£85.11	£51.75	-£68,717.81	£3,097,413	£0.00

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

7.1 Use of amantadine for Parkinson's disease and *herpes zoster* virus

It should be borne in mind that, as amantadine is also licensed for the treatment of Parkinson's Disease and *herpes zoster*, individuals receiving the drug for these conditions may be protected against influenza A.

7.2 Herd immunity

The concept of herd immunity postulates that the higher the proportion of individuals in a population who are protected from an infection, the less likely it is that an outbreak of the same infection may become established in that community. With respect to influenza, it could be proposed that, where the number of individuals who are able to transmit the virus is reduced, via vaccination and/or influenza prophylaxis, unprotected individuals are less likely to become exposed to infection and are thus indirectly protected. Whilst this concept has not been modelled within this assessment, it should be considered that influenza prophylaxis in at-risk groups may result in herd immunity effects within the population with which they are in contact. Additional studies that examine the degree of viral shedding amongst subjects receiving prophylaxis versus placebo may provide further information with regards to this effect.

A further issue relating to immunity against influenza was raised by study authors, who proposed that, whilst antivirals may be effective in preventing the development of SLCI, asymptomatic individuals may in actual fact have sub-clinical influenza infection, which may have the potential to confer immunity to the circulating strain upon the exposed individual.

7.3 Additional support in using antivirals

In the clinical effectiveness review, a number of issues were identified relating to the external validity of a minority of the oseltamivir and zanamivir trials and are discussed in Section 8. It was noted that in some studies, subjects who had lower levels of cognitive function and/or manual dexterity were excluded from participation. It is therefore possible that the reported levels of adherence and acceptability of the use of the Diskhaler device for delivery of zanamivir and ability of subjects to independently take oral antivirals may not accurately reflect the scenario within the general population, and that older individuals or those with lower cognitive functioning

and/or manual dexterity may require additional support from health and social care professionals or carers in administration of antivirals.

7.4 Prescribing patterns for influenza prophylaxis

Within the clinical trials of the use of oseltamivir and zanamivir in post-exposure prophylaxis, it was typically stipulated within the study inclusion criteria that the administration of antivirals should be commenced within 48 hours of exposure to the ILI index case for oseltamivir and 36 hours for zanamivir. In clinical practice, this requirement may be problematic, since it relies on the identification of both index cases and the initiation of prophylaxis in contact cases within the recommended cut-off period. In addition, initiation of post-exposure prophylaxis relies on the patient having access to GP services within the specified time period. The requirement for testing of creatinine clearance for dose adjustment for amantadine and oseltamivir also has the potential to impact upon the speed with which prophylaxis may be implemented.

A GP can usually only prescribe medication for individuals presenting for consultation. The requirement for early identification of index cases and contact cases in post-exposure prophylaxis may lead to variations in prescribing practices e.g. giving multiple prescriptions of prophylaxis to household contacts.

The future use of rapid diagnostic tests for influenza in clinical practice could be anticipated to facilitate the rapid identification of influenza-positive index cases and the circulation of influenza in the local community and, as such, has the potential to increase the clinical effectiveness of antivirals in prophylaxis.

7.5 Impact upon primary care

Raised awareness of the availability of antiviral prophylaxis amongst the general population may lead to increased workloads for general practitioners and other primary care health professionals. It should be noted that the economic analysis presented here makes very few assumptions about the way in which prophylaxis would be implemented, or the infrastructure required to manage this. In certain patient groups, this may be a lesser issue (for example using post-exposure prophylaxis to opportunistically manage outbreaks in residential care homes) whilst for other settings the infrastructure may be of greater concern (for example introducing routine prophylaxis within schools).

7.6 Involvement of pharmacist in use of powder for oral suspension.

As noted in Section 3.3.1.2, the summary of product characteristics for oseltamivir recommends that powder for oral suspension should be constituted by a pharmacist before dispensing to the patient.

8. DISCUSSION

8.1 Statement of principal findings

8.1.1. Clinical effectiveness review

Twenty six published references and one unpublished report relating to a total of 23 RCTs were included in the review of clinical effectiveness. The quality of the studies identified was variable and gaps in the evidence base limited the assessment of the clinical effectiveness of the interventions across population subgroups and settings. The evidence for amantadine prophylaxis across subgroups was very limited. However, evidence of the effectiveness of amantadine in preventing SLCI in outbreak control amongst adolescent subjects was identified. Oseltamivir was shown to be effective in preventing SLCI in a number of subgroups, particularly in seasonal prophylaxis in at-risk elderly subjects and in post-exposure prophylaxis within households of mixed composition. The effectiveness of zanamivir in preventing SLCI was also demonstrated, and was most convincing in trials of seasonal prophylaxis in at-risk adults and adolescents, healthy and at-risk elderly subjects and in post-exposure prophylaxis in mixed households. Interventions appeared to be reasonably well tolerated by subjects, with a relatively low proportion of subjects experiencing drug-related adverse events and drug-related withdrawals. Very limited evidence was reported for the effectiveness of the interventions in preventing complications, hospitalisations and in minimizing length of illness and time to return to normal activities. No data could be identified for health-related quality of life or mortality outcomes. Additional consideration should be paid to the issues of antiviral resistance and adverse events associated with amantadine during the interpretation of the findings of the review.

8.1.2. Cost effectiveness review

8.1.2.1 Cost-effectiveness of amantadine, zanamivir and oseltamivir as seasonal prophylaxis

Seasonal prophylaxis for healthy children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the healthy children subgroup. The proposed reduction in the price of zanamivir does not affect this finding. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £44,000 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis produces the greatest level of net benefit is expected to be around 0.97.

Seasonal prophylaxis for at-risk children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the at-risk children subgroup. Again, the proposed reduction in the price of zanamivir does not affect this finding. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £17,000 per QALY gained for at-risk children who have not been vaccinated. For at-risk children who have previously been vaccinated, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be in excess of £50,000 per QALY gained. The cost-effectiveness estimates for oseltamivir are based on efficacy data which have been drawn from a trial of seasonal prophylaxis in healthy adults. Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that oseltamivir is optimal in unvaccinated at-risk children is approximately 0.70 (this probability is also 0.70 when the proposed price reduction for zanamivir is included). Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that oseltamivir is optimal in unvaccinated at-risk children is around 0.94 (probability = 0.91 when the proposed price reduction for zanamivir is included). For at-risk children who have previously been vaccinated, the probability that no prophylaxis is optimal at £30,000 per QALY gained is approximately 0.96 or higher.

Seasonal prophylaxis for healthy adults

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the healthy adult subgroup. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £148,000 per QALY gained for healthy adults who have not been vaccinated and greater than £427,000 per QALY gained for healthy adults who have been vaccinated. These estimates are based on a trial of oseltamivir as seasonal prophylaxis in healthy adults. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is close to 1.0, irrespective of vaccination status.

Seasonal prophylaxis for at-risk adults

Based on the current list price for zanamivir, the model suggests that both amantadine and zanamivir are ruled out of the analysis in at-risk adults. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £64,000 per QALY gained in unvaccinated at-risk adults and around £187,000 per QALY gained in previously vaccinated at-risk adults. These estimates are based on a trial of oseltamivir as seasonal prophylaxis in healthy adults. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis produces the greatest amount of net benefit is close to 1.0.

When the proposed price reduction for zanamivir is included in the analysis for at-risk adults, zanamivir is no longer dominated. The incremental cost-effectiveness of seasonal prophylaxis using zanamivir versus no prophylaxis is expected to be around £53,000 per QALY gained in unvaccinated at-risk adults and £157,000 per QALY gained in at-risk adults who have previously been vaccinated. The incremental cost-effectiveness of oseltamivir is expected to be around £108,000 per QALY gained in unvaccinated at-risk adults and around £314,000 per QALY gained in previously vaccinated at-risk adults. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is around 0.99 for unvaccinated at-risk adults and close to 1.0 for previously vaccinated at-risk adults.

Seasonal prophylaxis for healthy elderly

For healthy elderly individuals, amantadine and zanamivir are expected to be dominated or extendedly dominated. The proposed reduction in the price of zanamivir does not affect this result. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in healthy elderly individuals who have not been vaccinated is expected to be around £50,000 per QALY gained. For previously vaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £120,000 per QALY gained. These estimates are based on a trial of oseltamivir as seasonal prophylaxis in elderly individuals. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is expected to be optimal is close to 1.0 (this probability is around 0.97 and 1.0 when the proposed price reduction for zanamivir is included in the analysis for unvaccinated and vaccinated subgroups respectively).

Seasonal prophylaxis for at-risk elderly

For at-risk elderly individuals, amantadine and zanamivir are expected to be extendedly dominated despite the proposed reduction in the price of zanamivir. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in at-risk elderly individuals who have not been vaccinated is expected to be around £38,000 per QALY gained. For previously vaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £94,000 per QALY gained. These estimates are based on a trial of oseltamivir as seasonal prophylaxis in elderly subjects. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is around 0.77 or higher.

The simple sensitivity analysis suggests that the cost-effectiveness of seasonal prophylaxis using amantadine, oseltamivir and zanamivir is sensitive to assumptions regarding the influenza attack rate, the level of resistance against oseltamivir, vaccine efficacy, the threshold used to describe when influenza is circulating in the community, the risk of hospitalisation in uncomplicated cases, and the discount rate.

8.1.2.2 Cost-effectiveness of amantadine, zanamivir and oseltamivir as post-exposure prophylaxis

Post-exposure prophylaxis for healthy children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the healthy children subgroup. For unvaccinated healthy children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £23,000 per QALY gained at the current list price, and around £19,000 per QALY gained when the proposed price reduction for zanamivir is included in the analysis. For vaccinated healthy children, the incremental cost-effectiveness of zanamivir is expected to be at least £59,000 per QALY gained; this estimate includes the proposed price reduction for zanamivir. These cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). Based on the current list price for zanamivir, the probability that zanamivir is optimal in unvaccinated healthy children is expected to be 0.15 and 0.45 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the proposed price reduction is included in the analysis, the probability that zanamivir is optimal in unvaccinated healthy children is expected to be 0.47 and 0.79 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. For the vaccinated subgroup, the probability that no prophylaxis is optimal at a threshold of £30,000 per QALY gained is close to 1.0 (probability = 0.99 when the proposed price reduction for zanamivir is included).

For children under the age of 5 years, oseltamivir is the only licensed antiviral prophylaxis option. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £24,000 per QALY gained and £74,000 per QALY gained in unvaccinated and vaccinated groups respectively.

Post-exposure prophylaxis for at-risk children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the at-risk children subgroup. For unvaccinated at-risk children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8,000 per QALY gained at the current list price, and around £6,000 per QALY gained when the proposed price reduction for zanamivir is included in the analysis. For vaccinated at-risk children, the incremental cost-effectiveness of zanamivir is expected to be around £28,000 per QALY gained at the current list price, and £23,000 per QALY gained when the proposed price reduction is included in the analysis. Again, these cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). Based on its current list price, the probability that zanamivir is optimal in unvaccinated at-risk children is expected to be 0.67 and 0.73 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the proposed price reduction is included in the analysis, the probability that zanamivir is optimal in unvaccinated at-risk children is expected to be 0.85 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. Based on the current list price for zanamivir, the probability that zanamivir is optimal in vaccinated at-risk children is expected to be 0.08 and 0.31 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. When the proposed price reduction is included in the analysis, the probability that zanamivir is optimal in vaccinated at-risk children is expected to be 0.26 and 0.65 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively.

For at-risk children under the age of 5 years, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £9,000 per QALY gained for unvaccinated at-risk children and around £29,000 per QALY gained for vaccinated at-risk children.

Post-exposure prophylaxis for healthy adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the healthy adult subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated healthy adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £34,000 per QALY gained. For previously vaccinated healthy adults, the incremental cost-effectiveness of oseltamivir is expected to be around £104,000 per QALY gained. These cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition

(children and adults). The probability that oseltamivir is optimal in unvaccinated otherwise healthy adults is expected to be around 0 and 0.19 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. For healthy adults who have previously been vaccinated, the probability that oseltamivir is optimal is close to zero at a willingness to pay threshold of £30,000 per QALY gained.

Post-exposure prophylaxis for at-risk adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the at-risk adult subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated at-risk adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £13,000 per QALY gained. For previously vaccinated at-risk adults, the incremental cost-effectiveness of oseltamivir is expected to be around £44,000 per QALY gained. These cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). Based on the current list price for zanamivir, the probability that oseltamivir is optimal in unvaccinated at-risk adults is 0.89 and 0.84 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively (probability = 0.59 when the proposed price reduction for zanamivir is included in the analysis). For at-risk adults who have previously been vaccinated, the probability that no prophylaxis is optimal is around 0.96 at a willingness to pay threshold of £30,000 per QALY gained (probability = 0.95 when the proposed price reduction for zanamivir is included).

Post-exposure prophylaxis for healthy elderly

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the healthy elderly subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £11,000 per QALY gained. For previously vaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir is expected to be around £28,000 per QALY gained. These cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). Based on the current list price for zanamivir, the probability that oseltamivir is optimal in unvaccinated healthy elderly individuals is 0.87 and 0.82 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively (probability = 0.62 when the proposed price reduction for zanamivir is included in

the analysis). For healthy elderly individuals who have previously been vaccinated, the probability that oseltamivir is optimal is 0.09 and 0.50 at willingness to pay thresholds of £20,000 per QALY gained and £30,000 per QALY gained respectively (probability = 0.07 and 0.38 when the proposed price reduction for zanamivir is included in the analysis).

Post-exposure prophylaxis for at-risk elderly

Amantadine and zanamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the at-risk elderly subgroup. For unvaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8,000 per QALY gained. For vaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir is expected to be around £22,000 per QALY gained. Again, these cost-utility estimates are based on effectiveness data derived from trials of post-exposure prophylaxis in households of mixed composition (children and adults). The probability that oseltamivir is optimal in unvaccinated at-risk elderly individuals is around 0.83 and 0.77 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained (this probability is around 0.60 when the proposed price reduction for zanamivir is included in the analysis). For vaccinated at-risk elderly individuals, the probability that oseltamivir is optimal is 0.35 and 0.78 at willingness to pay thresholds of £20,000 per QALY gained and £30,000 per QALY gained respectively (probability = 0.25 and 0.54 when the proposed price reduction for zanamivir is included in the analysis).

The simple sensitivity analysis suggests that the cost-effectiveness of post-exposure prophylaxis using amantadine, oseltamivir and zanamivir is sensitive to assumptions regarding the influenza attack rate, the level of resistance against oseltamivir, assumptions regarding the comparative efficacy of oseltamivir and zanamivir, the efficacy of influenza vaccination, multiple prescribing of prophylaxis to contact cases, the risk of hospitalisation in uncomplicated cases, and the discount rate.

8.2 Strengths and limitations of the assessment

The methods used for reviewing the evidence for the clinical effectiveness of amantadine, oseltamivir and zanamivir in seasonal and post-exposure prophylaxis against influenza were comprehensive and systematic and we are confident that we identified all RCTs suitable for inclusion in the assessment. However, a limitation of the review was the necessity to exclude non-

English studies, due to time constraints. Where abstracts in English could be obtained for potentially relevant trials, the available data were discussed. An additional limitation was that a small number of full papers could not be retrieved by information specialists. However, as discussed earlier, it was considered unlikely that these articles were suitable for inclusion in the review.

The health economic model presented in Chapter 6 was developed following a detailed critical review of previous economic evaluations of influenza prophylaxis and clinical input. The review highlighted a number of concerns with previous health economic evaluations of amantadine, oseltamivir and zanamivir prophylaxis (see Section 6.1); the model presented here addresses each of these concerns. Despite this, the evidence base is subject to considerable uncertainty, and the evidence identified for the model is far from ideal, particularly in terms of the expected benefits of prophylaxis. The main limitation of the health economic model presented within this assessment is the use of a static rather than dynamic modelling approach. As such, the model captures only the benefits accrued by patients receiving prophylaxis, and does not include other potential indirect benefits accrued through decreased transmission of influenza through the use of prophylaxis. However, the use of a more sophisticated modelling approach would require additional assumptions and would not serve to reconcile the problems associated with an already limited evidence base (See Section 8.3).

8.3 Uncertainties

Whilst a considerable amount of evidence was identified relating to the use of amantadine, oseltamivir and zanamivir in seasonal and post-exposure prophylaxis against influenza, the assessment of the clinical effectiveness of these interventions was limited by the variation in the quality of trials in terms of internal validity and clarity of reporting and by the heterogeneity between studies. The capacity of a number of trials to demonstrate efficacy against SLCI was hindered by low attack rates during the seasons under study. The quality of the study design and reporting of the amantadine prophylaxis trials was particularly poor and few data could be abstracted to inform the clinical effectiveness review. Further trials would be required to enable a meaningful evaluation of the effectiveness of this intervention. Stronger evidence was identified for the efficacy of both oseltamivir and zanamivir in preventing SLCI, with some limited data being available on the impact of the interventions on complications, hospitalisations, and reducing length and severity of clinical disease across age groups, risk status groups and settings.

However, significant gaps in knowledge still exist, which require further research. Further studies amongst those population groups considered at higher risk of influenza-associated complications are necessary to strengthen the evidence base for efficacy in the most clinically relevant subgroups. There is a particular requirement for further evidence relating to the clinical effectiveness of antivirals in post-exposure prophylaxis amongst elderly subjects, particularly in long-term care settings, since subjects over 65 years of age were not well represented within the post-exposure prophylaxis trials. Further research to investigate the use of zanamivir by patients with low cognitive function is warranted. RCTs to investigate oseltamivir in seasonal prophylaxis in both healthy and at-risk children, at-risk adults, healthy elderly subjects and the representation of a range of risk and age subgroups within post-exposure prophylaxis studies would be of value. Although the report by LaForce *et al.*⁷⁵ presented considerable evidence since the last HTA review¹⁰ concerning the protective efficacy of zanamivir in seasonal prophylaxis for at-risk adolescents and adults, further research is required on zanamivir in seasonal prophylaxis in both healthy and at-risk children, healthy elderly subjects and a more comprehensive representation of age and risk subgroups within studies of post-exposure prophylaxis in households is needed. Studies of influenza antiviral prophylaxis in which the effect of the confounding variable of vaccination is further explored are recommended. Research to assess the impact of seasonal prophylaxis in certain groups, such as children, on the transmission and circulation of influenza within the community would also be of value.

A number of head-to-head trials of antiviral interventions used in prophylaxis against influenza were identified and excluded in the clinical effectiveness review. Research was identified in which the efficacies of amantadine and rimantadine in prophylaxis against influenza were compared,^{133,134} whilst the evidence base for amantadine and rimantadine prophylaxis was reviewed in a recent Cochrane publication.³³ Additional data identified and excluded in this assessment examined the prophylactic efficacies of ribavirin versus amantadine¹³⁵ and zanamivir versus rimantadine.⁷⁸ However, no relevant head-to-head RCTs in which amantadine, oseltamivir and/or zanamivir were directly compared could be identified. Such trials would be of significant value in determining the relative clinical effectiveness of these interventions in prophylaxis against influenza. The undertaking of a large-scale RCT of the efficacy of these interventions in seasonal and post-exposure prophylaxis with the incorporation of quality of life and resistance measurements would significantly expand the evidence base, although it is acknowledged that such a trial would require considerable resources.

The weaknesses in the clinical evidence base are directly relevant to the interpretation of the health economic model results. There is a marked paucity of robust evidence concerning the relative efficacy of alternative antiviral prophylactic drugs in specific subgroups. The non-exchangeability of studies of individual antivirals and the absence of head-to-head trials suggests that the use of more advanced Bayesian meta-analytic techniques (e.g. mixed treatment comparisons) would add little to the findings. As such, the economic analysis is pivoted on assumptions of equivalent efficacy of antivirals across numerous subgroups based on few trials (this is particularly the case for amantadine).

A number of attributes of the study designs of identified trials have implications for the interpretation of study findings. One issue relates to the variation in timing of prophylaxis within trials. Variation was evident in the timing of the onset of prophylaxis in experimental challenge studies, with subjects being dosed 1 day^{62,69} to 4 days⁶³ before viral challenge. In the post-exposure prophylaxis studies based within households, prophylaxis in contact cases with oseltamivir began within 48 hours of the onset of symptoms in the index case;^{49,48} however, within the zanamivir trials prophylaxis was initiated within 36 hours of the onset of symptoms in the index case in 2 studies^{47,46} and where contacts had been exposed to an index case with ILI of no longer than 4 days' duration.⁷⁴ Considerable variation was also present in the timing of the initiation of prophylaxis within trials of amantadine^{59,60,61} and zanamivir^{76,78} in outbreak control, where medications were administered upon levels of influenza activity reaching a level specific to that study. These variations in the onset of prophylaxis following exposure to influenza have the potential to impact upon estimates of efficacy. Most studies of seasonal prophylaxis were initiated when influenza virus activity was detected locally or when virus was identified in the community and there was an increase in the observed cases of ILI. However, only two studies^{58,72} described the rationale for the length of prophylaxis administered, typically due to cessation of local activity. Therefore, the proportion of the influenza season across which subjects received prophylaxis varied from study to study. This variation in the period of prophylaxis is especially pertinent, since the risk of developing SLCI following antiviral prophylaxis is considered to be ongoing, with an apparent drop-off in efficacy upon cessation of prophylaxis. Additional consideration should be afforded to the timing of the measurement of the primary outcome of SLCI in relation to the prophylactic period. In most cases, SLCI was reported across the whole prophylactic period. Some studies undertook additional analyses of data from days 2 to 4 of prophylaxis onwards, in order to exclude subjects who may have been infected with influenza virus prior to receipt of prophylaxis, but in whom clinical illness did not manifest until during the

early stages of the prophylaxis period. Only a small number of trials undertook follow-up measurement of SLCI beyond the period of prophylaxis, with obvious limitations for evaluation of any longer-term outcomes, such as the potential impact of sub-clinical infection on subjects. Variation was observed between the post-exposure prophylaxis trials undertaken in households in terms of whether index cases were treated with antivirals, which would be expected to impact upon the transmission of virus to contacts. An additional area of inconsistency between the different studies was the definition of clinical or symptomatic influenza, which was used to define SLCI. Around half the included studies defined symptomatic influenza as a raised temperature plus one or two additional symptoms, whilst other studies defined it as the presence of at least two of a list of symptoms which included raised temperature as one of the options. Also, of the twelve studies giving a specific value for a raised temperature, eight used $\geq 37.8^{\circ}\text{C}$, while three used $\geq 37.2^{\circ}\text{C}$ and one used $\geq 37.3^{\circ}\text{C}$. The study by Ambrozaitis *et al.*⁷⁶ defined SLCI as the presence of a new influenza-like sign or symptom, but also separately reported cases of ‘febrile SLCI’, which was defined as a new symptom plus a temperature of $\geq 37.8^{\circ}\text{C}$ (and gave fewer cases than SLCI alone). Therefore, the number of cases of SLCI identified, and the protective efficacies reported by the different studies may vary due to the definition of SLCI used.

The external validity of the RCTs must also be considered. A study by Diggory *et al.*¹³⁶ previously demonstrated that elderly individuals experienced difficulties in loading and priming the Diskhaler via which zanamivir is administered by oral inhalation and suggested that such practical difficulties posed a barrier to use amongst older patients. Conversely, the adherence data presented within the identified zanamivir trials would suggest that the use of the Diskhaler was acceptable to elderly study participants.^{76,78} However, subjects who were unable to understand study personnel were excluded from trial participation by Ambrozaitis *et al.*⁷⁶ and Gravenstein *et al.*⁷⁸ whilst a requirement of participation in the trials by Monto *et al.*⁴⁷ and LaForce *et al.*⁷⁵ was that subjects should be able to use the Diskhaler adequately. It is therefore important to consider that individuals with low cognitive function or poor manual dexterity would not be represented in some of the study populations, and that such groups may experience difficulties in administering zanamivir independently in clinical practice. Similar external validity issues apply to the trials by Peters *et al.*⁶⁴ and Welliver *et al.*⁴⁹ in which individuals scoring below 7 on a mental status questionnaire were excluded from participation. Such patients may require support in taking oral antiviral prophylaxis.

It is important to highlight the emerging clinical evidence surrounding serious adverse events due to neuraminidase inhibitors, in order to reflect the effects of these interventions on patients in clinical practice. Whilst a higher incidence of severe adverse events in oseltamivir and zanamivir were not apparent in the RCTs identified in this review, the occurrence of serious neuropsychiatric events amongst a minority of patients treated with neuraminidase inhibitors have been described,^{137,20} circumstances which should be monitored and should be taken into account during the interpretation of this evidence. Indeed, the assumptions made within the economic analysis reflect the current uncertainties regarding the incidence, duration and quality of life impact of adverse events due to individual prophylactic drugs.

The emergence of variants of influenza that are resistant to amantadine, oseltamivir and/or zanamivir has significant potential to reduce the efficacy of these interventions in clinical practice. Whilst a number of identified trials tested viral isolates for resistance to oseltamivir and zanamivir in vitro and found no evidence of reduced sensitivity, as noted in Section 3.3.1.1, Section 5.2.2.1.6 and Section 5.2.2.2.6, the emergence of strains of influenza resistant to, in particular, amantadine and also oseltamivir has been demonstrated and it is therefore important that, during interpretation of the clinical effectiveness evidence, such issues relating to antiviral resistance should be taken into account. Susceptibility should be continued to be monitored and testing of isolates should continue to be undertaken in future clinical trials. Variation in the levels of resistance to antivirals amongst influenza isolates was taken into account in the cost-effectiveness analysis. Although the base case assumes oseltamivir resistance to be zero (since current levels of resistance to oseltamivir were considered sufficiently low to warrant exclusion from the base case), multiple sensitivity analyses were undertaken in order to assess the impact of variation in levels of resistance amongst influenza strains to the interventions under study. It should be noted that in the 2 weeks preceding completion of this assessment report, the HPA issued a press release stating that approximately 5% (8/162) of H1N1 influenza tested isolates were resistant to oseltamivir. However, further research and monitoring is required to fully assess the impact of this resistance. The sensitivity analysis undertaken using the economic model suggests that low levels of resistance do not have a marked impact upon the cost-effectiveness of oseltamivir. However, increasing levels of resistance to oseltamivir do have the capacity to dramatically influence the conclusions of the economic analysis. It is therefore centrally important that the results of the economic analysis are interpreted in the light of current levels of influenza activity and resistance.

A further problem noted within Chapter 6 is the complete absence of preference-based estimates of the impact of influenza and influenza prophylaxis on health-related quality of life. In addition, systematic searches were unable to identify robust estimates of the impact of influenza complications on quality of life. As such, the benefit side of the economic analysis is based entirely on an intermediate outcome measure (SLCI) and indirect estimates of its impact on health outcomes.

9 CONCLUSIONS

The availability of clinical effectiveness data used to inform the cost-effectiveness modelling was limited for a number of population subgroups. This should be considered during the interpretation of the review findings.

Conclusions on the clinical effectiveness of influenza prophylaxis

Few data relating to the use of amantadine in prophylaxis could be identified and were taken from older trials of poorer quality. Oseltamivir and zanamivir were demonstrated to be effective in preventing SLCI in a number of subgroups. Interventions appeared to be well tolerated by subjects, with a relatively low incidence of few drug-related adverse events and drug-related withdrawals. Very limited evidence could be identified for the effectiveness of the interventions in preventing complications, hospitalisations and in minimizing length of illness and time to return to normal activities. No data were identified relating to health-related quality of life or mortality outcomes. The increasing emergence of antiviral resistance amongst influenza isolates (particularly in the case of amantadine but also for oseltamivir) and the high frequency of adverse events associated with amantadine pose significant challenges to the use of the interventions in clinical practice and, whilst not directly reflected within the trials identified in the review, such issues must be considered during interpretation of the findings from the clinical effectiveness review.

Conclusions on the cost-effectiveness of influenza prophylaxis

Seasonal prophylaxis

Seasonal prophylaxis for healthy children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the healthy children subgroup. The proposed reduction in the price of zanamivir does not affect this finding. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £44,000 per QALY gained.

Seasonal prophylaxis for at-risk children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the at-risk children subgroup. Again, the proposed reduction in the price of zanamivir does not affect this finding. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £17,000 per QALY gained for at-risk children who have not been vaccinated. For at-risk children who have previously been vaccinated, the incremental cost-

effectiveness of oseltamivir versus no prophylaxis is expected to be in excess of £50,000 per QALY gained.

Seasonal prophylaxis for healthy adults

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated in the healthy adult subgroup. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £148,000 per QALY gained for healthy adults who have not been vaccinated and greater than £427,000 per QALY gained for healthy adults who have been vaccinated.

Seasonal prophylaxis for at-risk adults

Based on the current list price for zanamivir, the model suggests that both amantadine and zanamivir are ruled out of the analysis in at-risk adults. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £64,000 per QALY gained in unvaccinated at-risk adults and around £187,000 per QALY gained in previously vaccinated at-risk adults. When the proposed price reduction for zanamivir is included in the analysis for at-risk adults, zanamivir is no longer dominated. The incremental cost-effectiveness of seasonal prophylaxis using zanamivir versus no prophylaxis is expected to be around £53,000 per QALY gained in unvaccinated at-risk adults and £157,000 per QALY gained in at-risk adults who have previously been vaccinated. The incremental cost-effectiveness of oseltamivir is expected to be around £108,000 per QALY gained in unvaccinated at-risk adults and around £314,000 per QALY gained in previously vaccinated at-risk adults.

Seasonal prophylaxis for healthy elderly

For healthy elderly individuals, amantadine and zanamivir are expected to be dominated or extendedly dominated. The proposed reduction in the price of zanamivir does not affect this result. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in healthy elderly individuals who have not been vaccinated is expected to be around £50,000 per QALY gained. For previously vaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £120,000 per QALY gained.

Seasonal prophylaxis for at-risk elderly

For at-risk elderly individuals, amantadine and zanamivir are expected to be extendedly dominated despite the proposed reduction in the price of zanamivir. The incremental cost-

effectiveness of oseltamivir versus no prophylaxis in at-risk elderly individuals who have not been vaccinated is expected to be around £38,000 per QALY gained. For previously vaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £94,000 per QALY gained.

Post-exposure prophylaxis

Post-exposure prophylaxis for healthy children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the healthy children subgroup. For unvaccinated healthy children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £23,000 per QALY gained at the current list price, and around £19,000 per QALY gained when the proposed price reduction for zanamivir is included in the analysis. For vaccinated healthy children, the incremental cost-effectiveness of zanamivir is expected to be at least £59,000 per QALY gained; this estimate includes the proposed price reduction for zanamivir.

For children under the age of 5 years, oseltamivir is the only licensed antiviral prophylaxis option. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £24,000 per QALY gained and £74,000 per QALY gained in unvaccinated and vaccinated groups respectively.

Post-exposure prophylaxis for at-risk children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the at-risk children subgroup. For unvaccinated at-risk children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8,000 per QALY gained at the current list price, and around £6,000 per QALY gained when the proposed price reduction for zanamivir is included in the analysis. For vaccinated at-risk children, the incremental cost-effectiveness of zanamivir is expected to be around £28,000 per QALY gained at the current list price, and £23,000 per QALY gained when the proposed price reduction is included in the analysis.

For at-risk children under the age of 5 years, the incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £9,000 per QALY gained for unvaccinated at-risk children and around £29,000 per QALY gained for vaccinated at-risk children.

Post-exposure prophylaxis for healthy adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the healthy adult subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated healthy adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £34,000 per QALY gained. For previously vaccinated healthy adults, the incremental cost-effectiveness of oseltamivir is expected to be around £104,000 per QALY gained.

Post-exposure prophylaxis for at-risk adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the at-risk adult subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated at-risk adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £13,000 per QALY gained. For previously vaccinated at-risk adults, the incremental cost-effectiveness of oseltamivir is expected to be around £44,000 per QALY gained.

Post-exposure prophylaxis for healthy elderly

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated in the healthy elderly subgroup. The proposed price reduction for zanamivir does not affect this result. For unvaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £11,000 per QALY gained. For previously vaccinated healthy elderly individuals, the incremental cost-effectiveness of oseltamivir is expected to be around £28,000 per QALY gained.

Post-exposure prophylaxis for at-risk elderly

Amantadine and zanamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated in the at-risk elderly subgroup. For unvaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8,000 per QALY gained. For vaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir is expected to be around £22,000 per QALY gained.

It should be noted that increasing levels of resistance to antiviral prophylaxis have the capacity to dramatically influence the conclusions of the economic analysis. The results of the economic analysis should be interpreted in the light of current levels of influenza activity and resistance. The evidence base relating to the clinical and cost-effectiveness of amantadine, oseltamivir and zanamivir in seasonal and post-exposure influenza prophylaxis would be reinforced by further research in the following areas:

1. Additional RCTs in subgroups for which data are currently lacking (as described in Section 8 and including assessments of oseltamivir in seasonal prophylaxis in children, at-risk adults and healthy elderly subjects and zanamivir in seasonal prophylaxis in children and healthy elderly subjects, post-exposure prophylaxis trials of the interventions in elderly subjects and individuals with low cognitive function and/or manual dexterity).
2. RCTs in which the follow-up period extends beyond the duration of prophylaxis
3. Head-to-head RCTs in which the clinical effectiveness of amantadine, oseltamivir and/or zanamivir in different subgroups are directly compared
4. Quality of life studies to inform future economic decision modelling
5. Further research concerning the incidence and management of complications caused by influenza

10. APPENDICES

Appendix 1 Literature search strategies

Medline search strategy to identify clinical trials

- 1 Oseltamivir/ 526
- 2 (gs 4071 or gs 4104 or gs4104 or gs4071 or tamiflu).mp.
- 3 Amantadine/
- 4 amantadine.mp.
- 5 aman.mp.
- 6 amanta.mp.
- 7 amantadin.mp.
- 8 amantadina.mp.
- 9 amixx.mp.
- 10 cerebramed.mp.
- 11 endantadine.mp.
- 12 gen-amantadine.mp.
- 13 infecto-flu.mp.
- 14 infex.mp.
- 15 mantadix.mp.
- 16 midrantan.mp.
- 17 pms-amantadine.mp.
- 18 symadine.mp.
- 19 symmetrel.mp.
- 20 viregyt.mp.
- 21 wiregyt.mp.
- 22 tregor.mp.
- 23 oseltami.mp.
- 24 Zanamivir/
- 25 zanamivir.mp.
- 26 2,3-didehydro-2,4-dideoxy-4-guanidino-n-acetyl-d-neuraminic acid.mp.
- 27 2,3-didehydro-2,4-dideoxy-4-guanidinyl-n-acetylneuraminic acid.mp.
- 28 4-guanidino-2,4-dideoxy-2,3-didehydro-n-acetylneuraminic acid.mp.

29 4-guanidino-2-deoxy-2,3-didehydro-n-acetylneuraminic acid.mp.
 30 4-guanidino-neu5ac2en.mp.
 31 5-acetylamino-2,6-anhydro-4-guanidino-3,4,5-trideoxy-d-galacto-non-enoic acid.mp.
 -
 32 (gg 167 or gg167).mp.
 33 relenza.mp.
 34 or/1-33
 35 prophyla\$.ti,ab.
 36 prevent\$.ti,ab.
 37 35 or 36
 38 37 and 34
 39 randomized controlled trial.pt.
 40 controlled clinical trial.pt.
 41 randomized controlled trials/
 42 random allocation/
 43 double blind method/
 44 single blind method/
 45 or/39-44
 46 clinical trial.pt.
 47 exp clinical trials/
 48 (clin\$ adj25 trial\$).tw.
 49 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).tw.
 50 placebos/
 51 placebo\$.tw.
 52 random\$.tw.
 53 research design/
 54 or/46-53
 55 "comparative study"/
 56 exp evaluation studies/
 57 follow-up studies/
 58 prospective studies/
 59 (control\$ or prospectiv\$ or volunteer\$).tw.
 60 (control\$ or prospectiv\$ or volunteer\$).tw.
 61 or/55-60

62 45 or 54 or 61
63 "animal"/
64 "human"/
65 63 not 64
66 62 not 65
67 66 and 38
68 Influenza, Human/
69 68 and 67

Medline search strategy to identify utility estimates for influenza and related complications

1 Influenza/
2 (influenza or flu).tw.
3 1 or 2
4 "Quality of Life"/
5 (quality of life or qol).ti,ab.
6 (quality adjusted life year or qaly).ti,ab.
7 utilit\$.ti,ab.
8 Health Status Indicators/
9 disability adjusted life.tw.
10 daly\$.tw.
11 (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).tw.

12 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
13 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
14 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
15 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
16 (euroqol or euro qol or eq5d or eq 5d).tw.

17 (hql or hqol or h qol or hrqol or hr qol).tw.
18 (hye or hyes).tw.
19 health\$ year\$ equivalent\$.tw.
20 health utilit\$.tw.
21 (hui or hui1 or hui2 or hui3).tw.
22 disutili\$.tw.
23 rosser.tw.
24 quality of wellbeing.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble\$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 exp models, economic/
32 economic model\$.tw.
33 markov\$.tw.
34 monte carlo.tw.
35 (decision\$ adj2 (tree\$ or analy\$ or model\$)).tw.
36 letter.pt.
37 editorial.pt.
38 comment.pt.
39 or/36-38
40 or/4-35
41 (40 and 3) not 39

Appendix 2 Quality assessment

Quality assessment criteria for experimental studies (based on the criteria proposed by the NHS Centre for Reviews and Dissemination)³⁶

	Yes/No/Unclear/ Not Applicable
Was the method used to assign participants to the treatment groups really random?	
What method of assignment was used?	
Was the allocation of treatment concealed?	
What method was used to conceal treatment allocation?	
Was the number of participants who were randomised stated?	
Were the eligibility criteria for study entry specified?	
Were details of baseline comparability presented?	
Was baseline comparability achieved?	
Were the participants who received the intervention blinded to the treatment allocation?	
Were the individuals who administered the intervention blinded to the treatment allocation?	
Were the outcome assessors blinded to the treatment allocations?	
Was the success of the blinding procedure assessed?	
Were any co-interventions identified that may influence the outcomes for each group?	
Was an intention-to-treat analysis included?	
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	

Appendix 3 Study quality characteristics for amantadine prophylaxis trials

(Y, N and U are used to denote positive, negative and unclear decisions with respect to each quality criterion).

Quality criterion	Reuman <i>et al.</i> , 1989* (1) 57	Reuman <i>et al.</i> , 1989* (2) 57	Aoki <i>et al.</i> , 1986 ⁵⁸	Pettersson <i>et al.</i> , 1980 ⁵⁵	Payler & Purdham, 1984 ⁵⁹	Smorodintsev <i>et al.</i> , 1970a,b ^{60, 61}	Sears & Clements, 1987 ⁶³	Smorodintsev <i>et al.</i> , 1970c ⁶²
Was the method used to assign participants to the treatment groups really random?	Y	U	Y	Y	U	U	U	U
Was the allocation of treatment concealed?	U	U	U	U	U	Y	U	U
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y	Y	U
Were details of baseline comparability presented?	N	N	N	Y	N	N	N	N
Was baseline comparability achieved?	U	U	U	N	U	U	U	U

Were the eligibility criteria for study entry specified?	Y	Y	Y	N	Y	N	Y	N
Were the outcome assessors blinded to allocation?	U For self-notification of illness: Y	U	For measurement of amantadine concentrations in plasma and urine: Y For incidence of illness and adverse events: self-recorded. Y For serum HAI assessment: U Nurses classifying illness: U	U For self-recorded symptoms and adverse effects: Y	U	For adverse effect and morbidity assessment: Y	U	U
Were the individuals who administered the intervention blinded to allocation?	U Described as double blind but no further details	U Described as double blind but no further details	U Described as single blind but no further details	U Described as double blind but no further details	N	Y	U Described as double blind but no further details	U Described as double blind but no further details

Were the participants receiving intervention blinded to allocation?	Y	U Described as double blind but no further details	Y	Y	N	Y	U Described as double blind but no further details	U Described as double blind but no further details
Were the reasons for withdrawal stated?	Y	Y	Y	Y	Y	N	Y	N/A
Was intention-to-treat analysis included?	Y	Y	N	Mixed For efficacy analysis: N. For adverse event analysis: Y.	N	N	Y	Y

Appendix 4 Study quality characteristics for oseltamivir prophylaxis trials

(Y, N and U are used to denote positive, negative and unclear decisions with respect to each quality criterion).

	Peters <i>et al.</i> , 2001 ⁶⁴	Hayden <i>et al.</i> , 1999a ⁶⁶	Welliver <i>et al.</i> , 2001 ⁴⁹	Hayden <i>et al.</i> , 2004 ^{48,68,67}	Hayden <i>et al.</i> , 2000 ⁶⁹
Was the method used to assign participants to the treatment groups really random?	Y	Y	U	U	U
Was the allocation of treatment concealed?	Y	Y	U	U	U
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y	N
Was baseline comparability achieved?	Y	Y	Y	Y	U
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	U
Were the outcome assessors blinded to allocation?	U For self-recording of data: Y	U For self-recording of data: Y	U For self-recording of data: Y	U For self-recording of data: Y	U
Were the individuals who administered the intervention blinded to allocation?	U Described as double blind but no further details	Y Double-blind labelling	U Described as double blind but no further details	N Open-label	U Described as double blind but no further details

Were the participants receiving intervention blinded to allocation?	Y	Y Double-blind labelling	U Described as double blind but no further details	N Open-label	U Described as double blind but no further details
Were the reasons for withdrawal stated?	N	Y	Y	Y	N
Was intention-to-treat analysis included?	U	N	N	Y	Y

Appendix 5 Study quality characteristics for zanamivir prophylaxis trials

(Y, N and U are used to denote positive, negative and unclear decisions with respect to each quality criterion).

Quality criterion	Monto <i>et al.</i> , 1999a ^{72, 73}	LaForce <i>et al.</i> , 2007 ⁷⁵	Monto <i>et al.</i> , 2002 ⁴⁷	Hayden <i>et al.</i> , 2000 ⁴⁶	Kaiser <i>et al.</i> , 2000 ⁷⁴	Ambrozaitis <i>et al.</i> , 2005 ^{76, 77}	Gravenstein <i>et al.</i> , 2005 ⁷⁸	GSK study 167-101 ⁴⁴
Was the method used to assign participants to the treatment groups really random?	Y	Y	U	U	U	Y	Y	U
Was the allocation of treatment concealed?	Y	Y ⁴⁴	N ⁴⁴	U	U	U	Y	U
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	Y	Y	Y	Y	Y	Y	N

Was baseline comparability achieved?	Y	Y	Y	Y	Y	Y	Y (albeit relatively weakly for age, sex, vaccination status, chronic cardiac condition and diabetes variables)	U
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	Y	Y	Y	N
Were the outcome assessors blinded to allocation?	U For self-recording of data: Y	U For self-recording of data: Y	U For self-recording of data: Y	U For self-recording of data: Y	U	Y	Y ⁴⁴	U
Were the individuals who administered the intervention blinded to allocation?	Y	Y ⁴⁴	Y ⁴⁴	U Described as double blind but no further details	U Described as double blind but no further details	Y	Y ⁴⁴	U Described as double blind but no further details
Were the participants receiving intervention blinded to allocation?	Y	Y	Y ⁴⁴	U Described as double blind but no further details	U Described as double blind but no further details	Y	Y ⁴⁴	U Described as double blind but no further details

Were the reasons for withdrawal stated?	Y	Y	Y	Y	Y	Y	Y	N
Was intention-to-treat analysis included?	Y	Y	Y	Y	Y	Y	Y	N

Appendix 6 Table of studies excluded after close scrutiny with rationale

Study	Reason for exclusion
Aoki <i>et al.</i> , 1985	Not in line with licensed indications
Bowles <i>et al.</i> , 1999	Not a randomised controlled trial
Bowles <i>et al.</i> , 2002	Not a randomised controlled trial
Bryson <i>et al.</i> , 1980	Not in line with licensed indications
Bush <i>et al.</i> , 2004	Not a randomised controlled trial
Calfée <i>et al.</i> , 1999a	Not in line with licensed indications
Calfée <i>et al.</i> , 1999b	Not in line with licensed indications
Callmender <i>et al.</i> , 1968	Not in line with licensed indications
Cass <i>et al.</i> , 2000	Not in line with licensed indications
Cohen <i>et al.</i> , 1976	Not in line with licensed indications
Davies <i>et al.</i> , 1988	Not a randomised controlled trial
Dawkins <i>et al.</i> , 1968	Analogue of amantadine hydrochloride. Not in line with licensed indications
Degelau <i>et al.</i> , 1990	Not a randomised controlled trial
Diaz-Pedroche <i>et al.</i> , 2006	Not available to read in English
Dolin <i>et al.</i> , 1982	Not in line with licensed indications
Drinka <i>et al.</i> , 1998	Comparison of short and long-term amantadine prophylaxis protocols
Finklea <i>et al.</i> , 1967	Not in line with licensed indications – dosage not established in children
Galbraith <i>et al.</i> , 1969a	Data for subgroup in line with licensed indications not presented
Galbraith <i>et al.</i> , 1969b	Data for subgroup in line with licensed indications not presented
Galbraith <i>et al.</i> , 1971	Data for subgroup in line with licensed indications not presented
Hayden <i>et al.</i> , 1981	Not in line with licensed indications
Hayden <i>et al.</i> , 1996	Not in line with licensed indications
Hayden <i>et al.</i> , 1999b ¹³⁸	Not in line with licensed indications
Hayden, 2001	Abstract only. Insufficient data
Hess, 1982	Not available to read in English
Hirji <i>et al.</i> , 2001	Not a randomised controlled trial
Hirji <i>et al.</i> , 2002	Not a randomised controlled trial
Jackson <i>et al.</i> , 1963	Not in line with licensed indications
Kantor <i>et al.</i> , 1980	Not in line with licensed indications
Kashiwagi <i>et al.</i> , 2000	Not available to read in English
Lee <i>et al.</i> , 2000	Not a randomised controlled trial
Leeming <i>et al.</i> , 1969	Not in line with licensed indications
Leung <i>et al.</i> , 1979	Not in line with licensed indications
Libow <i>et al.</i> , 1996	Not a randomised controlled trial
Mate <i>et al.</i> , 1970	Not in line with licensed indications
McLeod & Lau, 2001	Not a randomised controlled trial
Millet <i>et al.</i> , 1982	Not in line with licensed indications
Monto <i>et al.</i> , 1979	Not in line with licensed indications
Monto <i>et al.</i> , 2004	Not a randomised controlled trial
Muldoon <i>et al.</i> , 1976	Not in line with licensed indications
Nafta <i>et al.</i> , 1970	Not in line with licensed indications
O'Donoghue <i>et al.</i> , 1973	Not in line with licensed indications
Oker-Blom <i>et al.</i> , 1970	Not in line with licensed indications
Peckinpugh <i>et al.</i> , 1970	Not in line with licensed indications
Peters <i>et al.</i> , 1989	Not a randomised controlled trial
Plesnik <i>et al.</i> , 1977	Not available to read in English
Quarles <i>et al.</i> , 1981	Not in line with licensed indications

Quilligan <i>et al.</i> , 1966a	Not in line with licensed indications – dosage not established in children
Quilligan <i>et al.</i> , 1966	Not available to read in English
Schapira <i>et al.</i> , 1971	Not in line with licensed indications
Schilling <i>et al.</i> , 1998	Not in line with licensed indications
Shinjoh <i>et al.</i> , 2004	Not available to read in English
Smorodintsev <i>et al.</i> , 1972	Not available to read in English
Somani <i>et al.</i> , 1991	Not a randomised controlled trial
Stanley <i>et al.</i> , 1965	Not in line with licensed indications
Togo <i>et al.</i> , 1968	Not in line with licensed indications
Tyrrell <i>et al.</i> , 1965	Not in line with licensed indications
Vogel, 2002	Not a randomised controlled trial
Walker <i>et al.</i> , 1997	Not in line with licensed indications
Wendel <i>et al.</i> , 1966	Not in line with licensed indications
Wright <i>et al.</i> , 1974	Not in line with licensed indications
Wright <i>et al.</i> , 1976	Not in line with licensed indications – dosage not established in children

Appendix 7 List of all model parameters

Distribution parameter key

Distribution type	Parameter1	Parameter2
Normal	Mean	SE
Beta	Alpha	Alpha+Beta
Gamma	Alpha	Beta
Lognormal	Ln mean	SE ln mean
Dirichlet (multinomial)	Alpha	Beta

List of model parameters - Seasonal prophylaxis - Healthy children

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.17	256	1469
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.36	-1.02	0.14
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.40	-0.92	0.83
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.24	-1.43	0.45
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.32	-1.13	0.34
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	0.53	0.53	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	0.70	0.70	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.06	13.56	237.89
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.52	38	73
25	Probability patient given antiviral Tx presents < 48 hours	N/a	0.00	0	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	1.00	1	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.00	0	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.14	2417.00	17201.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.65	0	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.70	-0.36	0.16
33	Probability complication is respiratory	Dirichlet	0.70	1698	2423
34	Probability complication is cardiac	Dirichlet	0.00	1	2423
35	Probability complication is CNS	Dirichlet	0.01	18	2423
36	Probability complication is renal	Dirichlet	0.00	3	2423
37	Probability complication is otitis media	Dirichlet	0.28	685	2423
38	Probability complication is other	Dirichlet	0.01	18	2423
39	Probability respiratory complication is pneumonia	Beta	0.02	29	1697
40	Probability patient receives antibiotics no complication	Beta	0.28	4997	17910
41	Probability patient receives antibiotics complication	Beta	0.74	2183	2962
42	Probability of influenza death complication	Beta	0.00	1	2311
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£14.40	£14.40	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£9.60	£9.60	-
45	Cost of oseltamivir prophylaxis course	N/a	£49.08	£49.08	-
46	Cost of zanamivir prophylaxis course	N/a	£73.65	£73.65	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£42.00	£42.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	21	21	-
51	Days per course - oseltamivir prophylaxis	N/a	42	42	-
52	Days per course - zanamivir prophylaxis	N/a	28	28	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.05	4.00	73.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.05	4	73
64	Cost of uncomplicated influenza presentation	N/a	£29.52	£29.52	-
65	Cost of complicated influenza presentation	N/a	£29.52	£29.52	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.11	5.00	46.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	2.30	1	4
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£2,430.18	£2,430.18	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.04	4146	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.04	4247	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.04	4247	100000
80	QALY loss for flu case - no treatment	N/a	0.01	0.01	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.01	0.01	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.01	0.01	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.02	6.92	1.14
92	Duration cardiac complication (years)	Gamma	0.02	6.92	1.14
93	Duration CNS complication (years)	Gamma	0.02	6.92	1.14
94	Duration renal complication (years)	Gamma	0.02	6.92	1.14
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.02	6.92	1.14
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	24.74	24.74	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Seasonal prophylaxis – At-risk children

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.17	256	1469
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.36	-1.02	0.14
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.40	-0.92	0.83
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.24	-1.43	0.45
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.32	-1.13	0.34
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	0.53	0.53	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	0.70	0.70	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.06	13.56	237.89
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.52	38	73
25	Probability patient given antiviral Tx presents < 48 hours	N/a	1.00	1	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	1.00	1	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.00	0	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.18	675.00	3695.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.65	0	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.49	-0.71	0.38
33	Probability complication is respiratory	Dirichlet	0.77	521	681
34	Probability complication is cardiac	Dirichlet	0.00	1	681
35	Probability complication is CNS	Dirichlet	0.00	1	681
36	Probability complication is renal	Dirichlet	0.00	1	681
37	Probability complication is otitis media	Dirichlet	0.23	154	681
38	Probability complication is other	Dirichlet	0.00	3	681
39	Probability respiratory complication is pneumonia	Beta	0.02	9	520
40	Probability patient receives antibiotics no complication	Beta	0.28	4997	17910
41	Probability patient receives antibiotics complication	Beta	0.74	2183	2962
42	Probability of influenza death complication	Beta	0.00	1	650
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£14.40	£14.40	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£9.60	£9.60	-
45	Cost of oseltamivir prophylaxis course	N/a	£49.08	£49.08	-
46	Cost of zanamivir prophylaxis course	N/a	£73.65	£73.65	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£42.00	£42.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	21	21	-
51	Days per course - oseltamivir prophylaxis	N/a	42	42	-
52	Days per course - zanamivir prophylaxis	N/a	28	28	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.05	4.00	73.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.05	4	73
64	Cost of uncomplicated influenza presentation	N/a	£29.52	£29.52	-
65	Cost of complicated influenza presentation	N/a	£29.52	£29.52	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.16	15.00	95.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	2.30	1	4
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£2,430.18	£2,430.18	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.03	2820	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.03	2977	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.03	2977	100000
80	QALY loss for flu case - no treatment	N/a	0.02	0.02	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.02	0.02	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.02	0.02	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.02	7.24	1.11
92	Duration cardiac complication (years)	Gamma	0.02	7.24	1.11
93	Duration CNS complication (years)	Gamma	0.02	7.24	1.11
94	Duration renal complication (years)	Gamma	0.02	7.24	1.11
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.02	7.24	1.11
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	24.74	24.74	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Seasonal prophylaxis – Healthy adults

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.06	104	1670
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.35	-1.05	0.17
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.40	-0.92	0.83
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.24	-1.43	0.45
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.32	-1.13	0.34
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	0.53	0.53	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	0.70	0.70	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.06	13.56	237.89
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.16	104	668
25	Probability patient given antiviral Tx presents < 48 hours	N/a	0.00	0	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	0.89	0.89	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.11	0.11	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.08	6509.00	85248.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.40	-1	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.70	-0.36	0.16
33	Probability complication is respiratory	Dirichlet	0.87	5637	6515
34	Probability complication is cardiac	Dirichlet	0.00	12	6515
35	Probability complication is CNS	Dirichlet	0.02	102	6515
36	Probability complication is renal	Dirichlet	0.00	10	6515
37	Probability complication is otitis media	Dirichlet	0.08	501	6515
38	Probability complication is other	Dirichlet	0.04	253	6515
39	Probability respiratory complication is pneumonia	Beta	0.04	237	5636
40	Probability patient receives antibiotics no complication	Beta	0.42	19811	47169
41	Probability patient receives antibiotics complication	Beta	0.81	6983	8579
42	Probability of influenza death complication	Beta	0.01	33	6437
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£14.40	£14.40	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£9.60	£9.60	-
45	Cost of oseltamivir prophylaxis course	N/a	£81.80	£81.80	-
46	Cost of zanamivir prophylaxis course	N/a	£73.65	£73.65	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£42.00	£42.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	21	21	-
51	Days per course - oseltamivir prophylaxis	N/a	42	42	-
52	Days per course - zanamivir prophylaxis	N/a	28	28	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.08	56.00	674.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.08	56	674
64	Cost of uncomplicated influenza presentation	N/a	£30.73	£30.73	-
65	Cost of complicated influenza presentation	N/a	£30.73	£30.73	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.11	5.00	46.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	11.90	16	1
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£4,937.39	£4,937.39	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.04	4146	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.04	4247	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.04	4247	100000
80	QALY loss for flu case - no treatment	N/a	0.01	0.01	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.01	0.01	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.01	0.01	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.03	9.46	0.98
92	Duration cardiac complication (years)	Gamma	0.03	9.46	0.98
93	Duration CNS complication (years)	Gamma	0.03	9.46	0.98
94	Duration renal complication (years)	Gamma	0.03	9.46	0.98
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.03	9.46	0.98
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	13.37	13.37	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Seasonal prophylaxis – At-risk adults

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.06	104	1670
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.35	-1.05	0.17
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.40	-0.92	0.83
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.24	-1.43	0.45
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.17	-1.75	0.54
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	0.53	0.53	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	0.70	0.70	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.15	0.37	2.55
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.16	104	668
25	Probability patient given antiviral Tx presents < 48 hours	N/a	1.00	1	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	0.89	0.89	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.11	0.11	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.12	2166.00	17597.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.40	-1	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.49	-0.71	0.38
33	Probability complication is respiratory	Dirichlet	0.89	1942	2172
34	Probability complication is cardiac	Dirichlet	0.01	30	2172
35	Probability complication is CNS	Dirichlet	0.01	16	2172
36	Probability complication is renal	Dirichlet	0.00	6	2172
37	Probability complication is otitis media	Dirichlet	0.05	111	2172
38	Probability complication is other	Dirichlet	0.03	67	2172
39	Probability respiratory complication is pneumonia	Beta	0.03	62	1941
40	Probability patient receives antibiotics no complication	Beta	0.42	19811	47169
41	Probability patient receives antibiotics complication	Beta	0.81	6983	8579
42	Probability of influenza death complication	Beta	0.01	16	2142
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£14.40	£14.40	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£9.60	£9.60	-
45	Cost of oseltamivir prophylaxis course	N/a	£81.80	£81.80	-
46	Cost of zanamivir prophylaxis course	N/a	£73.65	£73.65	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£42.00	£42.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	21	21	-
51	Days per course - oseltamivir prophylaxis	N/a	42	42	-
52	Days per course - zanamivir prophylaxis	N/a	28	28	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.08	56.00	674.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.08	56	674
64	Cost of uncomplicated influenza presentation	N/a	£30.73	£30.73	-
65	Cost of complicated influenza presentation	N/a	£30.73	£30.73	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.16	15.00	95.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	11.90	16	1
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£4,937.39	£4,937.39	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.03	2820	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.03	2977	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.03	2977	100000
80	QALY loss for flu case - no treatment	N/a	0.02	0.02	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.02	0.02	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.02	0.02	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.03	12.60	0.85
92	Duration cardiac complication (years)	Gamma	0.03	12.60	0.85
93	Duration CNS complication (years)	Gamma	0.03	12.60	0.85
94	Duration renal complication (years)	Gamma	0.03	12.60	0.85
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.03	12.60	0.85
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	13.37	13.37	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Seasonal prophylaxis – Healthy elderly

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.05	57	1098
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.42	-0.87	0.23
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.40	-0.92	0.83
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.08	-2.50	1.04
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.20	-1.61	1.09
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	0.53	0.53	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	0.70	0.70	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.15	0.37	2.55
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.11	18.5	164
25	Probability patient given antiviral Tx presents < 48 hours	N/a	1.00	1	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	0.89	0.89	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.11	0.11	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.09	942.00	10145.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.40	-1	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.70	-0.36	0.16
33	Probability complication is respiratory	Dirichlet	0.86	820	948
34	Probability complication is cardiac	Dirichlet	0.01	10	948
35	Probability complication is CNS	Dirichlet	0.02	22	948
36	Probability complication is renal	Dirichlet	0.01	6	948
37	Probability complication is otitis media	Dirichlet	0.02	22	948
38	Probability complication is other	Dirichlet	0.07	68	948
39	Probability respiratory complication is pneumonia	Beta	0.13	106	819
40	Probability patient receives antibiotics no complication	Beta	0.55	8544	15620
41	Probability patient receives antibiotics complication	Beta	0.80	1527	1916
42	Probability of influenza death complication	Beta	0.11	110	981
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£14.40	£14.40	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£9.60	£9.60	-
45	Cost of oseltamivir prophylaxis course	N/a	£81.80	£81.80	-
46	Cost of zanamivir prophylaxis course	N/a	£73.65	£73.65	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£42.00	£42.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	21	21	-
51	Days per course - oseltamivir prophylaxis	N/a	42	42	-
52	Days per course - zanamivir prophylaxis	N/a	28	28	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.38	62.00	165.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.38	62	165
64	Cost of uncomplicated influenza presentation	N/a	£43.20	£43.20	-
65	Cost of complicated influenza presentation	N/a	£43.20	£43.20	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.16	15.00	95.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	15.00	25	1
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£5,747.01	£5,747.01	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.03	2820	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.03	2977	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.03	2977	100000
80	QALY loss for flu case - no treatment	N/a	0.02	0.02	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.01	0.01	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.01	0.01	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.03	13.15	0.83
92	Duration cardiac complication (years)	Gamma	0.03	13.15	0.83
93	Duration CNS complication (years)	Gamma	0.03	13.15	0.83
94	Duration renal complication (years)	Gamma	0.03	13.15	0.83
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.03	13.15	0.83
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	2.95	2.95	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Seasonal prophylaxis – At-risk elderly

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.05	57	1098
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.42	-0.87	0.23
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.40	-0.92	0.83
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.08	-2.50	1.04
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.20	-1.61	1.09
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	0.53	0.53	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	0.70	0.70	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.15	0.37	2.55
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.11	18.5	164
25	Probability patient given antiviral Tx presents < 48 hours	N/a	1.00	1	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	0.89	0.89	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.11	0.11	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.12	908.00	7407.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.40	-1	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.49	-0.71	0.38
33	Probability complication is respiratory	Dirichlet	0.83	755	914
34	Probability complication is cardiac	Dirichlet	0.07	60	914
35	Probability complication is CNS	Dirichlet	0.03	24	914
36	Probability complication is renal	Dirichlet	0.01	13	914
37	Probability complication is otitis media	Dirichlet	0.01	12	914
38	Probability complication is other	Dirichlet	0.05	50	914
39	Probability respiratory complication is pneumonia	Beta	0.13	97	754
40	Probability patient receives antibiotics no complication	Beta	0.55	8544	15620
41	Probability patient receives antibiotics complication	Beta	0.80	1527	1916
42	Probability of influenza death complication	Beta	0.12	114	936
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£14.40	£14.40	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£9.60	£9.60	-
45	Cost of oseltamivir prophylaxis course	N/a	£81.80	£81.80	-
46	Cost of zanamivir prophylaxis course	N/a	£73.65	£73.65	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£42.00	£42.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	21	21	-
51	Days per course - oseltamivir prophylaxis	N/a	42	42	-
52	Days per course - zanamivir prophylaxis	N/a	28	28	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.38	62.00	165.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.38	62	165
64	Cost of uncomplicated influenza presentation	N/a	£43.20	£43.20	-
65	Cost of complicated influenza presentation	N/a	£43.20	£43.20	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.16	15.00	95.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	15.00	25	1
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£5,747.01	£5,747.01	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.03	2820	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.03	2977	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.03	2977	100000
80	QALY loss for flu case - no treatment	N/a	0.02	0.02	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.01	0.01	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.01	0.01	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.03	13.13	0.83
92	Duration cardiac complication (years)	Gamma	0.03	13.13	0.83
93	Duration CNS complication (years)	Gamma	0.03	13.13	0.83
94	Duration renal complication (years)	Gamma	0.03	13.13	0.83
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.03	13.13	0.83
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	2.95	2.95	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Post-exposure prophylaxis – Healthy children

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.19	21	111
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.36	-1.02	0.14
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.10	-2.26	0.60
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.36	-1.03	0.41
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.21	-1.56	0.24
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	1.00	1.00	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	1.00	1.00	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.06	13.56	237.89
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.52	38	73
25	Probability patient given antiviral Tx presents < 48 hours	N/a	0.00	0	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	1.00	1	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.00	0	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.14	2417.00	17201.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.65	0	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.70	-0.36	0.16
33	Probability complication is respiratory	Dirichlet	0.70	1698	2423
34	Probability complication is cardiac	Dirichlet	0.00	1	2423
35	Probability complication is CNS	Dirichlet	0.01	18	2423
36	Probability complication is renal	Dirichlet	0.00	3	2423
37	Probability complication is otitis media	Dirichlet	0.28	685	2423
38	Probability complication is other	Dirichlet	0.01	18	2423
39	Probability respiratory complication is pneumonia	Beta	0.02	29	1697
40	Probability patient receives antibiotics no complication	Beta	0.28	4997	17910
41	Probability patient receives antibiotics complication	Beta	0.74	2183	2962
42	Probability of influenza death complication	Beta	0.00	1	2311
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£4.80	£4.80	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£4.80	£4.80	-
45	Cost of oseltamivir prophylaxis course	N/a	£16.36	£16.36	-
46	Cost of zanamivir prophylaxis course	N/a	£24.55	£24.55	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£10.00	£10.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	10	10	-
51	Days per course - oseltamivir prophylaxis	N/a	10	10	-
52	Days per course - zanamivir prophylaxis	N/a	10	10	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.05	4.00	73.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.05	4	73
64	Cost of uncomplicated influenza presentation	N/a	£29.52	£29.52	-
65	Cost of complicated influenza presentation	N/a	£29.52	£29.52	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.11	5.00	46.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	2.30	1	4
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£2,430.18	£2,430.18	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.04	4146	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.04	4247	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.04	4247	100000
80	QALY loss for flu case - no treatment	N/a	0.01	0.01	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.01	0.01	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.01	0.01	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.02	6.92	1.14
92	Duration cardiac complication (years)	Gamma	0.02	6.92	1.14
93	Duration CNS complication (years)	Gamma	0.02	6.92	1.14
94	Duration renal complication (years)	Gamma	0.02	6.92	1.14
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.02	6.92	1.14
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	24.74	24.74	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Post-exposure prophylaxis – at-risk children

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.19	21	111
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.36	-1.02	0.14
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.10	-2.26	0.60
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.36	-1.03	0.41
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.21	-1.56	0.24
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	1.00	1.00	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	1.00	1.00	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.06	13.56	237.89
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.52	38	73
25	Probability patient given antiviral Tx presents < 48 hours	N/a	1.00	1	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	1.00	1	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.00	0	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.18	675.00	3695.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.65	0	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.49	-0.71	0.38
33	Probability complication is respiratory	Dirichlet	0.77	521	681
34	Probability complication is cardiac	Dirichlet	0.00	1	681
35	Probability complication is CNS	Dirichlet	0.00	1	681
36	Probability complication is renal	Dirichlet	0.00	1	681
37	Probability complication is otitis media	Dirichlet	0.23	154	681
38	Probability complication is other	Dirichlet	0.00	3	681
39	Probability respiratory complication is pneumonia	Beta	0.02	9	520
40	Probability patient receives antibiotics no complication	Beta	0.28	4997	17910
41	Probability patient receives antibiotics complication	Beta	0.74	2183	2962
42	Probability of influenza death complication	Beta	0.00	1	650
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£4.80	£4.80	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£4.80	£4.80	-
45	Cost of oseltamivir prophylaxis course	N/a	£16.36	£16.36	-
46	Cost of zanamivir prophylaxis course	N/a	£24.55	£24.55	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£10.00	£10.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	10	10	-
51	Days per course - oseltamivir prophylaxis	N/a	10	10	-
52	Days per course - zanamivir prophylaxis	N/a	10	10	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.05	4.00	73.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.05	4	73
64	Cost of uncomplicated influenza presentation	N/a	£29.52	£29.52	-
65	Cost of complicated influenza presentation	N/a	£29.52	£29.52	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.16	15.00	95.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	2.30	1	4
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£2,430.18	£2,430.18	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.03	2820	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.03	2977	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.03	2977	100000
80	QALY loss for flu case - no treatment	N/a	0.02	0.02	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.02	0.02	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.02	0.02	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.02	7.24	1.11
92	Duration cardiac complication (years)	Gamma	0.02	7.24	1.11
93	Duration CNS complication (years)	Gamma	0.02	7.24	1.11
94	Duration renal complication (years)	Gamma	0.02	7.24	1.11
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.02	7.24	1.11
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	24.74	24.74	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Post-exposure prophylaxis – healthy adults

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.09	180	2051
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.35	-1.05	0.17
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.10	-2.26	0.60
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.19	-1.66	0.44
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.21	-1.56	0.24
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	1.00	1.00	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	1.00	1.00	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.06	13.56	237.89
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.16	104	668
25	Probability patient given antiviral Tx presents < 48 hours	N/a	0.00	0	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	0.89	0.89	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.11	0.11	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.08	6509.00	85248.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.40	-1	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.70	-0.36	0.16
33	Probability complication is respiratory	Dirichlet	0.87	5637	6515
34	Probability complication is cardiac	Dirichlet	0.00	12	6515
35	Probability complication is CNS	Dirichlet	0.02	102	6515
36	Probability complication is renal	Dirichlet	0.00	10	6515
37	Probability complication is otitis media	Dirichlet	0.08	501	6515
38	Probability complication is other	Dirichlet	0.04	253	6515
39	Probability respiratory complication is pneumonia	Beta	0.04	237	5636
40	Probability patient receives antibiotics no complication	Beta	0.42	19811	47169
41	Probability patient receives antibiotics complication	Beta	0.81	6983	8579
42	Probability of influenza death complication	Beta	0.01	33	6437
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£4.80	£4.80	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£4.80	£4.80	-
45	Cost of oseltamivir prophylaxis course	N/a	£16.36	£16.36	-
46	Cost of zanamivir prophylaxis course	N/a	£24.55	£24.55	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£10.00	£10.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	10	10	-
51	Days per course - oseltamivir prophylaxis	N/a	10	10	-
52	Days per course - zanamivir prophylaxis	N/a	10	10	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.08	56.00	674.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.08	56	674
64	Cost of uncomplicated influenza presentation	N/a	£30.73	£30.73	-
65	Cost of complicated influenza presentation	N/a	£30.73	£30.73	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.11	5.00	46.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	11.90	16	1
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£4,937.39	£4,937.39	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.04	4146	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.04	4247	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.04	4247	100000
80	QALY loss for flu case - no treatment	N/a	0.01	0.01	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.01	0.01	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.01	0.01	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.03	9.46	0.98
92	Duration cardiac complication (years)	Gamma	0.03	9.46	0.98
93	Duration CNS complication (years)	Gamma	0.03	9.46	0.98
94	Duration renal complication (years)	Gamma	0.03	9.46	0.98
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.03	9.46	0.98
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	13.37	13.37	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Post-exposure prophylaxis – At-risk adults

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.09	180	2051
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.35	-1.05	0.17
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.10	-2.26	0.60
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.19	-1.66	0.44
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.21	-1.56	0.24
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	1.00	1.00	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	1.00	1.00	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.15	0.37	2.55
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.16	104	668
25	Probability patient given antiviral Tx presents < 48 hours	N/a	1.00	1	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	0.89	0.89	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.11	0.11	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.12	2166.00	17597.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.40	-1	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.49	-0.71	0.38
33	Probability complication is respiratory	Dirichlet	0.89	1942	2172
34	Probability complication is cardiac	Dirichlet	0.01	30	2172
35	Probability complication is CNS	Dirichlet	0.01	16	2172
36	Probability complication is renal	Dirichlet	0.00	6	2172
37	Probability complication is otitis media	Dirichlet	0.05	111	2172
38	Probability complication is other	Dirichlet	0.03	67	2172
39	Probability respiratory complication is pneumonia	Beta	0.03	62	1941
40	Probability patient receives antibiotics no complication	Beta	0.42	19811	47169
41	Probability patient receives antibiotics complication	Beta	0.81	6983	8579
42	Probability of influenza death complication	Beta	0.01	16	2142
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£4.80	£4.80	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£4.80	£4.80	-
45	Cost of oseltamivir prophylaxis course	N/a	£16.36	£16.36	-
46	Cost of zanamivir prophylaxis course	N/a	£24.55	£24.55	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£10.00	£10.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	10	10	-
51	Days per course - oseltamivir prophylaxis	N/a	10	10	-
52	Days per course - zanamivir prophylaxis	N/a	10	10	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.08	56.00	674.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.08	56	674
64	Cost of uncomplicated influenza presentation	N/a	£30.73	£30.73	-
65	Cost of complicated influenza presentation	N/a	£30.73	£30.73	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.16	15.00	95.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	11.90	16	1
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£4,937.39	£4,937.39	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.03	2820	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.03	2977	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.03	2977	100000
80	QALY loss for flu case - no treatment	N/a	0.02	0.02	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.02	0.02	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.02	0.02	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.03	12.60	0.85
92	Duration cardiac complication (years)	Gamma	0.03	12.60	0.85
93	Duration CNS complication (years)	Gamma	0.03	12.60	0.85
94	Duration renal complication (years)	Gamma	0.03	12.60	0.85
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.03	12.60	0.85
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	13.37	13.37	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Post-exposure prophylaxis – healthy elderly

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.09	180	2051
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.42	-0.87	0.23
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.10	-2.26	0.60
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.19	-1.66	0.44
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.21	-1.56	0.24
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	1.00	1.00	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	1.00	1.00	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.15	0.37	2.55
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.11	18.5	164
25	Probability patient given antiviral Tx presents < 48 hours	N/a	1.00	1	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	0.89	0.89	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.11	0.11	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.09	942.00	10145.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.40	-1	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.70	-0.36	0.16
33	Probability complication is respiratory	Dirichlet	0.86	820	948
34	Probability complication is cardiac	Dirichlet	0.01	10	948
35	Probability complication is CNS	Dirichlet	0.02	22	948
36	Probability complication is renal	Dirichlet	0.01	6	948
37	Probability complication is otitis media	Dirichlet	0.02	22	948
38	Probability complication is other	Dirichlet	0.07	68	948
39	Probability respiratory complication is pneumonia	Beta	0.13	106	819
40	Probability patient receives antibiotics no complication	Beta	0.55	8544	15620
41	Probability patient receives antibiotics complication	Beta	0.80	1527	1916
42	Probability of influenza death complication	Beta	0.11	110	981
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£4.80	£4.80	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£4.80	£4.80	-
45	Cost of oseltamivir prophylaxis course	N/a	£16.36	£16.36	-
46	Cost of zanamivir prophylaxis course	N/a	£24.55	£24.55	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£10.00	£10.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	10	10	-
51	Days per course - oseltamivir prophylaxis	N/a	10	10	-
52	Days per course - zanamivir prophylaxis	N/a	10	10	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.38	62.00	165.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.38	62	165
64	Cost of uncomplicated influenza presentation	N/a	£43.20	£43.20	-
65	Cost of complicated influenza presentation	N/a	£43.20	£43.20	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.16	15.00	95.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	15.00	25	1
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£5,747.01	£5,747.01	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.03	2820	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.03	2977	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.03	2977	100000
80	QALY loss for flu case - no treatment	N/a	0.02	0.02	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.01	0.01	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.01	0.01	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.03	13.15	0.83
92	Duration cardiac complication (years)	Gamma	0.03	13.15	0.83
93	Duration CNS complication (years)	Gamma	0.03	13.15	0.83
94	Duration renal complication (years)	Gamma	0.03	13.15	0.83
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.03	13.15	0.83
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	2.95	2.95	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

List of model parameters - Post-exposure prophylaxis – At-risk elderly

No.	Parameter description	Distribution	Mean	Param 1	Param 2
Baseline event probabilities (disease)					
1	Baseline attack rate for influenza	Beta	0.09	180	2051
2	Probability ILI is influenza within epidemic period	Beta	0.50	622	1256
3	Probability influenza A strain is dominant	Beta	0.75	9	12
4	Probability flu is flu A in flu A dominant seasons	Beta	0.86	740	859
5	Probability flu is flu A in flu B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	N/a	0.72	0.72	-
7	Duration of influenza epidemic (days)	Gamma	40.00	32.65	1.23
Effectiveness parameters (prevention)					
8	Relative risk for influenza - vaccine	Lognormal	0.42	-0.87	0.23
9	Relative risk for influenza - amantadine prophylaxis	Lognormal	0.10	-2.26	0.60
10	Relative risk for influenza - oseltamivir prophylaxis	Lognormal	0.19	-1.66	0.44
11	Relative risk for influenza - zanamivir prophylaxis	Lognormal	0.21	-1.56	0.24
12					
13	Probability influenza case occurs within epidemic	Beta	1.00	1.00	1125.00
14	Probability influenza case avoidable - amantadine	N/a	1.00	1.00	-
15	Probability influenza case avoidable - amantadine (vacc)	N/a	1.00	1.00	-
16	Probability influenza case avoidable - oseltamivir	N/a	1.00	1.00	-
17	Percentage of influenza cases avoidable - zanamivir	N/a	1.00	1.00	-
Adverse events/withdrawals (prophylaxis)					
18	Probability adverse event - vaccination	Beta	0.02	2	100
19	Probability adverse event - amantadine prophylaxis	Beta	0.05	10	200
20	Probability withdrawal - amantadine prophylaxis	Beta	0.15	0.37	2.55
21	Probability withdrawal - oseltamivir prophylaxis	Beta	0.02	1.72	86.11
22	Probability withdrawal - zanamivir prophylaxis	Beta	0.01	10.41	800.78
ILI Event probabilities (treatment)					
23	Probability patient with ILI presents	Beta	0.25	5	20
24	Probability patient presents within 48 hours of ILI onset	Beta	0.11	18.5	164
25	Probability patient given antiviral Tx presents < 48 hours	N/a	1.00	1	-
26	Probability patient receives oseltamivir prescribed antiviral	N/a	0.89	0.89	-
27	Probability patient receives zanamivir prescribed antiviral	N/a	0.11	0.11	-
28	Probability adverse events - oseltamivir treatment	Beta	0.02	1.72	86.11
29	Probability adverse events - zanamivir treatment	Beta	0.01	10.41	800.78
30	Probability complication - no Tx	Beta	0.12	908.00	7407.00
31	Odds ratio complication - oseltamivir treatment	Lognormal	0.40	-1	0
32	Odds ratio complication - zanamivir treatment	Lognormal	0.49	-0.71	0.38
33	Probability complication is respiratory	Dirichlet	0.83	755	914
34	Probability complication is cardiac	Dirichlet	0.07	60	914
35	Probability complication is CNS	Dirichlet	0.03	24	914
36	Probability complication is renal	Dirichlet	0.01	13	914
37	Probability complication is otitis media	Dirichlet	0.01	12	914
38	Probability complication is other	Dirichlet	0.05	50	914
39	Probability respiratory complication is pneumonia	Beta	0.13	97	754
40	Probability patient receives antibiotics no complication	Beta	0.55	8544	15620
41	Probability patient receives antibiotics complication	Beta	0.80	1527	1916
42	Probability of influenza death complication	Beta	0.12	114	936
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (w/out vaccine)	N/a	£4.80	£4.80	-
44	Cost of amantadine prophylaxis course (with vaccine)	N/a	£4.80	£4.80	-
45	Cost of oseltamivir prophylaxis course	N/a	£16.36	£16.36	-
46	Cost of zanamivir prophylaxis course	N/a	£24.55	£24.55	-
47	Cost of oseltamivir treatment course	N/a	£16.36	£16.36	-
48	Cost of zanamivir treatment course	N/a	£24.55	£24.55	-
49	Days per course - amantadine prophylaxis	N/a	£10.00	£10.00	-
50	Days per course - amantadine prophylaxis (prior vac)	N/a	10	10	-
51	Days per course - oseltamivir prophylaxis	N/a	10	10	-
52	Days per course - zanamivir prophylaxis	N/a	10	10	-
53	Acquisition cost for vaccination	N/a	£5.63	£5.63	-
54	Administration cost for vaccination	N/a	£25.00	£25.00	-
55	Cost of attendance at GP surgery consultation	N/a	£25.00	£25.00	-
56	Cost of attendance at GP home visit	N/a	£69.00	£69.00	-
57	Cost of attendance at A&E	N/a	£95.56	£95.56	-
58	Probability A&E attendance patient presents (no comp)	Beta	0.03	8.35	270.11

59	Probability GP attendance patient presents (no comp)	N/a	0.97	0.97	-
60	Probability home GP visit GP presentation (no comp)	Beta	0.38	62.00	165.00
61	Probability A&E attendance patient presents (comp)	Beta	0.03	8.35	270.11
62	Probability GP attendance patient presents (comp)	N/a	0.97	0.97	-
63	Probability home GP visit GP presentation (comp)	Beta	0.38	62	165
64	Cost of uncomplicated influenza presentation	N/a	£43.20	£43.20	-
65	Cost of complicated influenza presentation	N/a	£43.20	£43.20	-
66	Cost of antibiotics course	N/a	£6.80	£6.80	-
67	Cost of anti-emetics course (metaclopramide 7 day course)	N/a	£1.69	£1.69	-
68	Cost of managing adverse events – vaccination	N/a	£25.00	£25.00	-
69	Cost of managing adverse events - amantadine prophylaxis	N/a	£25.00	£25.00	-
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no Tx complication	Beta	0.16	15.00	95.00
72	Probability ICU care complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	15.00	25	1
74	Cost of ITU day	Normal	£1,345.39	£1,345.39	£31.95
75	ITU LOS (days)	Gamma	28.00	11.60	2.41
76	Expected cost of hospitalisation	N/a	£5,747.01	£5,747.01	-
HRQoL parameters					
77	21 day QALYs for flu case - no treatment	Beta	0.03	2820	100000
78	21 day QALYs for flu case - oseltamivir treatment	Beta	0.03	2977	100000
79	21 day QALYs for flu case - zanamivir treatment	Beta	0.03	2977	100000
80	QALY loss for flu case - no treatment	N/a	0.02	0.02	-
81	QALY loss for flu case - oseltamivir treatment	N/a	0.01	0.01	-
82	QALY loss for flu case - zanamivir treatment	N/a	0.01	0.01	-
83	Utility decrement - adverse events	Beta	0.20	200	1000
84	Duration adverse events	Gamma	0.01	25	0
85	Utility decrement respiratory complication	Lognormal	0.15	-1.90	0.41
86	Utility decrement cardiac complication	Lognormal	0.37	-0.99	0.14
87	Utility decrement CNS complication	Lognormal	0.37	-0.99	0.14
88	Utility decrement renal complication	Lognormal	0.37	-0.99	0.14
89	Utility decrement otitis media complication	Lognormal	0.15	-1.90	0.41
90	Utility decrement other complication	Lognormal	0.37	-0.99	0.14
91	Duration respiratory complication (years)	Gamma	0.03	13.13	0.83
92	Duration cardiac complication (years)	Gamma	0.03	13.13	0.83
93	Duration CNS complication (years)	Gamma	0.03	13.13	0.83
94	Duration renal complication (years)	Gamma	0.03	13.13	0.83
95	Duration otitis media complication (years)	Gamma	0.03	9.73	0.96
96	Duration other complication (years)	Gamma	0.03	13.13	0.83
97	Utility general population 0-24	Normal	0.94	0.94	0.01
98	Utility general population 25-34	Normal	0.93	0.93	0.01
99	Utility general population 35-44	Normal	0.91	0.91	0.01
100	Utility general population 45-54	Normal	0.85	0.85	0.01
101	Utility general population 55-64	Normal	0.80	0.80	0.01
102	Utility general population 65-74	Normal	0.78	0.78	0.01
103	Utility general population 75	Normal	0.73	0.73	0.02
104	Percentage population female	N/a	0.51	0.51	-
105	QALY loss for premature death	N/a	2.95	2.95	-
106	Discount rate for QALYs	N/a	3.50%	3.50%	-

Appendix 8 Cost-effectiveness acceptability curves (base case analysis)

Cost-effectiveness acceptability curves for seasonal prophylaxis

Figure 6: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy children (no vaccination)

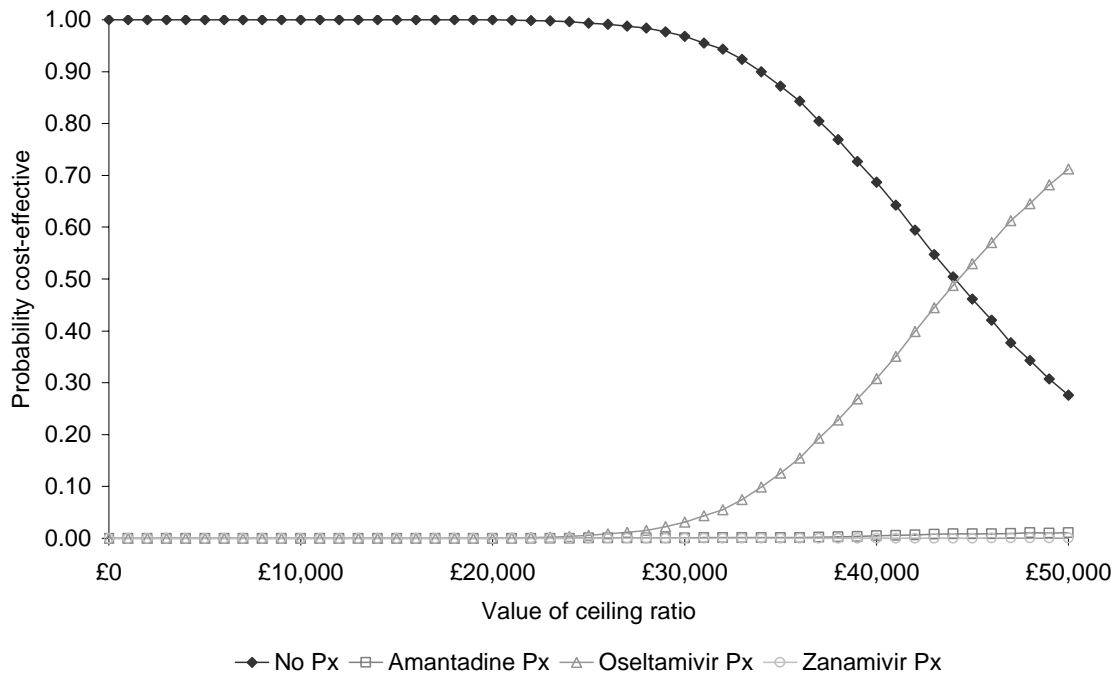


Figure 7: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy children (prior vaccination)

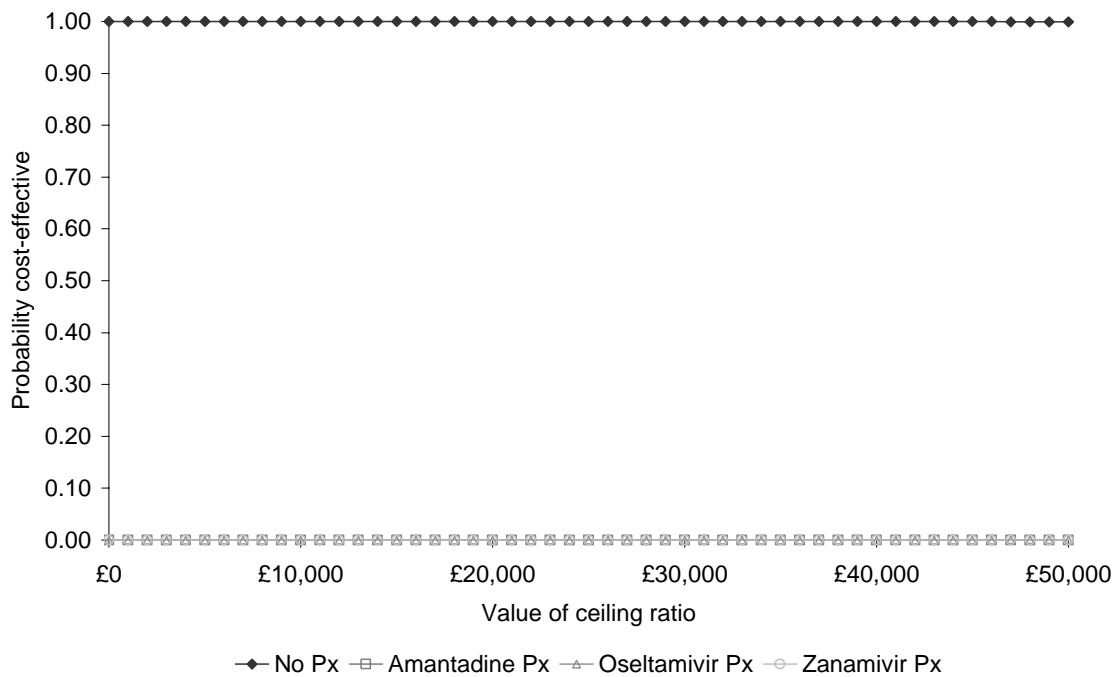


Figure 8: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk children (no vaccination)

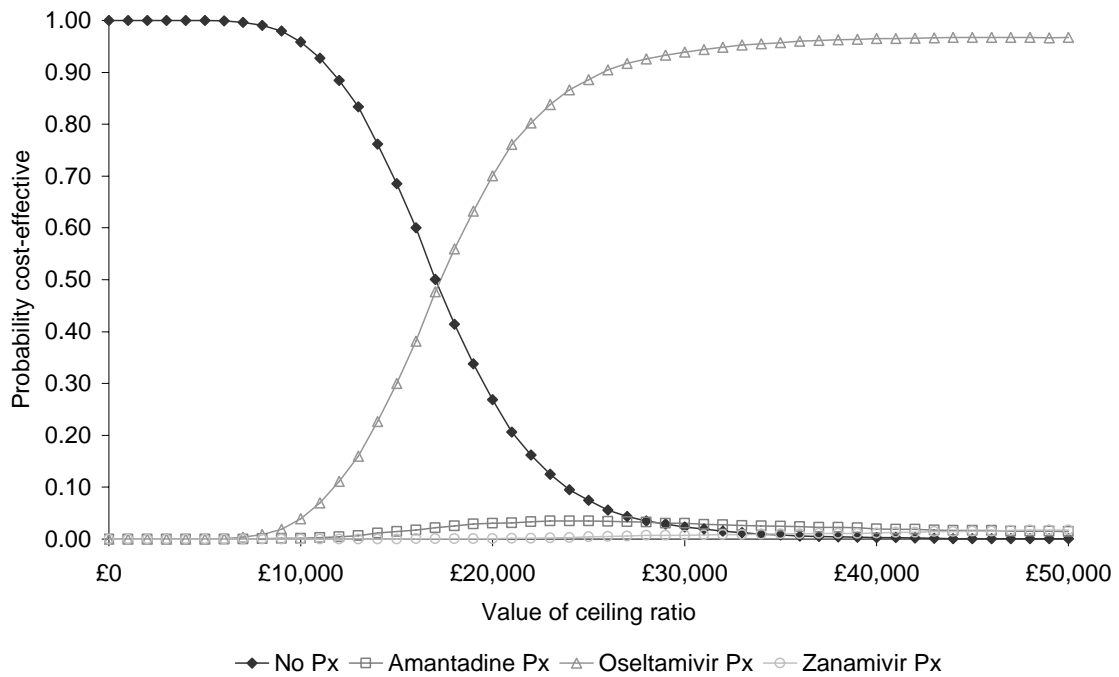


Figure 9: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk children (prior vaccination)

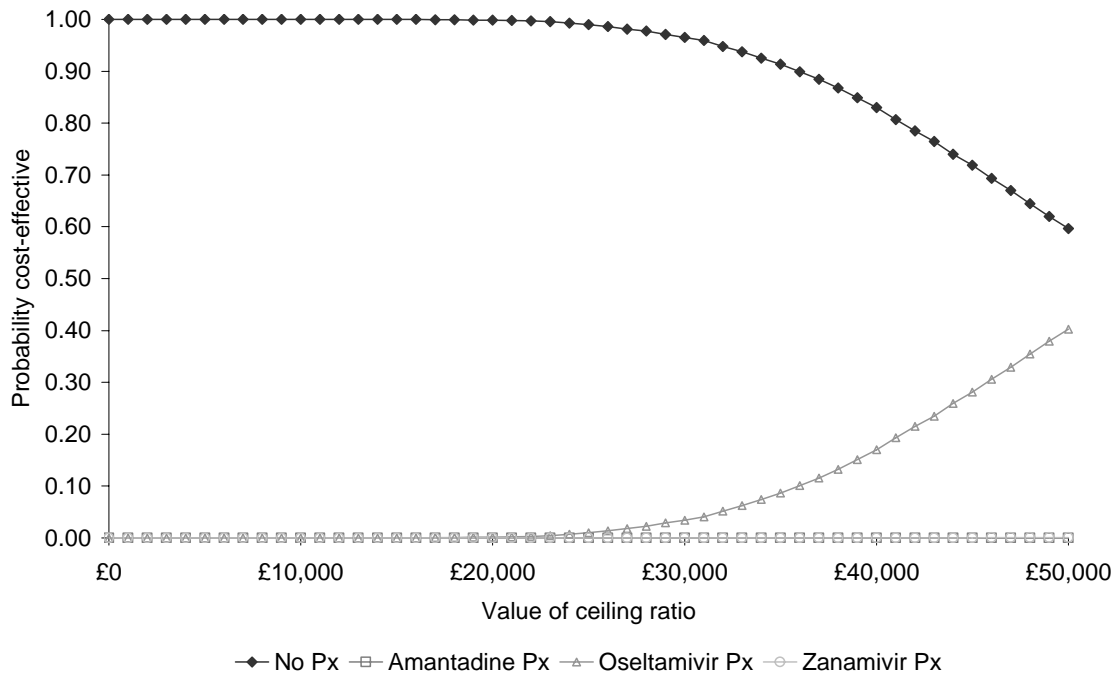


Figure 10: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy adults (no vaccination)

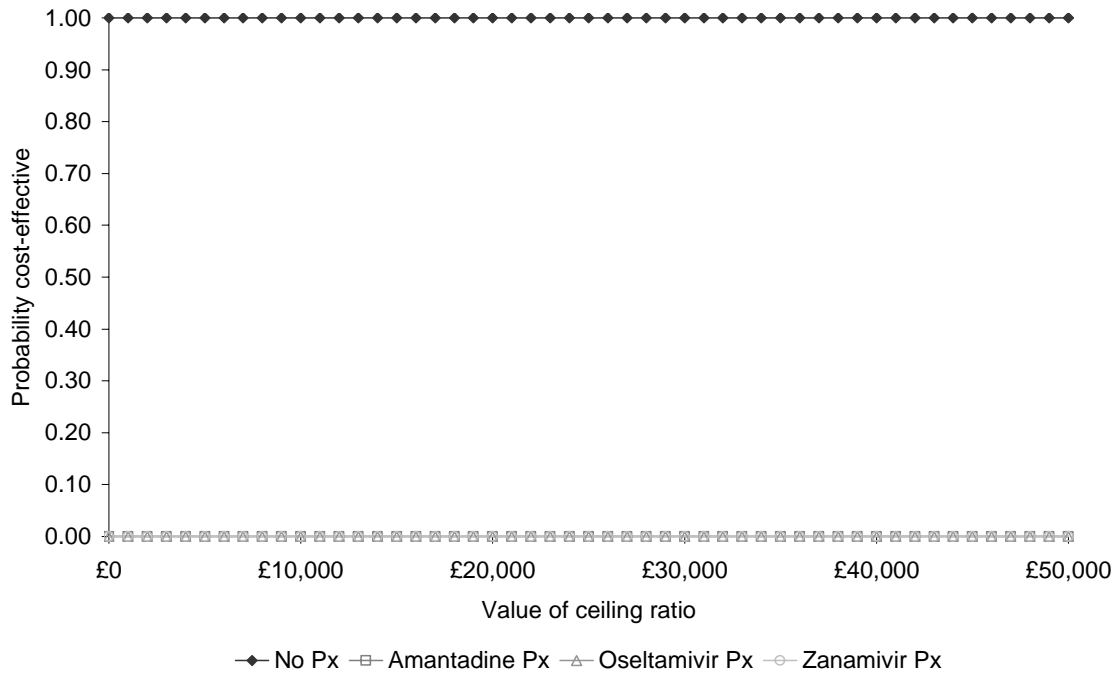


Figure 11: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy adults (prior vaccination)

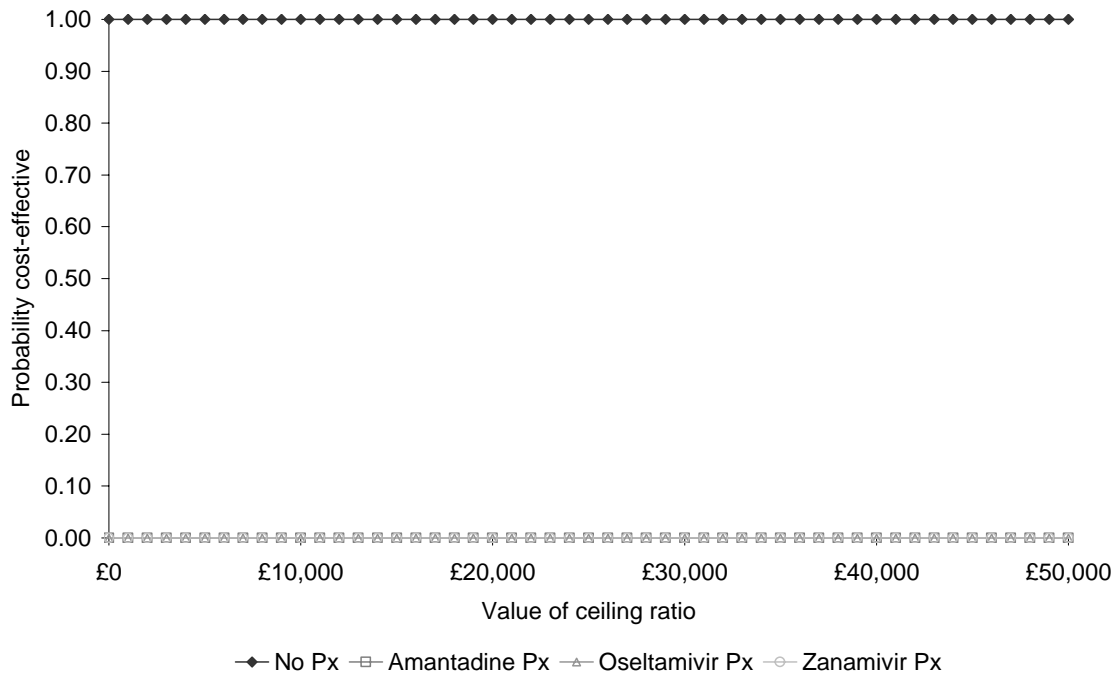


Figure 12: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk adults (no vaccination)

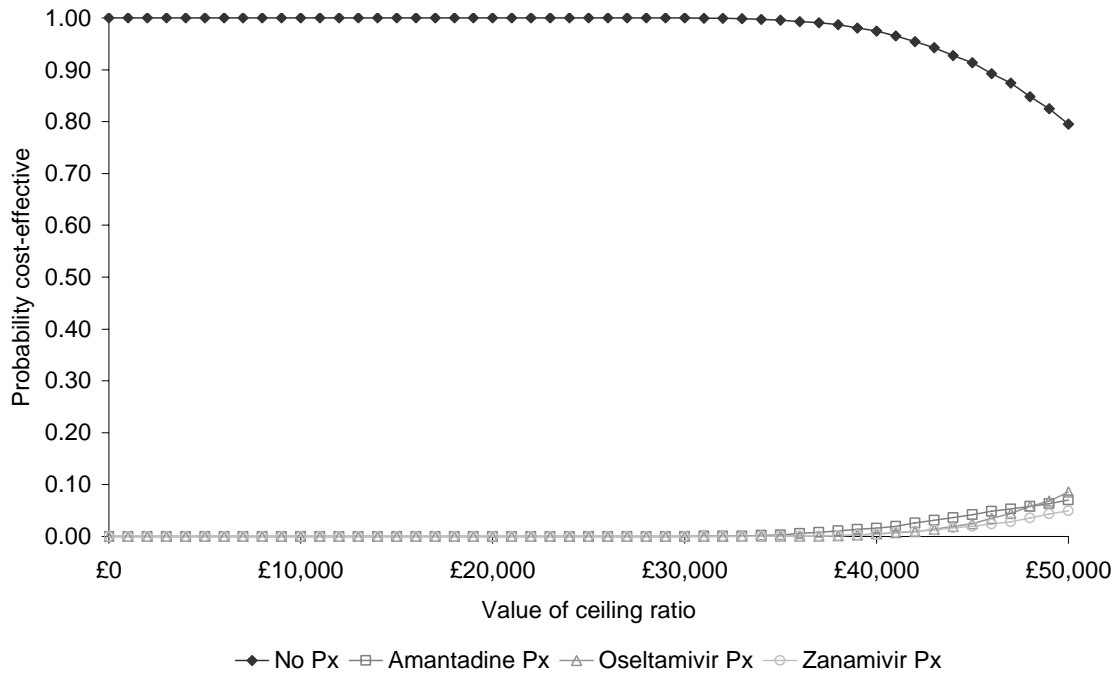


Figure 13: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk adults (prior vaccination)

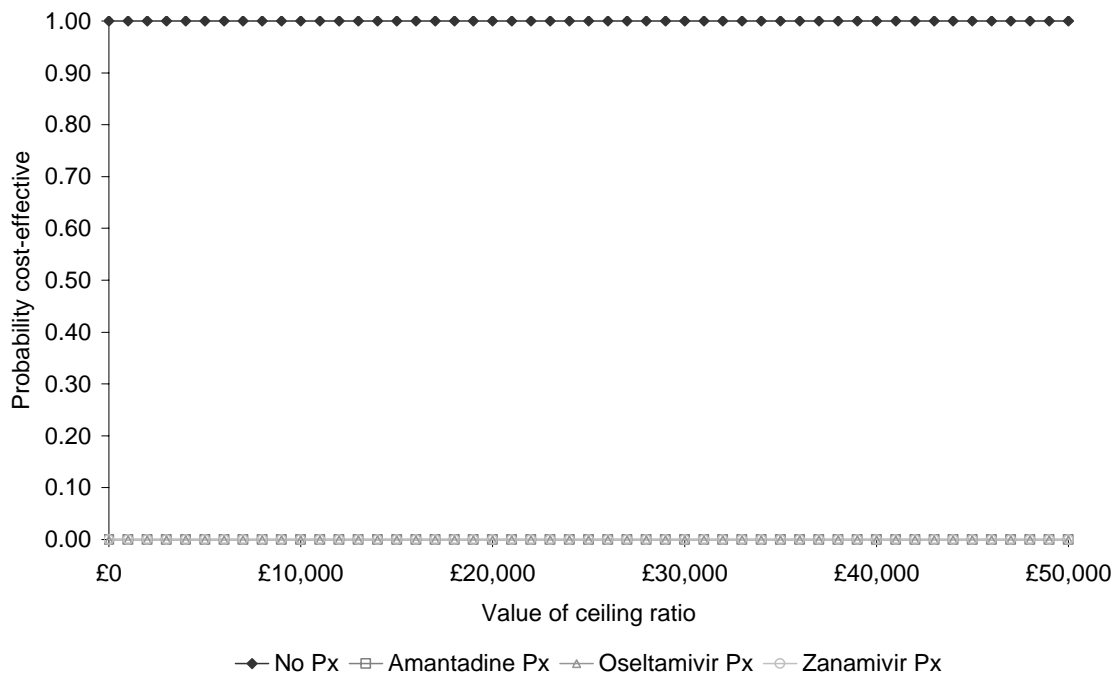


Figure 14: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy elderly (no vaccination)

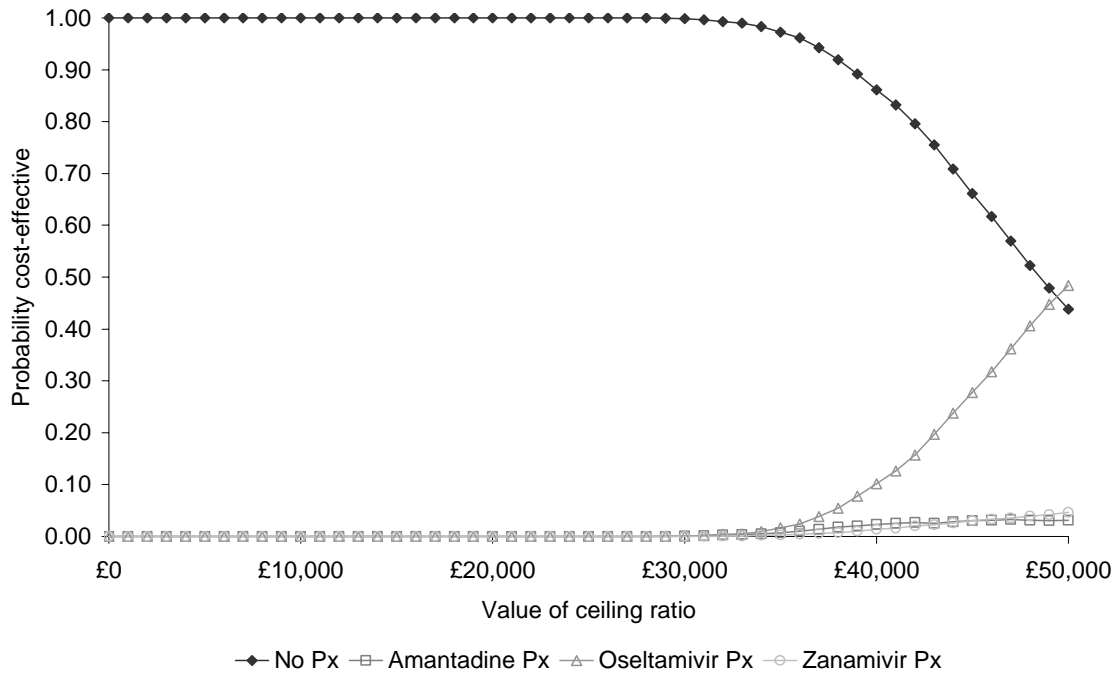


Figure 15: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy elderly (prior vaccination)

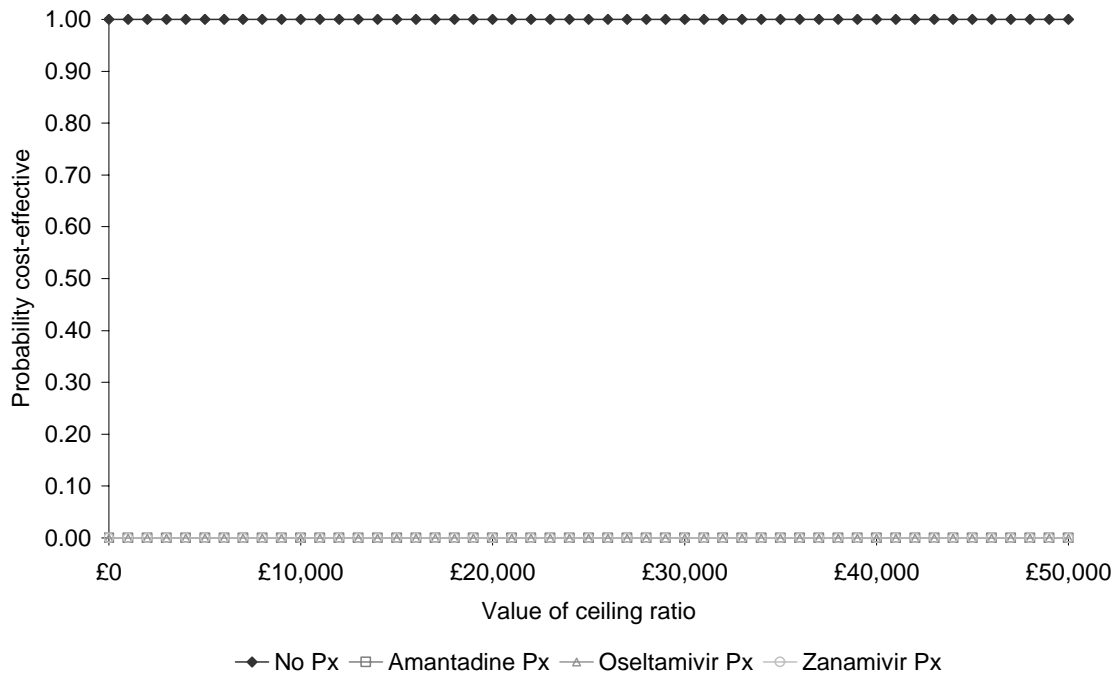


Figure 16: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk elderly (no vaccination)

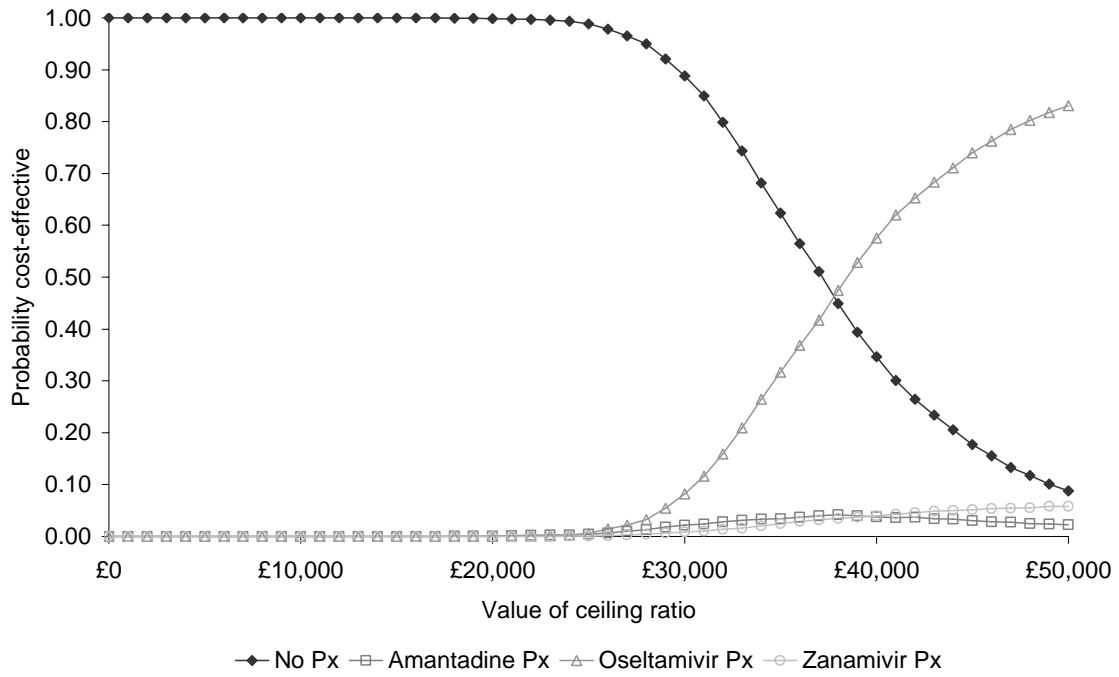
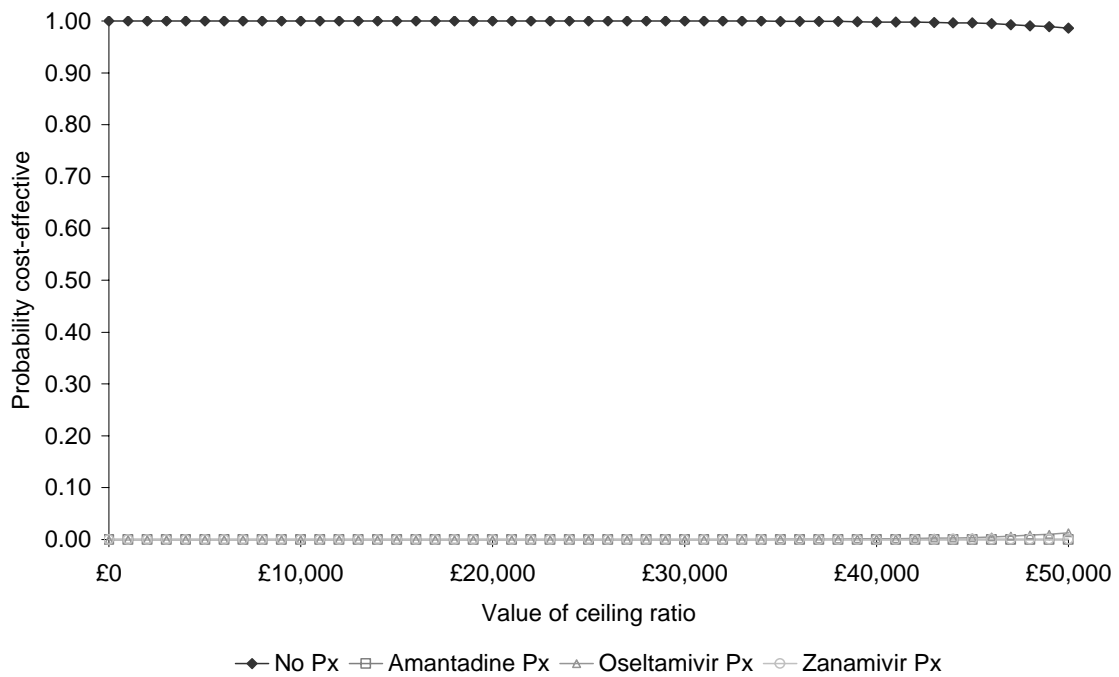


Figure 17: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk elderly (prior vaccination)



Cost-effectiveness acceptability curves for post-exposure prophylaxis

Figure 18: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy children (no vaccination)

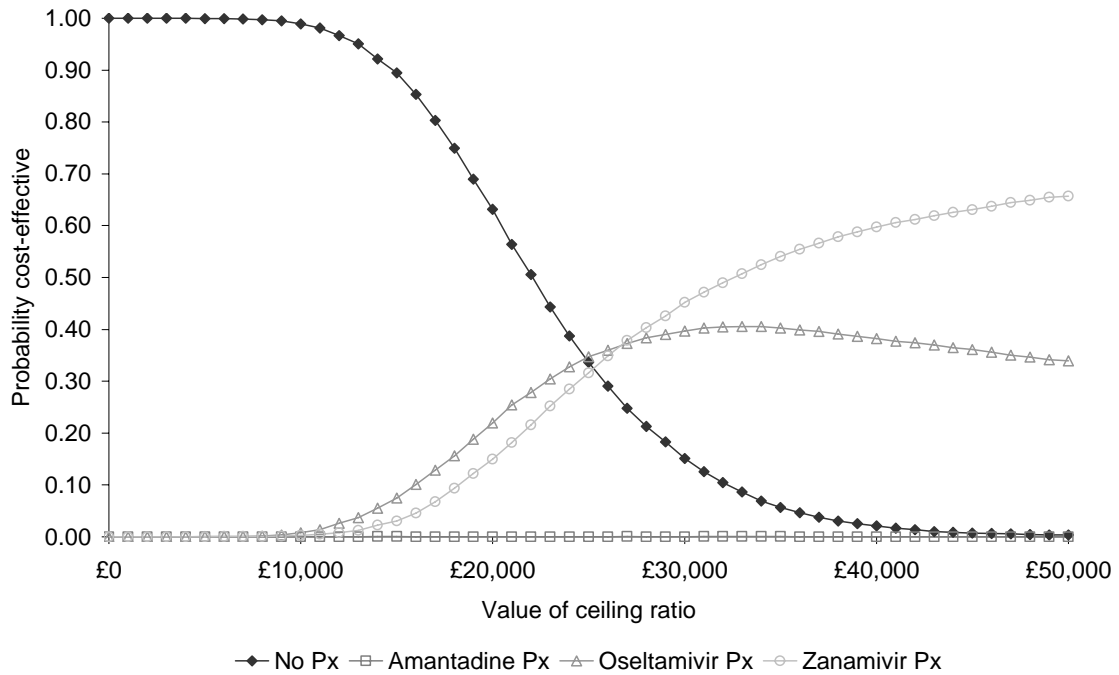


Figure 19: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy children (prior vaccination)

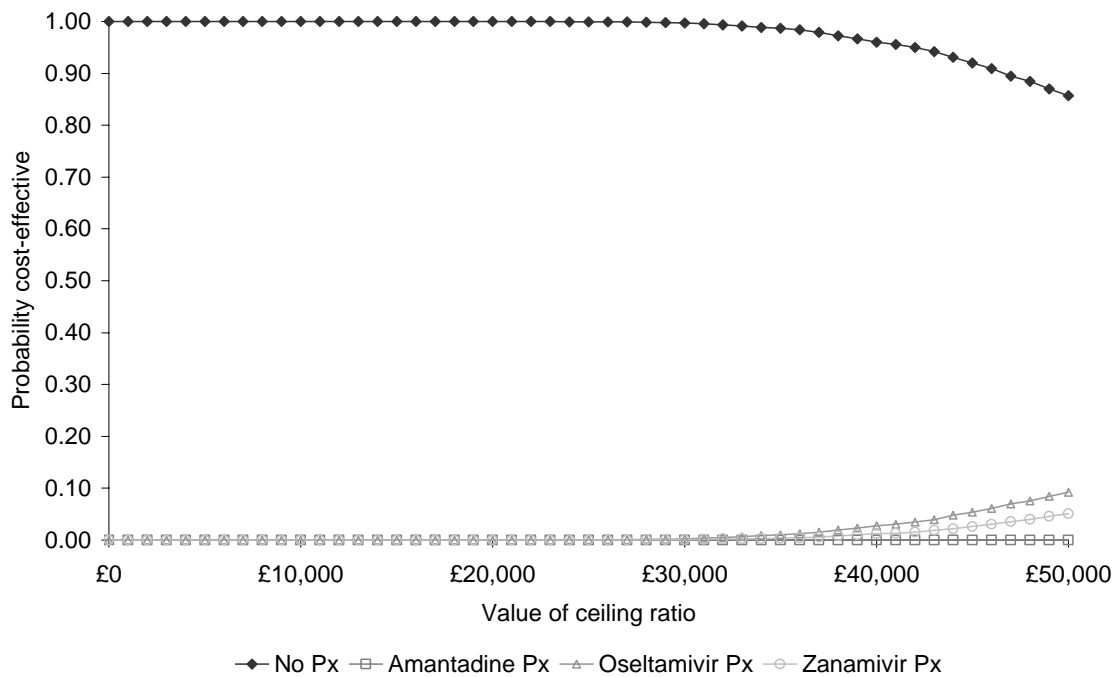


Figure 20: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk children (no vaccination)

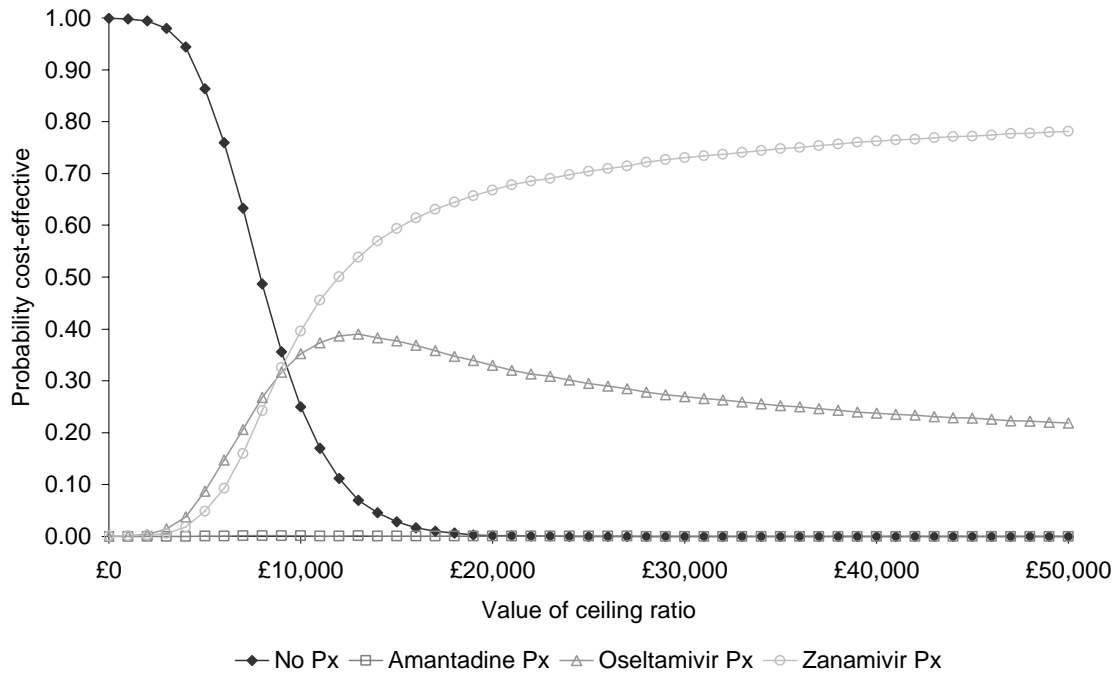


Figure 21: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk children (prior vaccination)

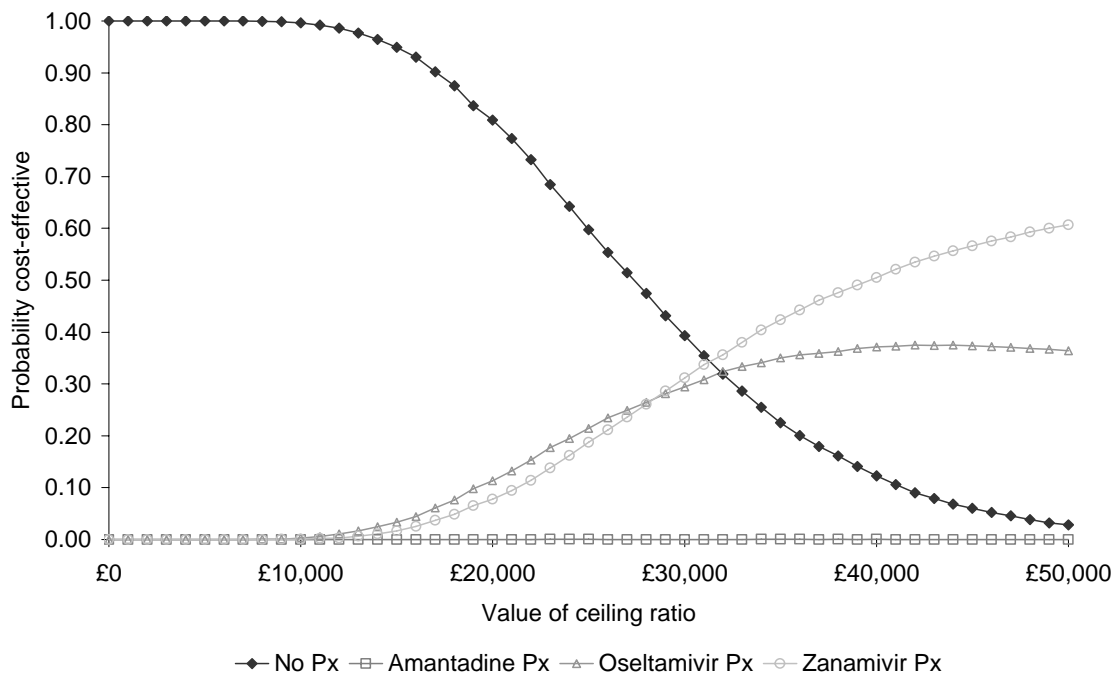


Figure 22: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy adults (no vaccination)

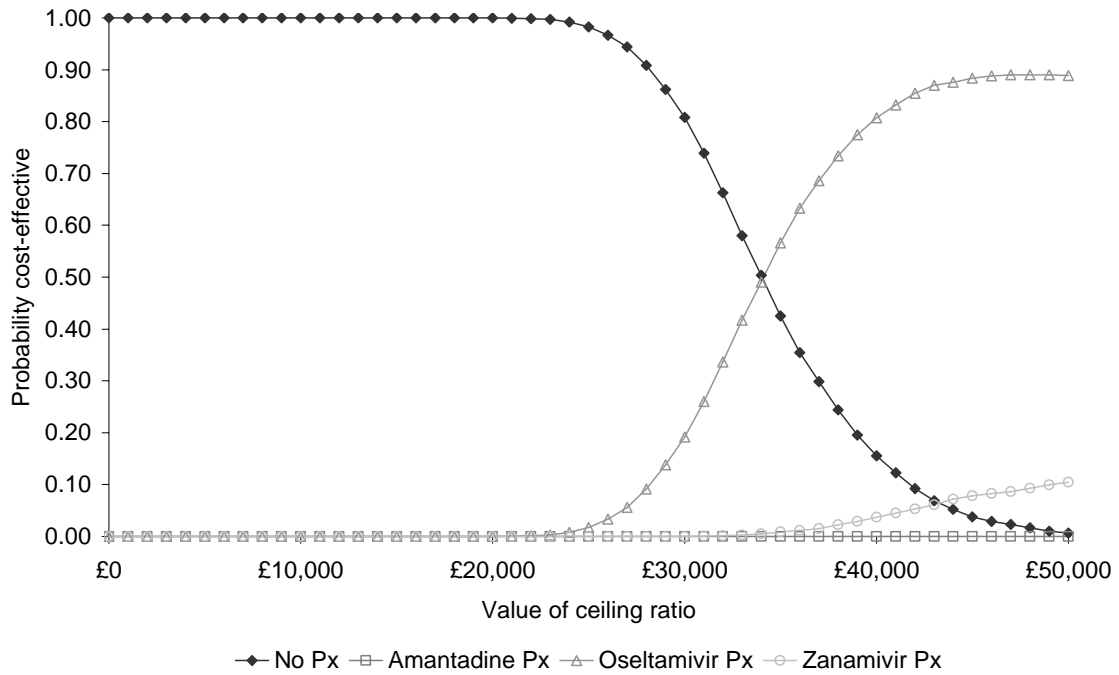


Figure 23: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy adults (prior vaccination)

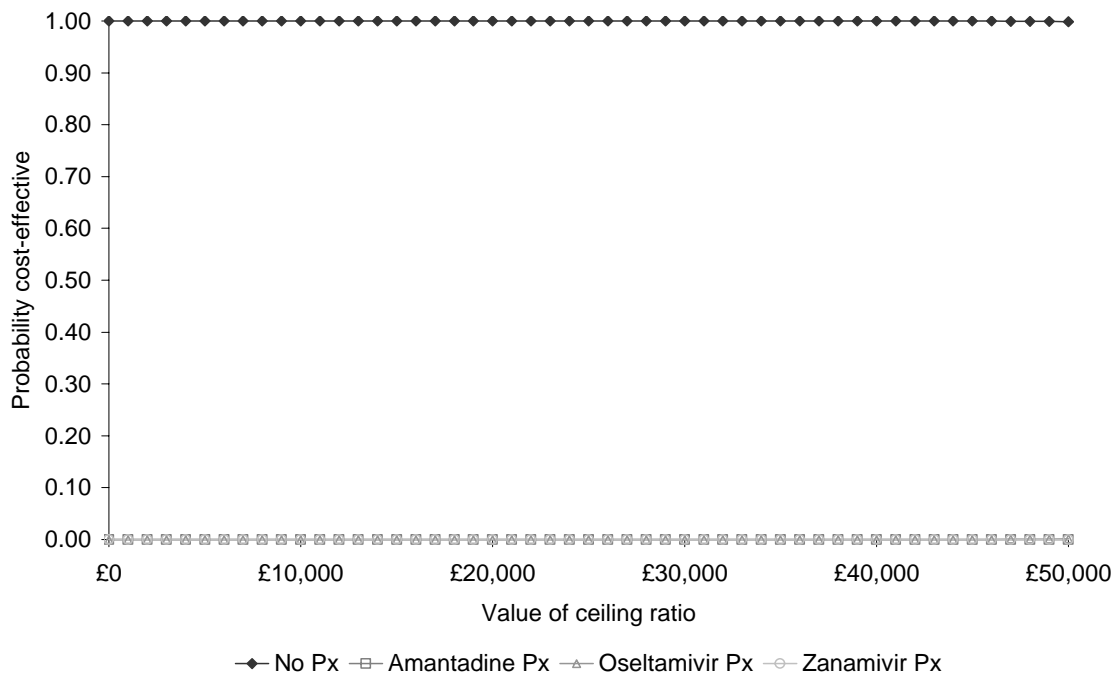


Figure 24: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk adults (no vaccination)

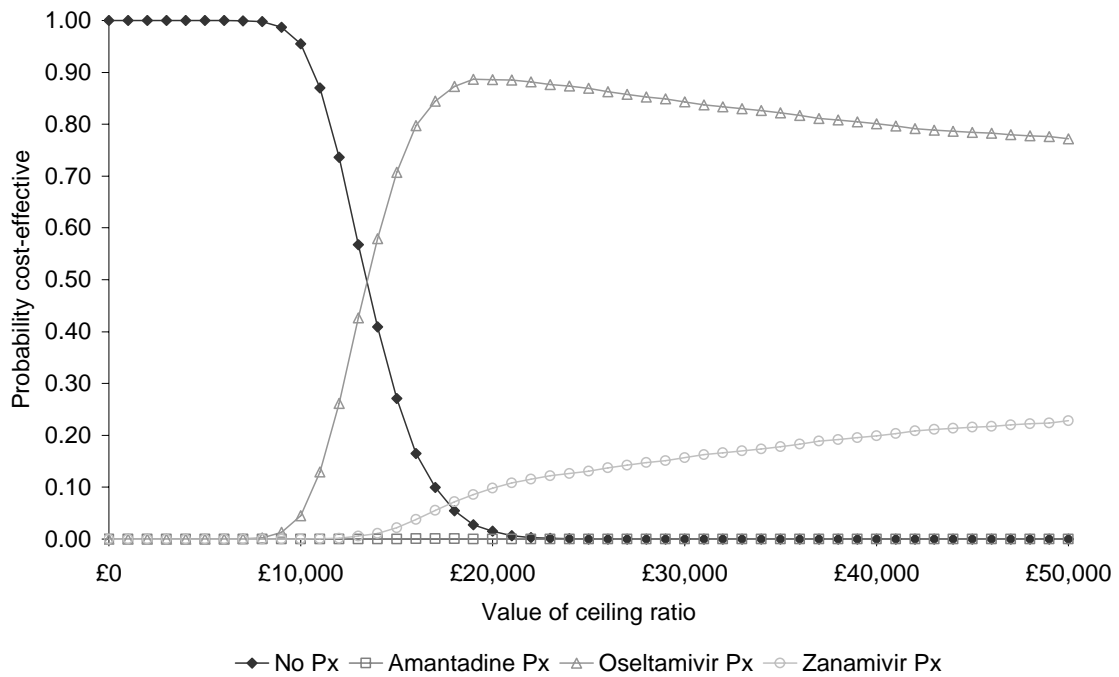


Figure 25: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk adults (prior vaccination)

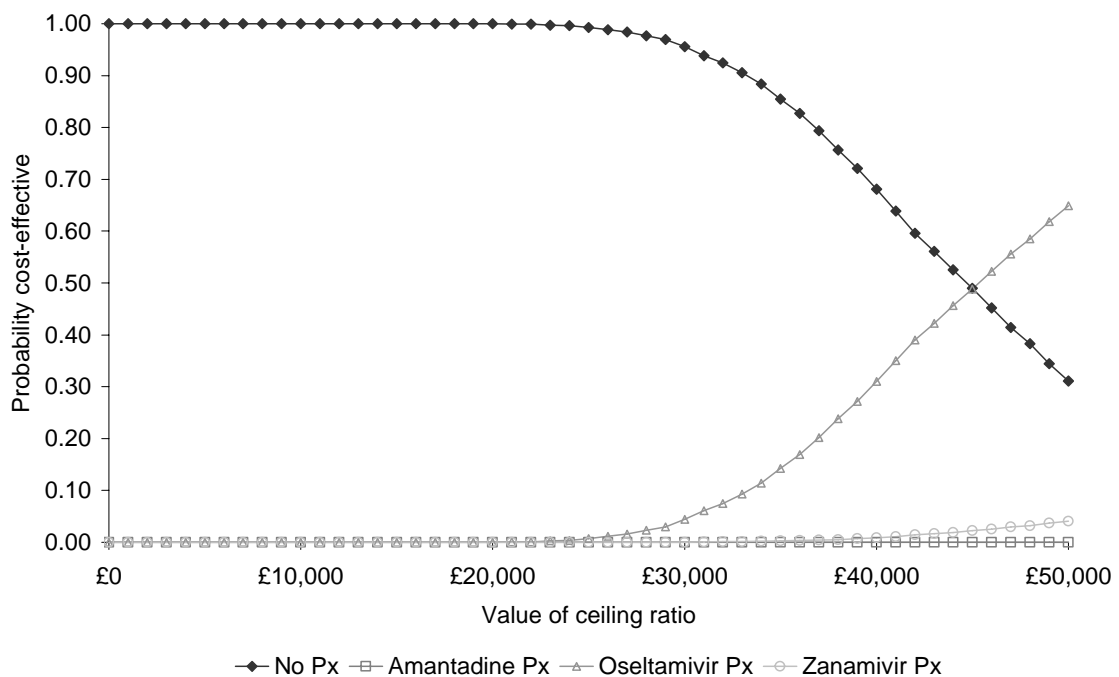


Figure 26: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy elderly (no vaccination)

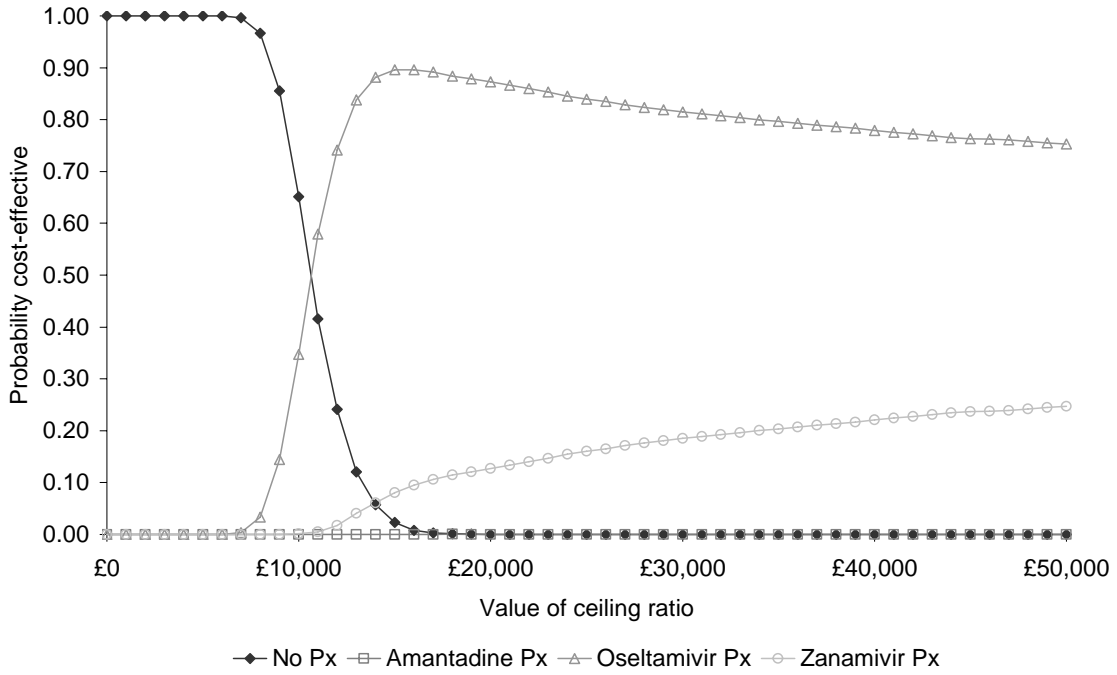


Figure 27: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy elderly (prior vaccination)

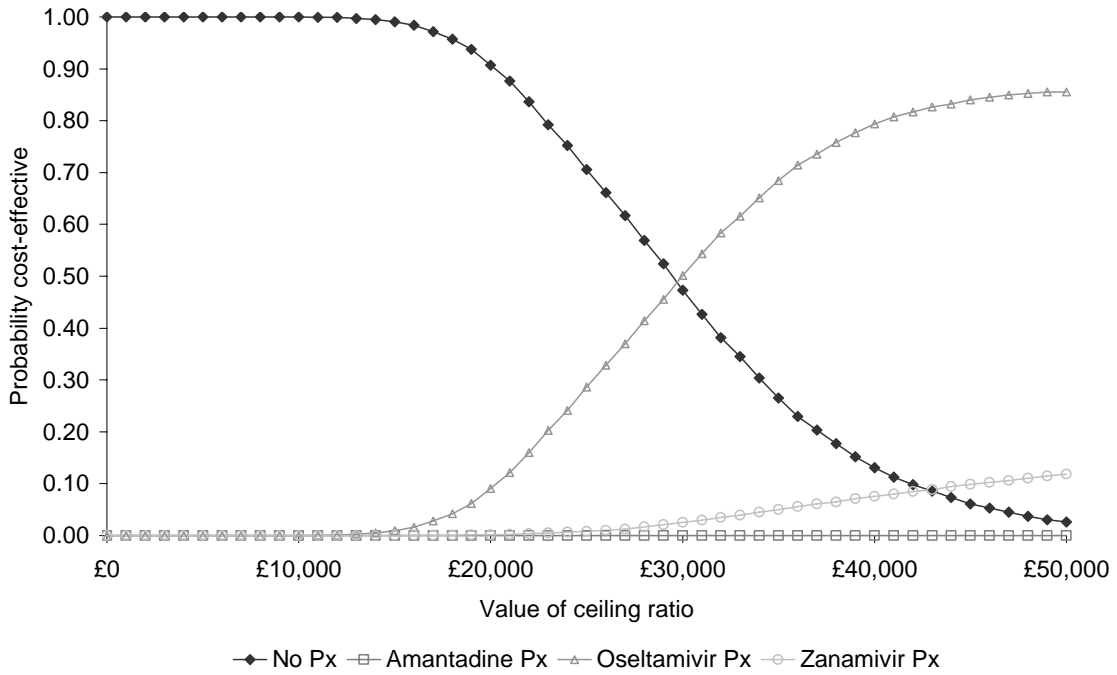


Figure 28: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk elderly (no vaccination)

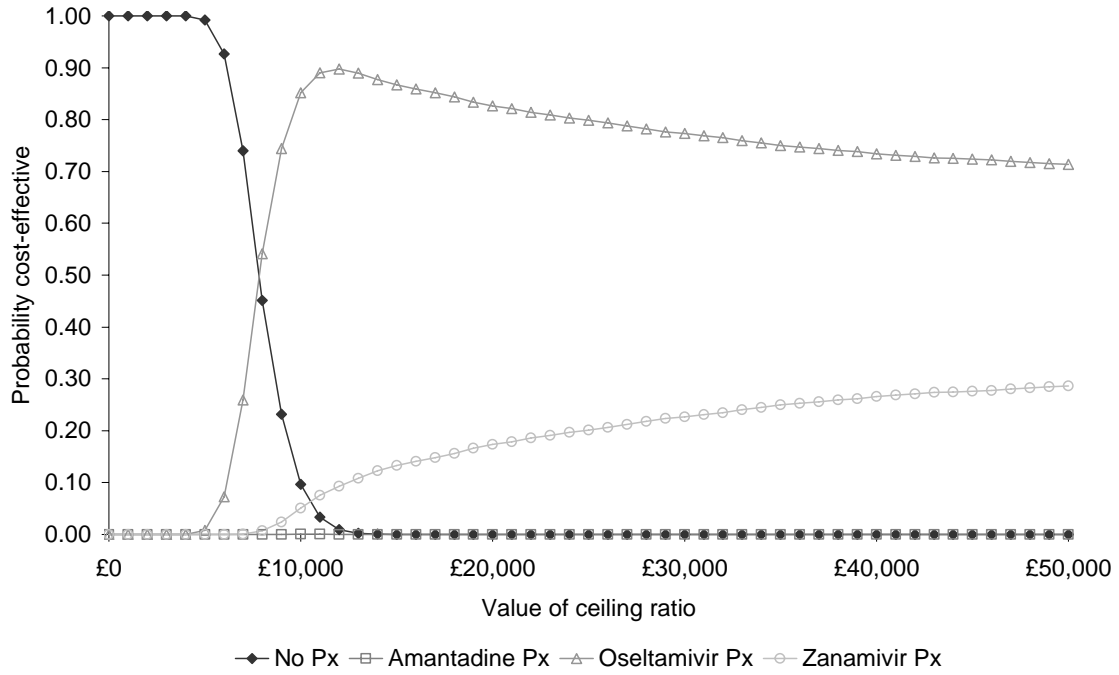
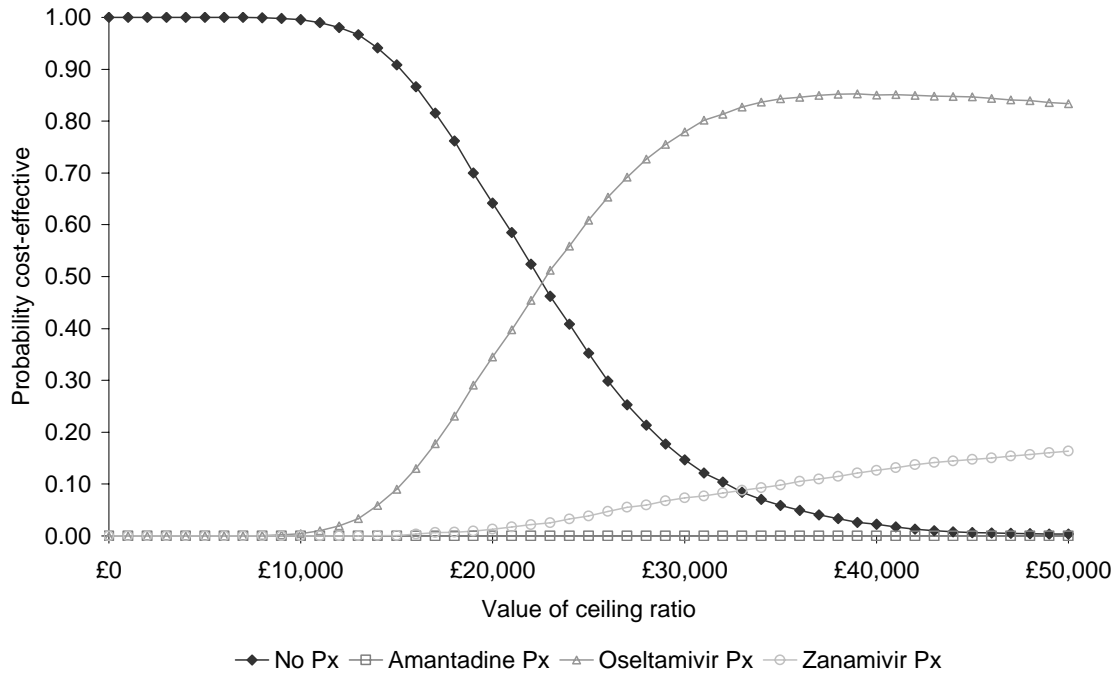


Figure 29: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk elderly (prior vaccination)



Appendix 9 Cost-effectiveness acceptability curves (incorporating proposed price reduction for zanamivir)

Cost-effectiveness acceptability curves for seasonal prophylaxis

Figure 30: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy children (no vaccination)

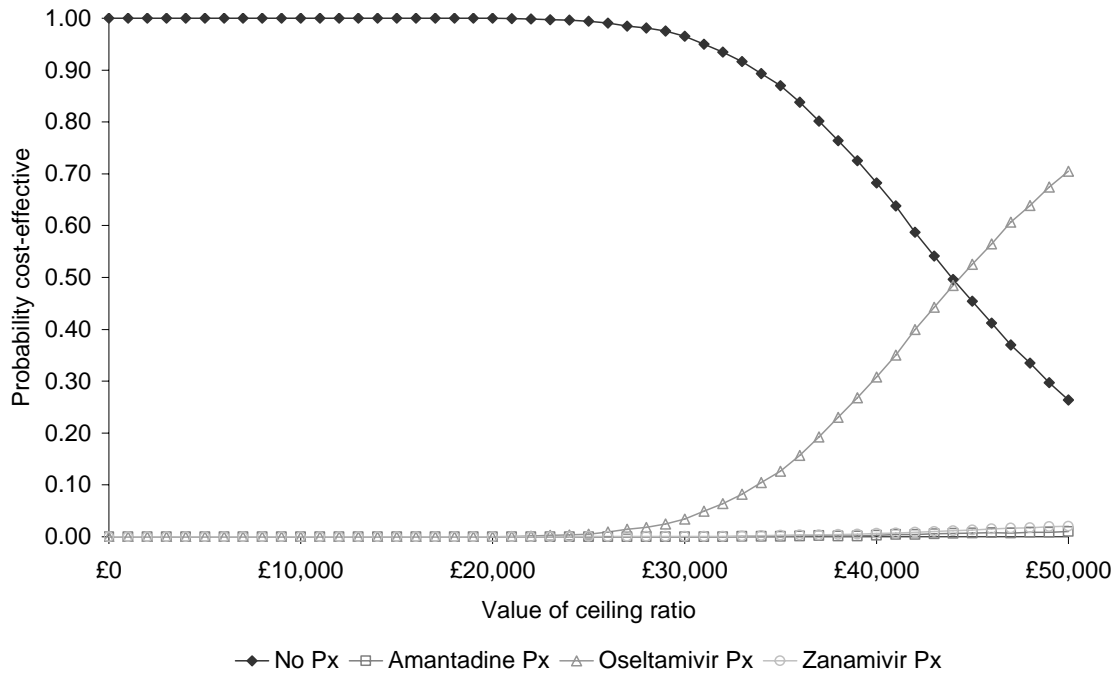


Figure 31: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy children (prior vaccination)

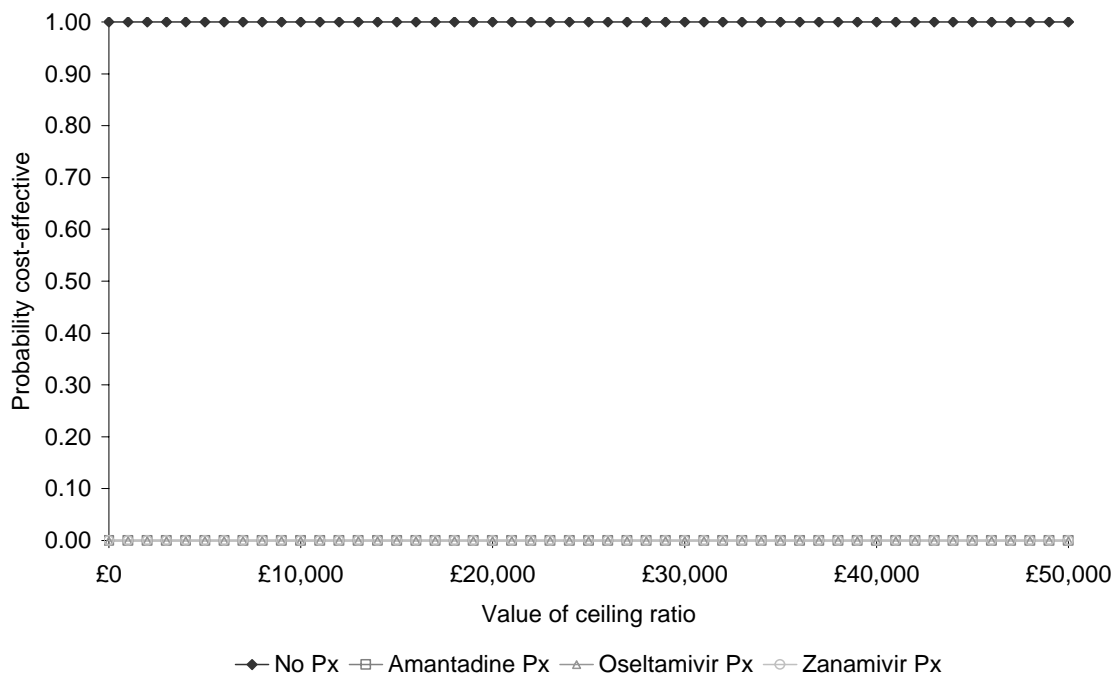


Figure 32: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk children (no vaccination)

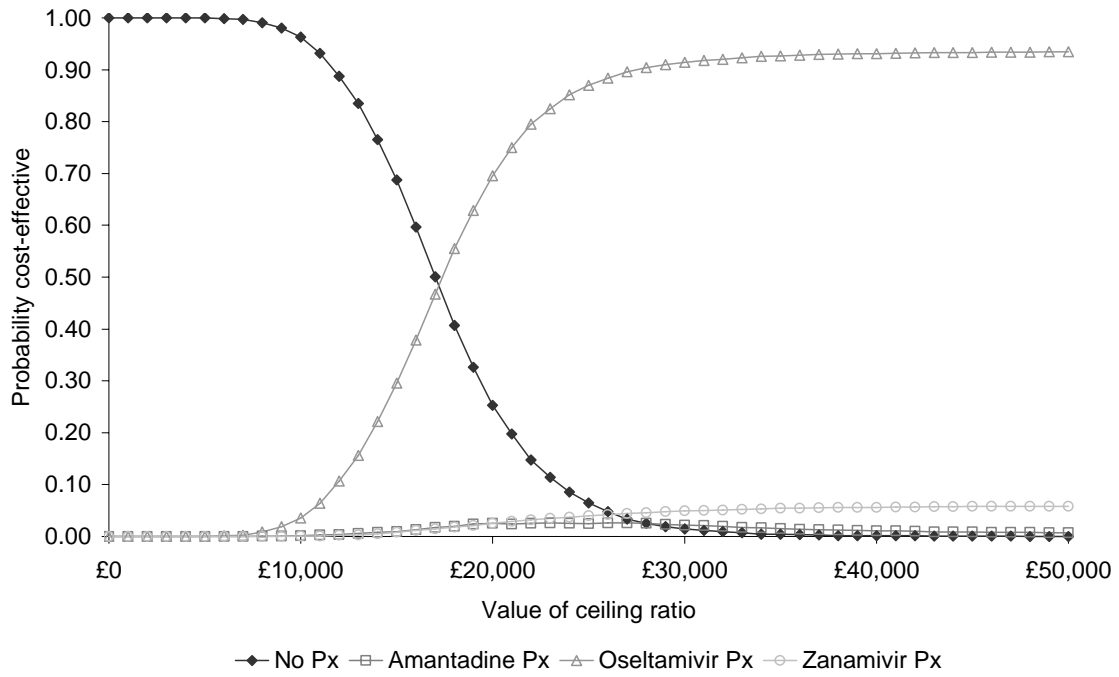


Figure 33: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk children (prior vaccination)

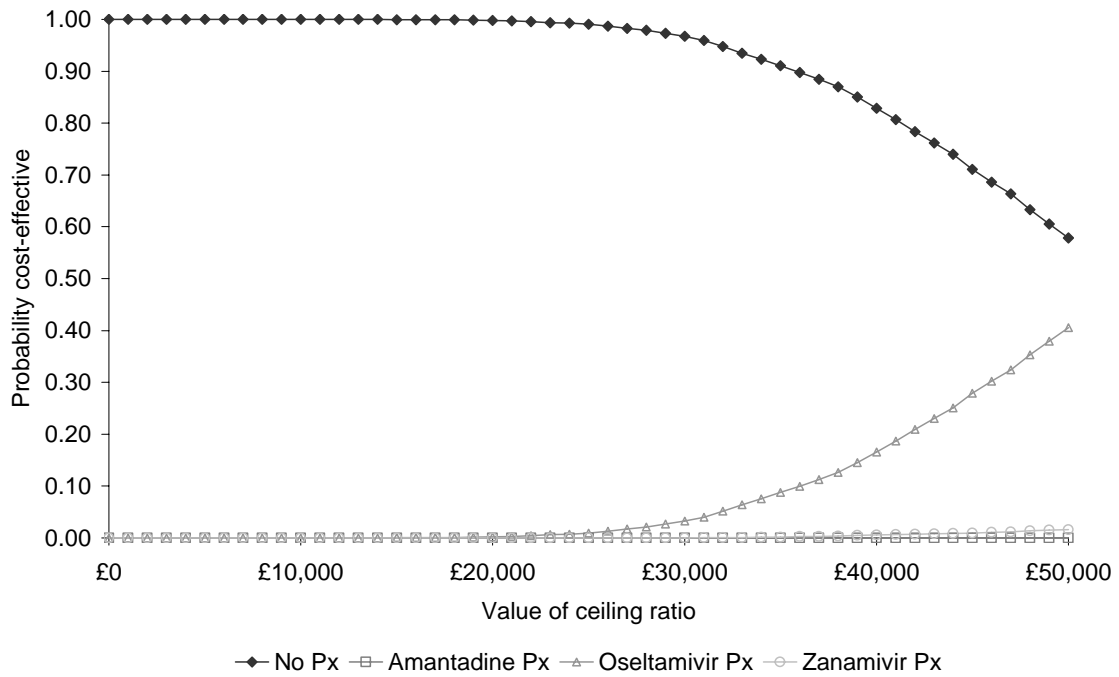


Figure 34: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy adults (no vaccination)

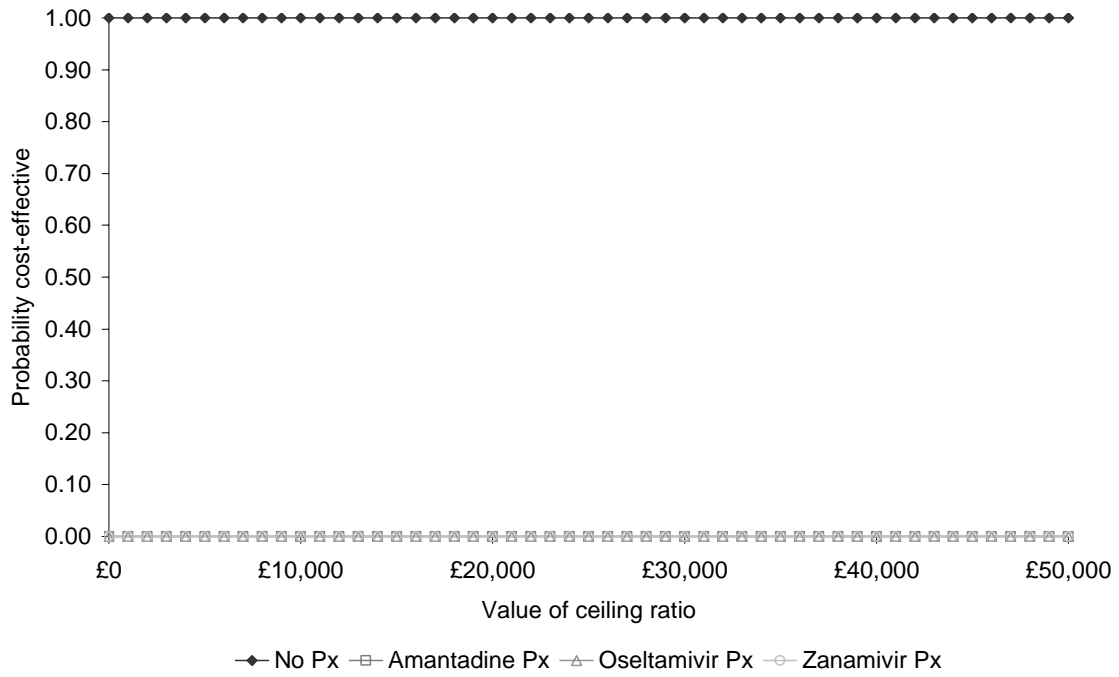


Figure 35: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy adults (prior vaccination)

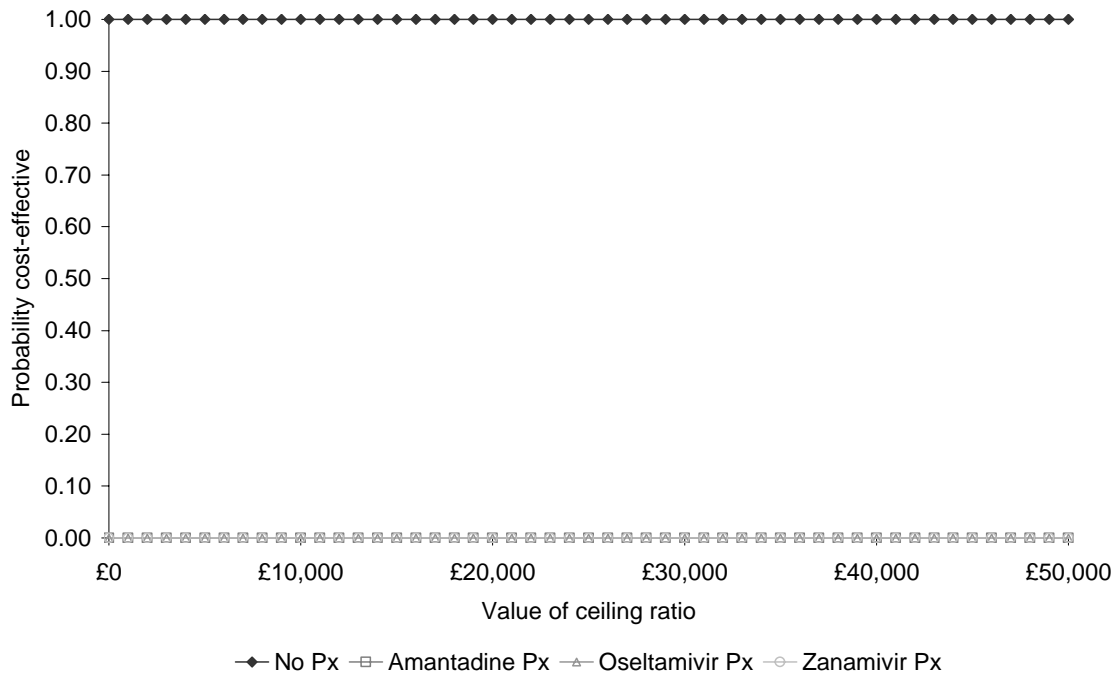


Figure 36: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk adults (no vaccination)

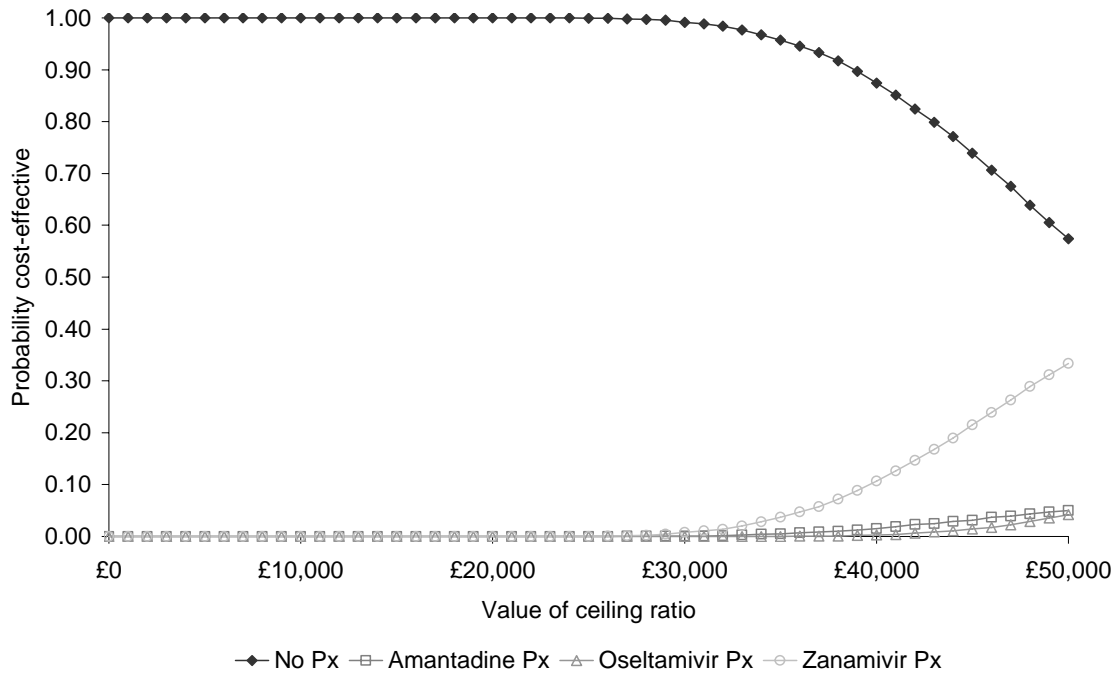


Figure 37: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk adults (prior vaccination)

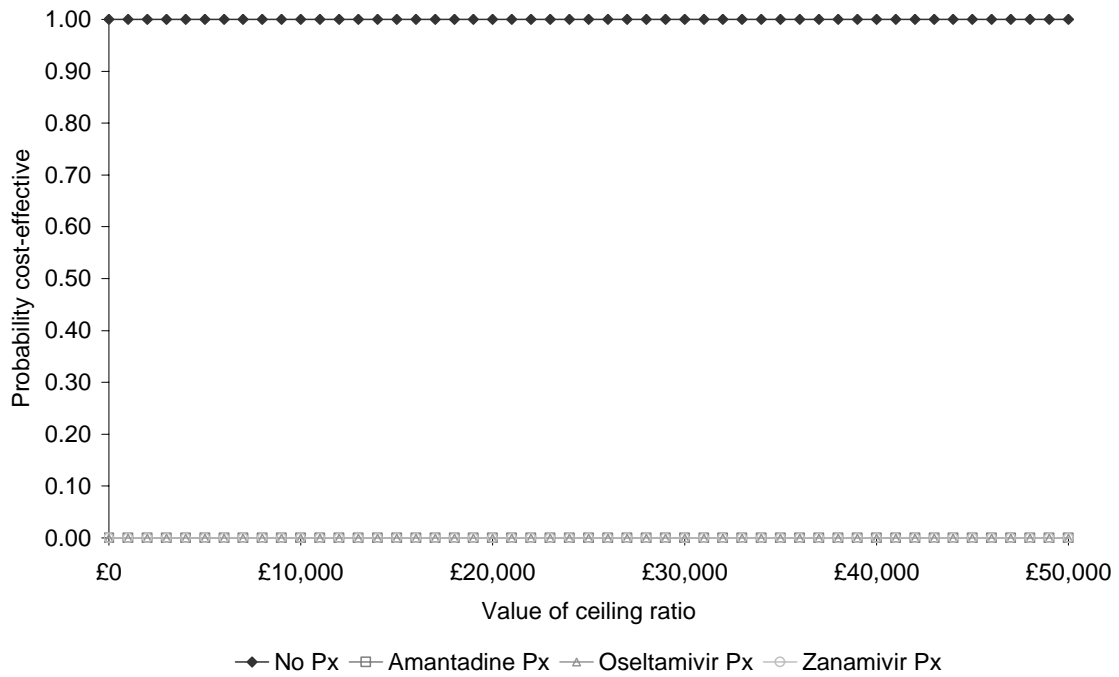


Figure 38: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy elderly (no vaccination)

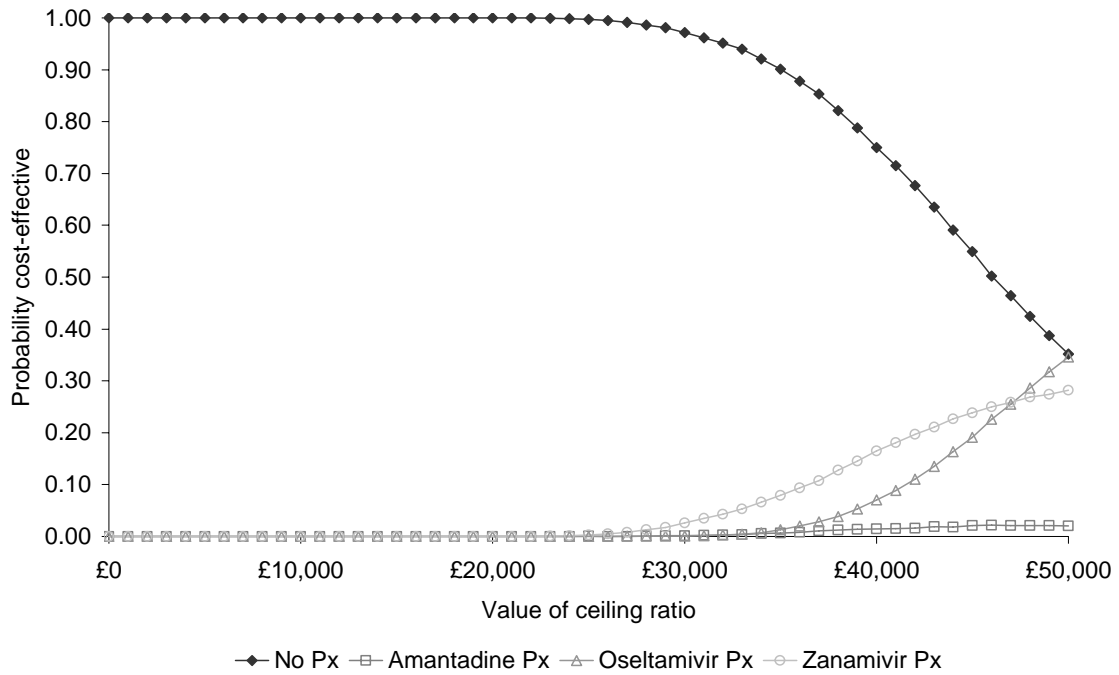


Figure 39: Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy elderly (prior vaccination)

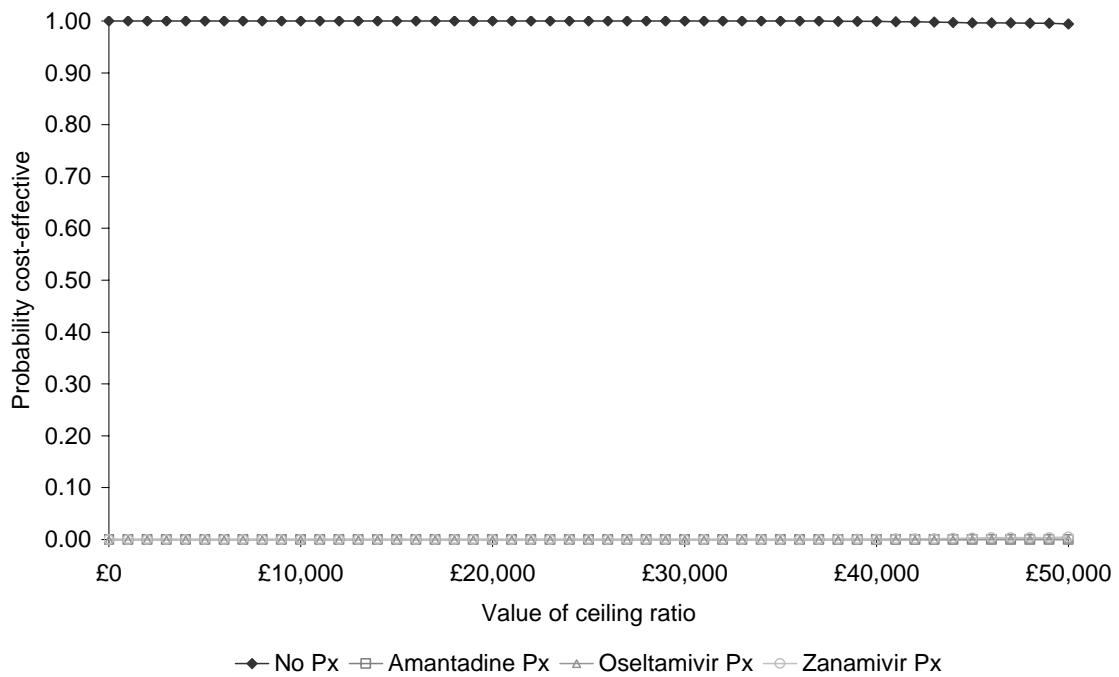


Figure 40: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk elderly (no vaccination)

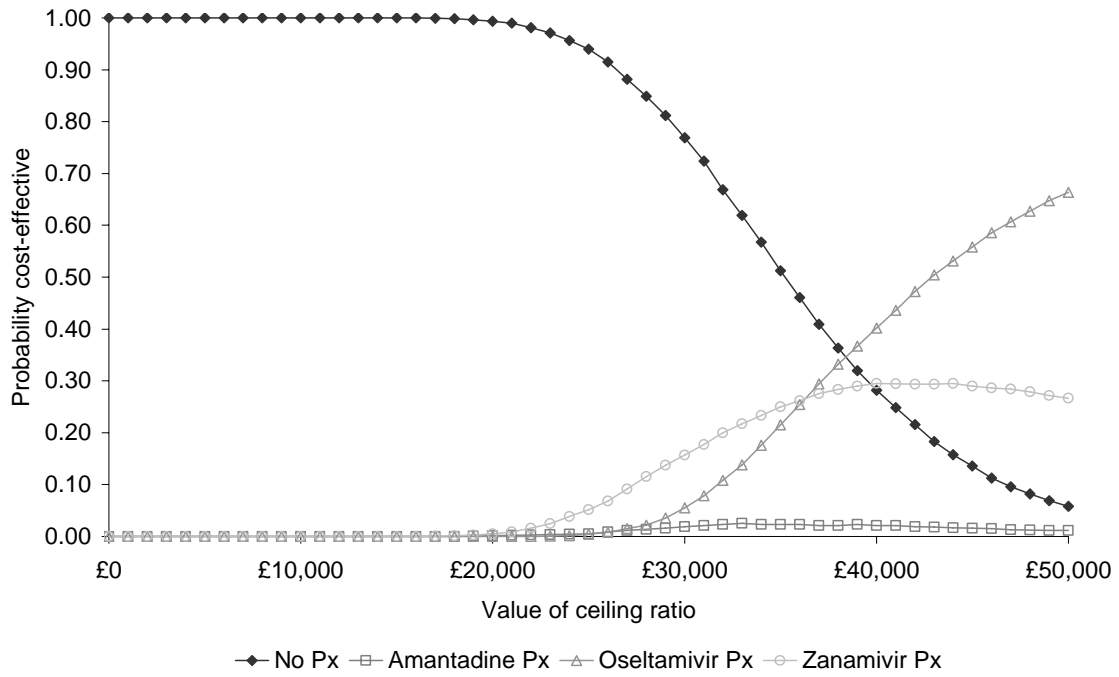
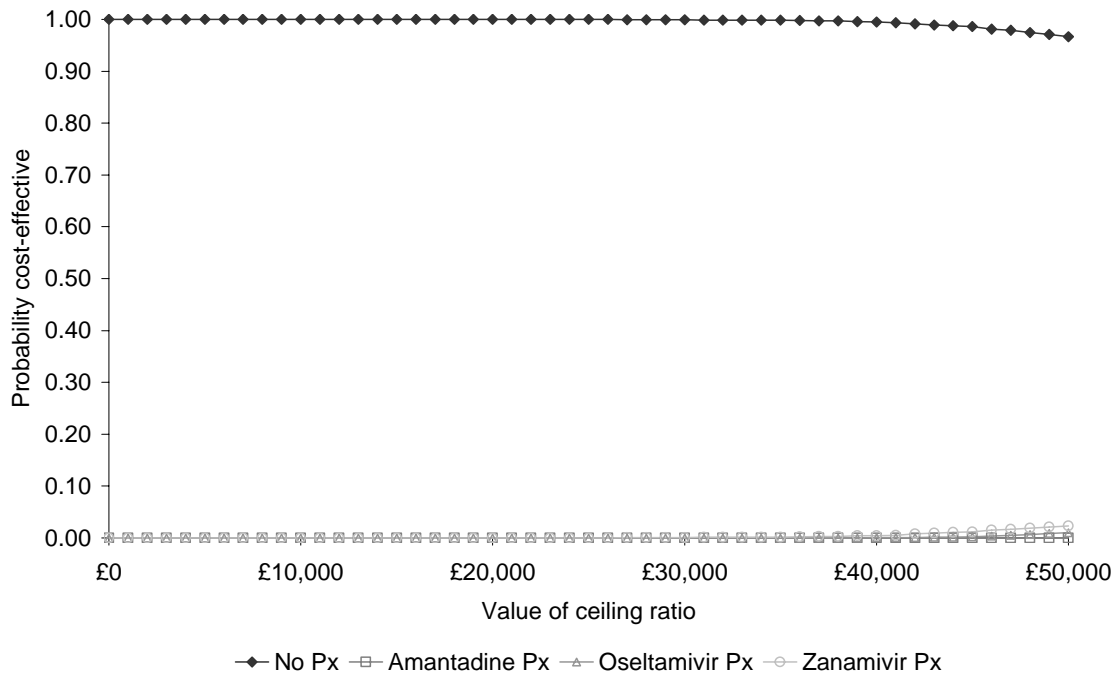


Figure 41: Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk elderly (prior vaccination)



Cost-effectiveness acceptability curves for post-exposure prophylaxis

Figure 42: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy children (no vaccination)

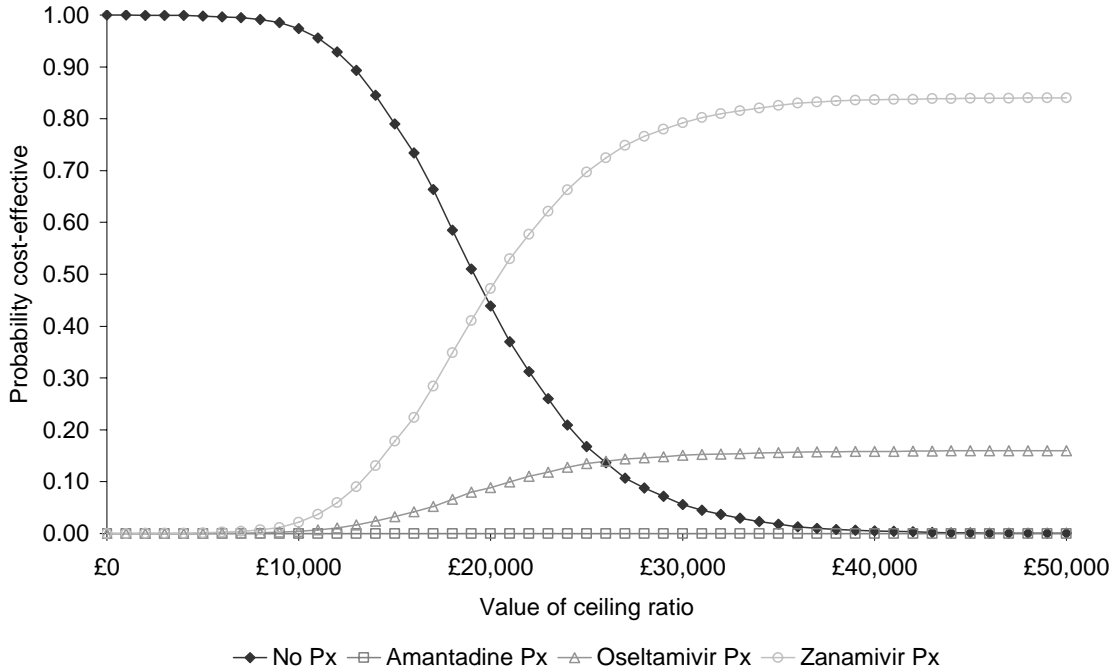


Figure 43: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy children (prior vaccination)

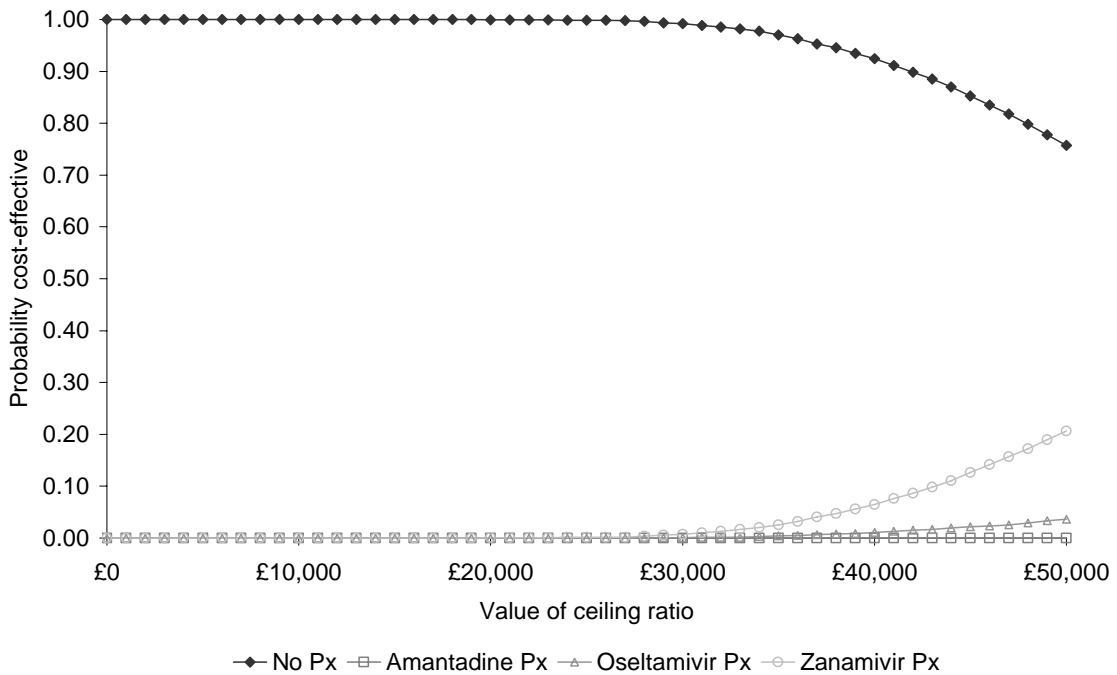


Figure 44: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk children (no vaccination)

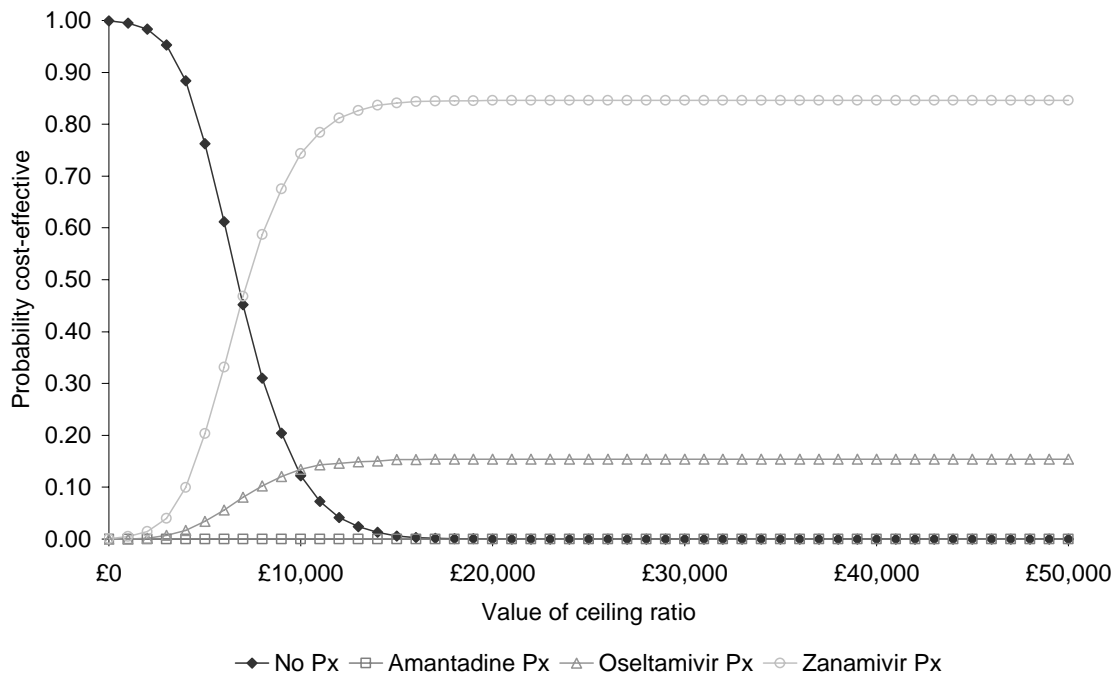


Figure 45: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk children (prior vaccination)

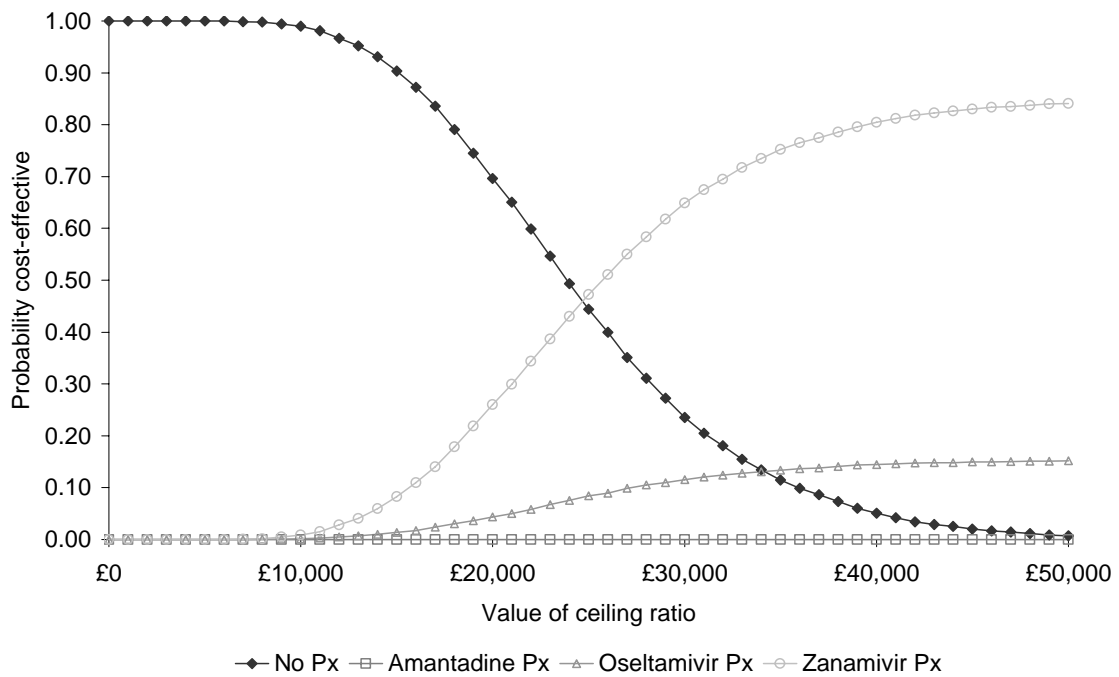


Figure 46: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy adults (no vaccination)

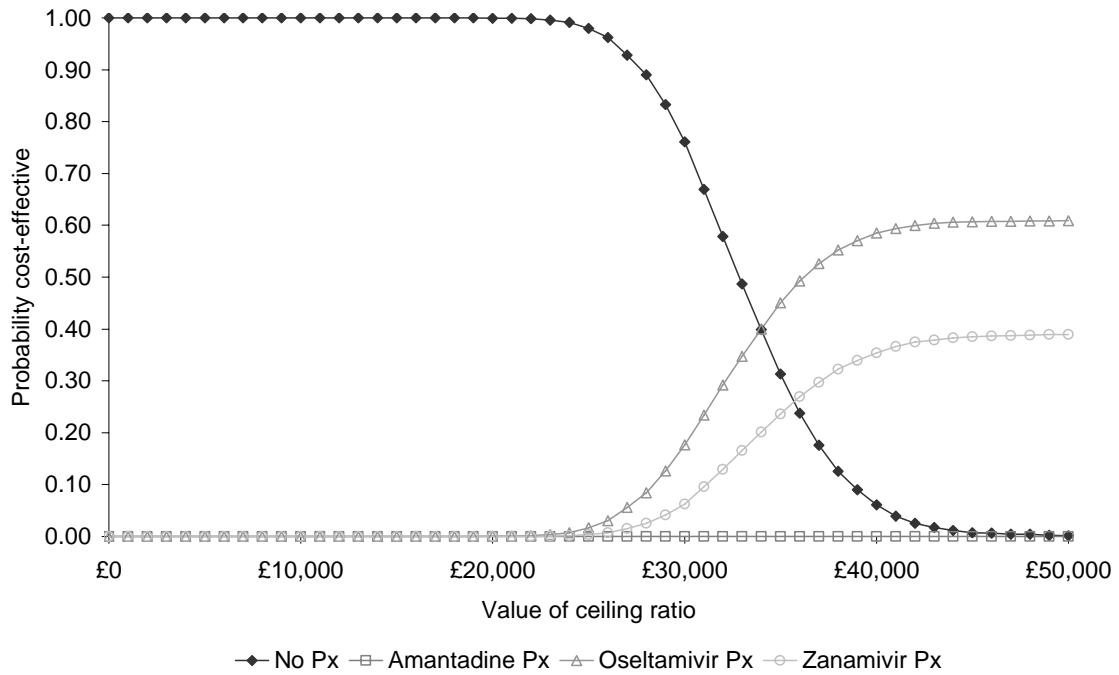


Figure 47: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy adults (prior vaccination)

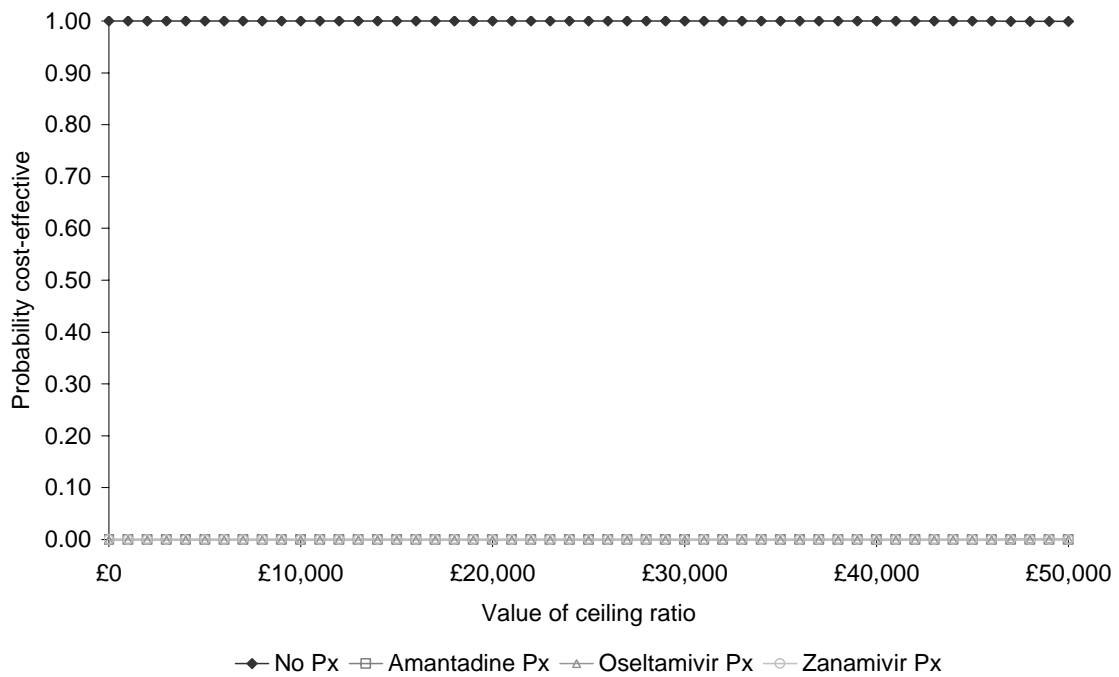


Figure 48: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk adults (no vaccination)

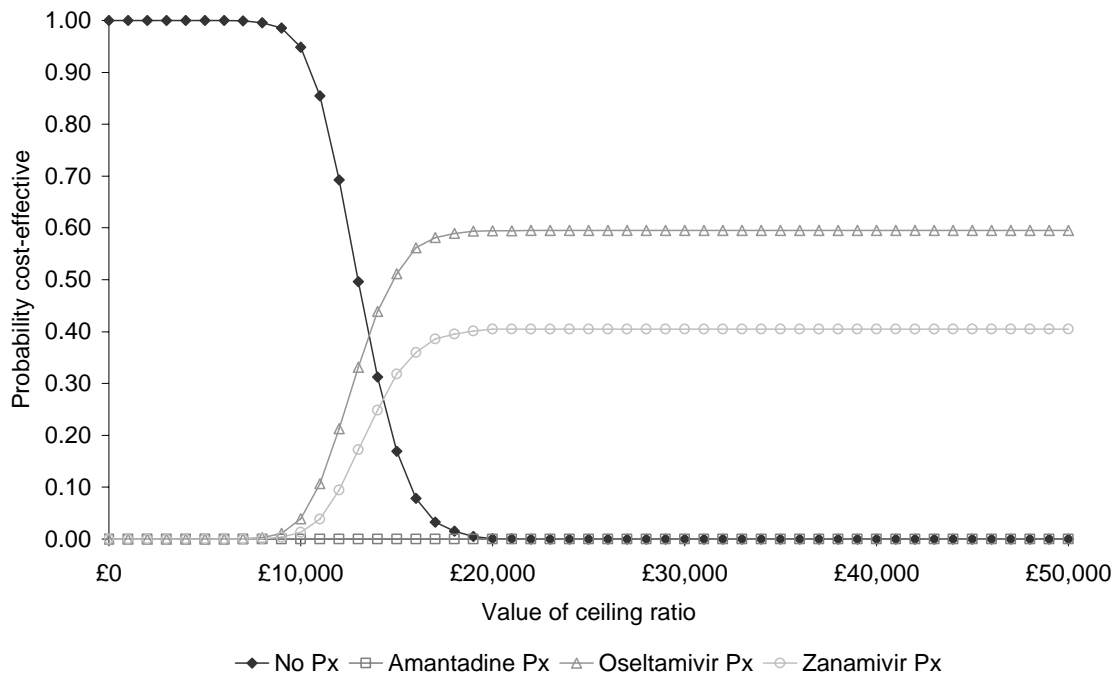


Figure 49: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk adults (prior vaccination)

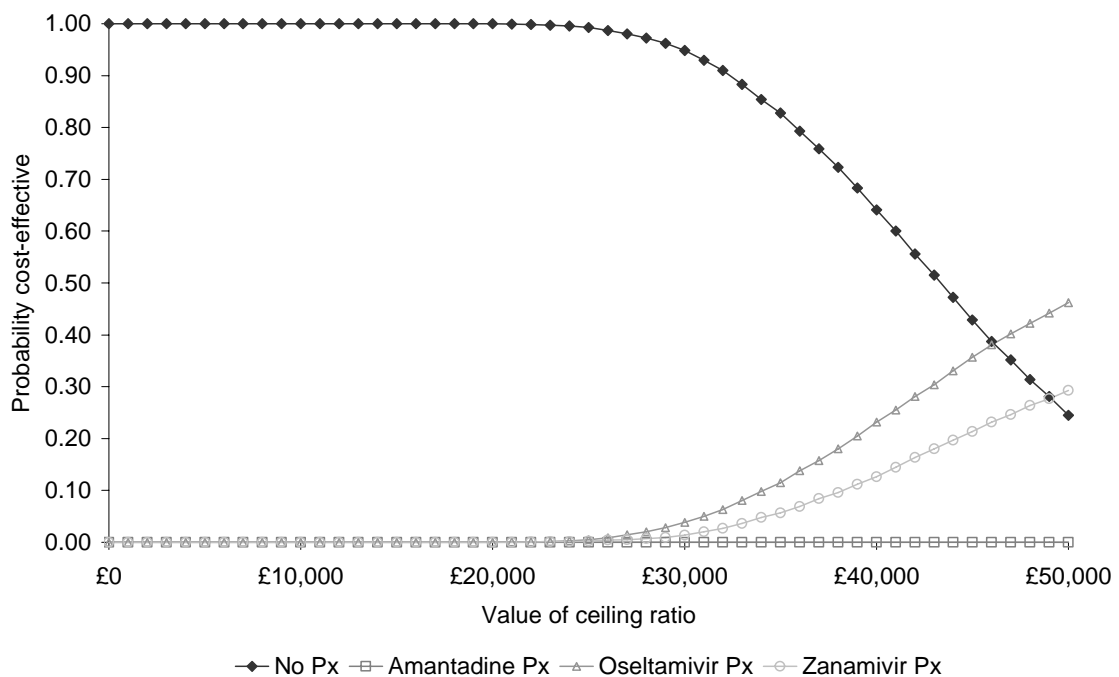


Figure 50: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy elderly (no vaccination)

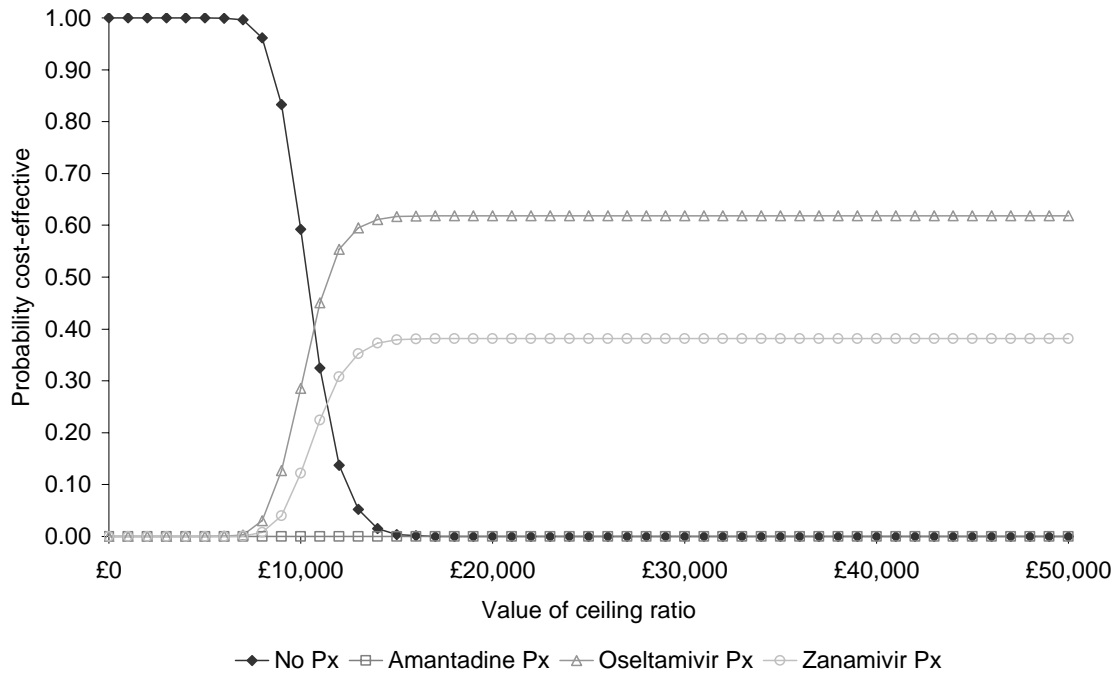


Figure 51: Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy elderly (prior vaccination)

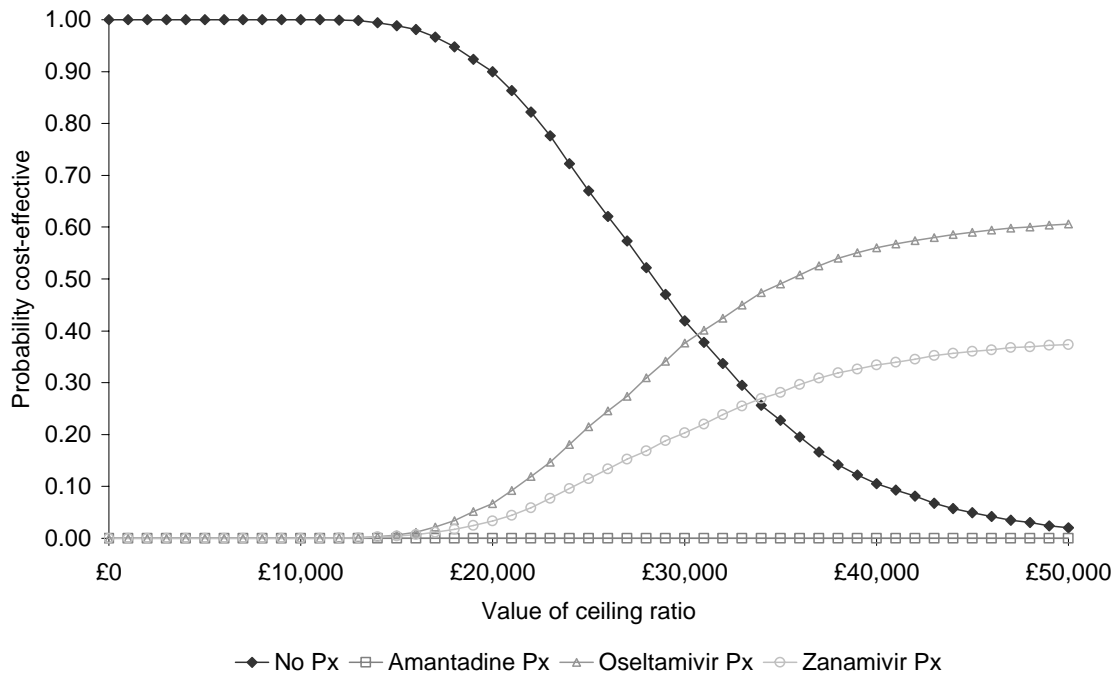


Figure 52: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk elderly (no vaccination)

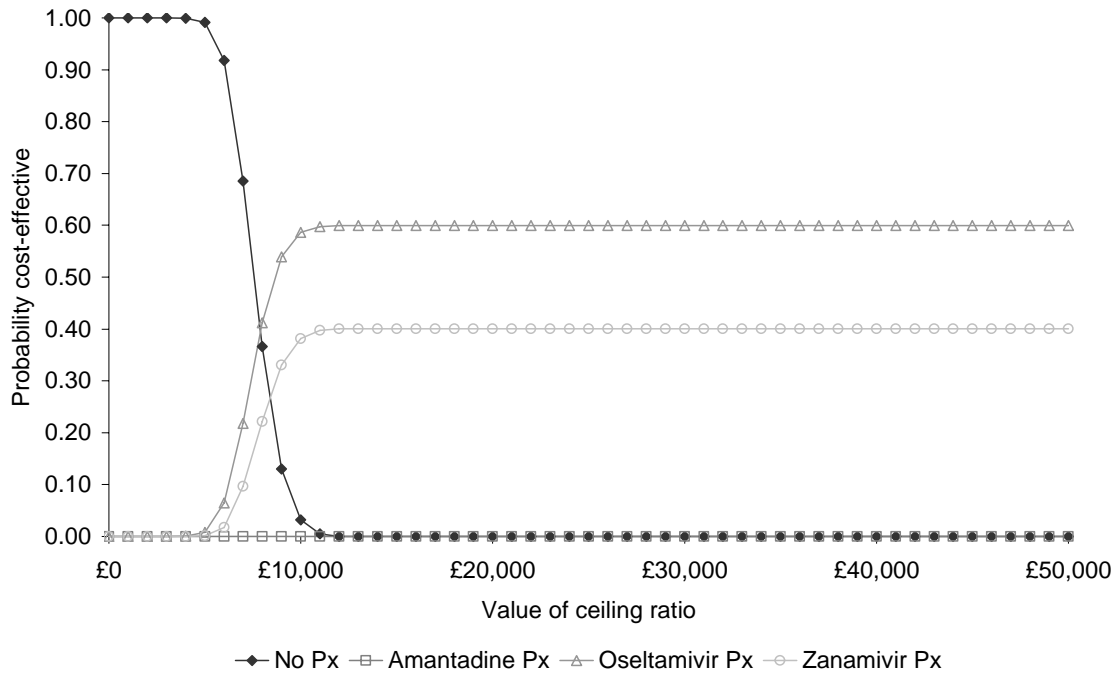
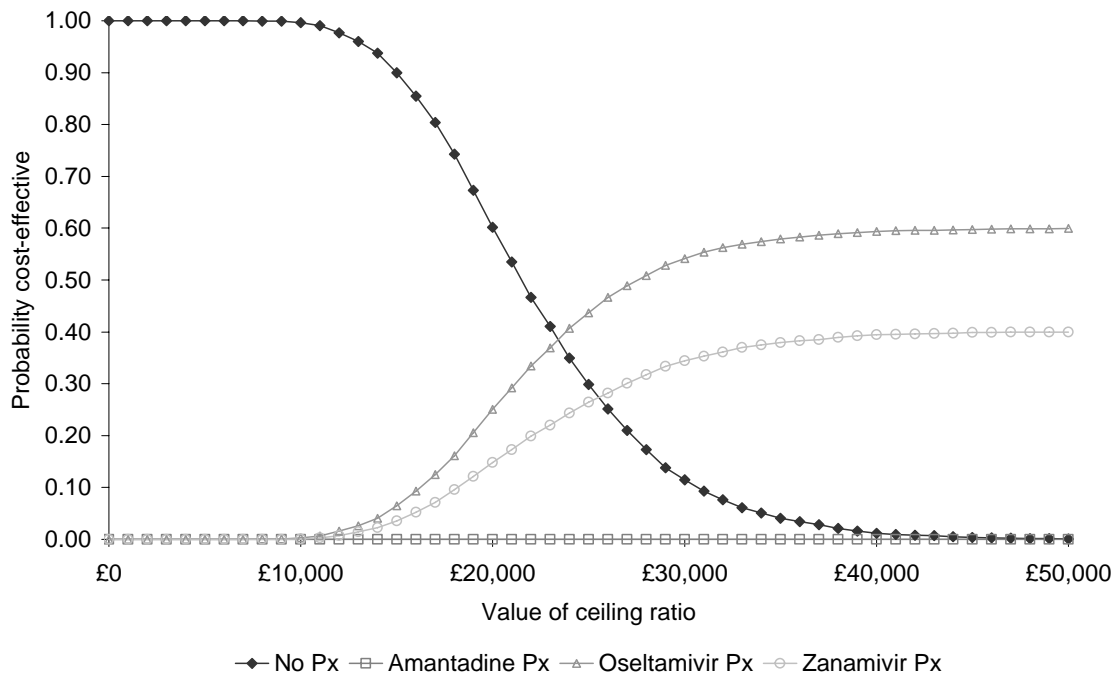


Figure 53: Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk elderly (prior vaccination)



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