Health Technology Assessment 2009; Vol. 13: No. 11

Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation

P Tappenden, R Jackson, K Cooper, A Rees, E Simpson, R Read and K Nicholson

February 2009
DOI: 10.3310/hta13110

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Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation

P Tappenden,[1*] R Jackson,[1] K Cooper,[1] A Rees,[1] E Simpson,[1] R Read[2] and K Nicholson[3]

[1]University of Sheffield, School of Health and Related Research (ScHARR), UK
[2]Department of Infectious Diseases, University of Sheffield, UK
[3]Department of Infectious Diseases, University of Leicester, UK

*Corresponding author

Declared competing interests of authors: none

Published February 2009
DOI: 10.3310/hta13110

This report should be referenced as follows:

Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al*. Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation. *Health Technol Assess* 2009; **13**(11).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

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The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 07/35/01. The protocol was agreed in October 2007. The assessment report began editorial review in February 2008 and was accepted for publication in July 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NCCHTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

Abstract

Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation

P Tappenden,[1*] R Jackson,[1] K Cooper,[1] A Rees,[1] E Simpson,[1] R Read[2] and K Nicholson[3]

[1]University of Sheffield, School of Health and Related Research (ScHARR), UK
[2]Department of Infectious Diseases, University of Sheffield, UK
[3]Department of Infectious Diseases, University of Leicester, UK

*Corresponding author

Objectives: To evaluate the clinical effectiveness and incremental cost-effectiveness of amantadine, oseltamivir and zanamivir for seasonal and post-exposure prophylaxis of influenza.
Data sources: A MEDLINE search strategy was used and searches were carried out in July 2007.
Review methods: An independent health economic model was developed based on a review of existing cost-effectiveness models and clinical advice. The model draws together a broad spectrum of evidence relating to the costs and consequences associated with influenza and its prevention. Where direct evidence concerning the effectiveness of prophylaxis within specific model subgroups was lacking, the model uses estimates from mixed subgroups or extrapolates from other mutually exclusive subgroups.
Results: Twenty-six published references relating to 22 randomised controlled trials (RCTs) were included in the clinical effectiveness review, along with one unpublished report. Eight, six and nine RCTs were included for amantadine, oseltamivir and zanamivir respectively. The study quality was variable and gaps in the evidence base limited the assessment of the clinical effectiveness of the interventions. For seasonal prophylaxis, there was limited evidence for the efficacy of amantadine in preventing symptomatic, laboratory-confirmed influenza (SLCI) in healthy adults [relative risk (RR) 0.40, 95% confidence interval (CI) 0.08–2.03]. Oseltamivir was effective in preventing SLCI, particularly when used in at-risk elderly subjects (RR 0.08, 95% CI 0.01–0.63). The preventative efficacy of zanamivir was most notable in at-risk adults and adolescents (RR 0.17, 95% CI 0.07–0.44), and healthy and at-risk elderly subjects (RR 0.20, 95% CI 0.02–1.72). For post-exposure prophylaxis, data on the use of amantadine were again limited: in adolescents an RR of 0.10 (95% CI 0.03–0.34) was reported for the prevention of SLCI. Oseltamivir was effective in households of mixed composition (RR 0.19, 95% CI 0.08–0.45). The efficacy of zanamivir in post-exposure prophylaxis within households was also reported (RR 0.21, 95% CI 0.13–0.33). Interventions appeared to be well tolerated. Limited evidence was available for the effectiveness of the interventions in preventing complications and hospitalisation and in minimising length of illness and time to return to normal activities. No clinical effectiveness data were identified for health-related quality of life or mortality outcomes. With the exception of at-risk children, the incremental cost–utility of seasonal influenza prophylaxis is expected to be in the range £38,000–£428,000 per QALY gained (depending on subgroup). The cost-effectiveness ratios for oseltamivir and zanamivir as post-exposure prophylaxis are expected to be below £30,000 per QALY gained in healthy children, at-risk children, healthy elderly and at-risk elderly individuals. Despite favourable clinical efficacy estimates, the incorporation of recent evidence of viral resistance to amantadine led to it being dominated in every economic comparison.
Conclusions: All three interventions showed some efficacy for seasonal and post-exposure prophylaxis. However, weaknesses and gaps in the clinical evidence base are directly relevant to the interpretation of the health economic model and rendered the use of advanced statistical analyses inappropriate. These data limitations should be borne in mind in interpreting the findings of the review.

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Glossary and list of abbreviations

Glossary

Attack rate A cumulative incidence rate in a population over time, such as in the circumstances of an epidemic

Dominated (simple) Where a given treatment alternative is less effective and more expensive than its comparator

Dominated (extended) The state when a strategy under study is both less effective and more costly than a linear combination of two other strategies with which it is mutually exclusive

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 7–10 days following presumed exposure

Protective efficacy 1 minus the RR value, expressed as a percentage

Relative risk (RR) 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

List of abbreviations

A&E	accident and emergency
ARI	acute respiratory illness
BNF	*British National Formulary*
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
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

continued

HPA	Health Protection Agency
HRG	Health-care Resource Group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
ILI	influenza-like illness
ITT	intention-to-treat
ITU	intensive therapy unit
MVH	Measurement and Valuation of Health
NAMCS	National Ambulatory Medical Care Survey
NI	neuraminidase inhibitor
NICE	National Institute for Health and Clinical Excellence
ONS	Office for National Statistics
PCR	polymerase chain reaction
PE	protective efficacy
PSSRU	Personal Social Services Research Unit
Px	prophylaxis
QALY	quality-adjusted life-year
QUOROM	quality of reporting of meta-analyses
RCGP	Royal College of General Practitioners
RCT	randomised controlled trial
RR	relative risk
RSV	respiratory syncytial virus
SAVE	simulating anti-influenza value and effectiveness
SE	standard error
SLCI	symptomatic, laboratory-confirmed influenza
SPC	Summary of Product Characteristics
TTO	time trade-off
VAS	visual analogue scale
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Influenza is an acute, febrile illness caused by infection of the respiratory system by the influenza virus. The 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, it carries the risk of increased morbidity, potentially serious complications and mortality. A Health Technology Assessment of amantadine, oseltamivir and zanamivir for the prophylaxis of influenza was reported earlier by Turner and colleagues. Since that review, the marketing authorisation for zanamivir has been extended to include intervention in the prophylaxis of influenza as well as in its treatment. This report presents an updated assessment of new and existing evidence for the clinical effectiveness and cost-effectiveness of amantadine, oseltamivir and zanamivir in the prevention of influenza.

Objectives

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 with each other and no prophylaxis.

Methods

A systematic review was undertaken and an independent health economic model 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 is 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, risk status and vaccination status. For the purposes of the model, 'at-risk' is defined as 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).

Results

Clinical effectiveness

Twenty-six published references relating to 22 randomised controlled trials (RCTs) were included in the clinical effectiveness review. An additional unpublished report was included in the assessment, giving a total of 23 RCTs. Eight, six and nine 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.

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 its efficacy in preventing symptomatic, laboratory-confirmed influenza (SLCI) in seasonal prophylaxis in healthy adults [relative risk (RR) = 0.40, 95% confidence interval (95% CI) 0.08–2.03]. Oseltamivir was effective in preventing SLCI, particularly when used in seasonal prophylaxis in at-risk elderly subjects (RR = 0.08, 95% CI 0.01–0.63). The preventative efficacy of zanamivir in seasonal prophylaxis was most notable in at-risk adults and adolescents (RR = 0.17, 95% CI 0.07–0.44) and healthy and at-risk elderly subjects (RR = 0.20, 95% CI 0.02–1.72)

Post-exposure prophylaxis

Again, 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% CI 0.03–0.34) for the prevention of SLCI in adolescents by post-exposure prophylaxis with amantadine was reported. Oseltamivir was effective in post-exposure prophylaxis within households of mixed composition (RR = 0.19, 95% CI 0.08–0.45), and the efficacy of zanamivir in post-exposure prophylaxis within households was also reported (RR = 0.21, 95% CI 0.13–0.33). Interventions appeared to be well tolerated, with a relatively low occurrence of subjects experiencing drug-related adverse events and withdrawals. Very limited evidence was available for their effectiveness in preventing complications and hospitalisations and in minimising length of illness and time to return to normal activities. No data were identified for health-related quality of life or mortality outcomes.

Cost-effectiveness

Seasonal prophylaxis

In healthy children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £44,000 per quality-adjusted life-year (QALY) gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is expected to be around 0.97.

In at-risk children

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be around £17,000 per QALY gained for unvaccinated at-risk children, and in previously vaccinated at-risk children greater than £50,000 per QALY gained. Assuming a willingness to pay threshold of £20,000 per QALY gained, the probability that oseltamivir is optimal in unvaccinated at-risk children is expected to be approximately 0.70, and assuming a threshold of £30,000 per QALY gained, the equivalent probability is around 0.94. For previously vaccinated at-risk children, the probability that no prophylaxis is optimal at £30,000 per QALY gained is 0.97 or higher.

In healthy adults

Amantadine and zanamivir as seasonal prophylaxis are expected to be dominated or extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £148,000 per QALY gained, irrespective of vaccination status. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is close to 1.0.

In at-risk adults

Based on the current list price for zanamivir, both amantadine and zanamivir are ruled out of the analysis. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is expected to be greater than £64,000 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is close to 1.0. When the proposed price reduction for zanamivir is incorporated, the incremental cost-effectiveness of zanamivir versus no prophylaxis is expected to be around £53,000 per QALY gained in unvaccinated at-risk adults and £157,000 in previously vaccinated at-risk adults. The incremental cost-effectiveness of oseltamivir is likely to be around £108,000 per QALY gained in unvaccinated at-risk adults and around £314,000 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 expected to be 0.99 or higher.

In healthy elderly

Amantadine and zanamivir are expected to be dominated or extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in healthy elderly individuals is expected to be greater than £50,000 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is expected to be close to 1.0.

In at-risk elderly

Amantadine and zanamivir are expected to be extendedly dominated. The incremental cost-effectiveness of oseltamivir versus no prophylaxis in at-risk elderly individuals is expected to be greater than £38,000 per QALY gained. Assuming a willingness to pay threshold of £30,000 per QALY gained, the probability that no prophylaxis is optimal is expected to be around 0.77 or higher.

Simple sensitivity analysis suggests that the cost-effectiveness of seasonal prophylaxis 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.

Post-exposure prophylaxis

In healthy children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated healthy children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be £19,000–£23,000 per QALY gained, depending on the list price for zanamivir, and for vaccinated healthy children at least £59,000 per QALY gained. 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 incorporated, the equivalent figures are expected to be 0.47 and 0.79 respectively. For the vaccinated subgroup, the probability that no prophylaxis is optimal at a threshold of £30,000 per QALY gained is expected to be close to 1.0.

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

In at-risk children

Amantadine and oseltamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated at-risk children, the incremental cost-effectiveness of zanamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8000 per QALY gained at the current list price, and around £6000 per QALY gained when the proposed price reduction for zanamivir is assumed. For vaccinated at-risk children, the equivalent figures are expected to be around £28,000 and £23,000 respectively. 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 is expected to be 0.85 at both thresholds. Based on the current list price for zanamivir, the probability that it 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 equivalent figures are expected to be 0.26 and 0.65 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 £9000 and £29,000 per QALY gained for unvaccinated and vaccinated at-risk children respectively.

In healthy adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated. 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, and for previously vaccinated healthy adults around £104,000 per QALY gained. 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, and for healthy adults who have previously been vaccinated close to zero at a threshold of £30,000 per QALY gained.

In at-risk adults

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated at-risk adults, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is around £13,000 per QALY gained, and for previously vaccinated at-risk adults around £44,000 per QALY gained. Based on the current list price for zanamivir, the probability that oseltamivir is optimal in unvaccinated at-risk adults is expected to be 0.89 and 0.84 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained respectively. The probability that oseltamivir is optimal in previously vaccinated at-risk adults is below 0.05.

In healthy elderly

Amantadine and zanamivir prophylaxis are expected to be dominated or extendedly dominated. 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, and for previously vaccinated healthy elderly individuals around £28,000 per QALY gained. Based on the current list price for zanamivir, the probability that oseltamivir is optimal in unvaccinated healthy elderly individuals is expected to be 0.87 and 0.82 at willingness to

pay thresholds of £20,000 and £30,000 per QALY gained respectively. For previously vaccinated healthy elderly individuals, the equivalent figures are expected to be 0.09 and 0.50 respectively.

In at-risk elderly
Amantadine and zanamivir as post-exposure prophylaxis are expected to be dominated or extendedly dominated. For unvaccinated at-risk elderly individuals, the incremental cost-effectiveness of oseltamivir post-exposure prophylaxis versus no prophylaxis is expected to be around £8000 per QALY gained, and for vaccinated at-risk elderly individuals around £22,000 per QALY gained. Based on its current list price, the probability that oseltamivir is optimal in unvaccinated at-risk elderly individuals is expected to be around 0.83 and 0.77 at willingness to pay thresholds of £20,000 and £30,000 per QALY gained. For vaccinated at-risk elderly individuals, the equivalent figures are 0.35 and 0.78 respectively.

The simple sensitivity analysis suggests that the cost-effectiveness of post-exposure prophylaxis is sensitive to assumptions regarding the influenza attack rate, the level of resistance against oseltamivir, and 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.

Discussion and conclusions

The clinical effectiveness data used in the cost-effectiveness modelling was limited for a number of population subgroups. This must be borne in mind in the interpretation of the findings. Additional consideration should be given to the occurrence of adverse events attributable to amantadine and the issue of resistance to antivirals among influenza isolates, which, although not directly reflected within the trials identified for inclusion, are factors that may have an important influence on the effectiveness of antiviral prophylaxis in clinical practice. Variation in the levels of resistance to antivirals among influenza isolates was taken into account in the cost-effectiveness analysis. Although the base case assumes oseltamivir resistance to be zero, 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 report, the Health Protection Agency issued a press release stating that approximately 5% (8/162) of H1N1 influenza tested isolates were resistant to oseltamivir. Further research is required to assess the impact of this resistance. Sensitivity analysis suggests that low levels of resistance are likely to have a minor impact upon the cost-effectiveness of oseltamivir. However, increasing levels of resistance could dramatically influence the conclusions of the economic analysis. It is 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, including variation in the quality of trials in terms of internal and external validity, study design and clarity of reporting. The absence of head-to-head RCTs meant that a direct comparison of the effectiveness of the interventions was not possible. These weaknesses are directly relevant to the interpretation of the health economic model results and rendered the use of more advanced statistical analyses inappropriate. A central area of uncertainty is the paucity of robust preference-based valuations of the impact of influenza and influenza prophylaxis on health-related quality of life.

Several areas warrant further research:

- additional RCTs of influenza prophylaxis in subgroups for which data are currently lacking
- RCTs in which the follow-up period extends beyond the duration of prophylaxis
- head-to-head RCTs in which the clinical effectiveness of the interventions in different subgroups is directly compared
- quality of life studies to inform future economic decision modelling
- further research concerning the incidence and management of complications of influenza.

Chapter 1
Background

Description of health problem

Influenza is a highly contagious, acute febrile respiratory infection caused by the influenza virus. Cases typically occur in a seasonal pattern, with localised epidemics during the winter months. 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

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 (GI) symptoms such as nausea, vomiting and diarrhoea. The duration of the acute illness is usually around 3–4 days, but cough and malaise may persist for 1–2 weeks. It is also possible for individuals to be asymptomatic while infected with the influenza virus.[1,2]

The symptoms of influenza can also arise 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 1–2 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 (COPD)], cardiovascular disease, chronic renal disease, diabetes mellitus or immunosuppression.[2]

Complications of influenza are often respiratory; these include 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 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. The mortality risk is highest in individuals who are elderly or have co-morbidities. Estimates of deaths each year in the UK that are thought to be caused by influenza range from 12,000 to 13,800.[3,4,5] The UK epidemic of 1989–90 was estimated to have caused in excess of 29,000 deaths.[1]

The influenza virus

Influenza is an orthomyxovirus, comprising a lipid membrane surrounding a matrix protein shell and a core consisting of seven or eight ribonucleic acid (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, while 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 tracts, attaching to the cell membranes, invading the host cell and using the host cell machinery to reproduce. New viral particles are released by lysis (breaking open) of the host cells, which damages the epithelium and increases susceptibility to secondary bacterial infections.[6]

Strains and subtypes

The World Health Organization (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, e.g. 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, i.e. 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, primarily ducks that serve as a reservoir for 16 different subtypes of H and nine subtypes of N for the influenza A virus. Other animal reservoirs may also be implicated in antigenic shift. Antigenic shift occurred in 1918, when an H1N1 influenza A virus adapted to man. It occurred also 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 1918–19 pandemic is estimated to have caused up to 40 million deaths worldwide. Pandemics usually originate in Asia where chickens, ducks, pigs and humans live in very close proximity and where other social factors favour interspecies transmission of virus. However, as discussed above, pandemic influenza and avian influenza are not considered within this review.

Transmission

Influenza virus is passed easily from person to person and 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 1–3 days. People with influenza may begin shedding virus 1–2 days before symptoms appear. Nasal shedding peaks about 48 hours after onset of symptoms and adults usually remain infectious for up to 1 week (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 caused by other viruses.[8] Infections with influenza A account for approximately 80% of outbreaks, while influenza B accounts for approximately 20%.[9] Comparative studies indicate that A/H3N2 infections produce more severe illness than A/H1N1 infections and that influenza B is intermediate in severity.[2] Typically, there is an annual outbreak which appears abruptly, peaks within 2–3 weeks and lasts for around 5–7 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 to the circulating strain), health status, age (both those aged 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, e.g. 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-aged 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*. The rate of general practitioner (GP) consultations for 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: more than 200 new GP consultations per 100,000 population per week.

The thresholds for Wales are slightly different: 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 defined as more 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, complications and mortality rates would also be anticipated to vary.

Impact of influenza and significance for the National Health Service (NHS)

For most people, influenza causes illness lasting 1–2 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 GP 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 was 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, groups recommended 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 or diabetes mellitus; the immunosuppressed; individuals with human immunodeficiency virus (HIV) infection; and 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 and health-care workers involved directly in patient care. Vaccination may also be considered for social care workers involved directly 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 the National Institute for Health and Clinical Excellence (NICE) for at-risk persons who are not adequately protected by vaccination and have been exposed to influenza (and for 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 Current usage in the NHS (later in this chapter).

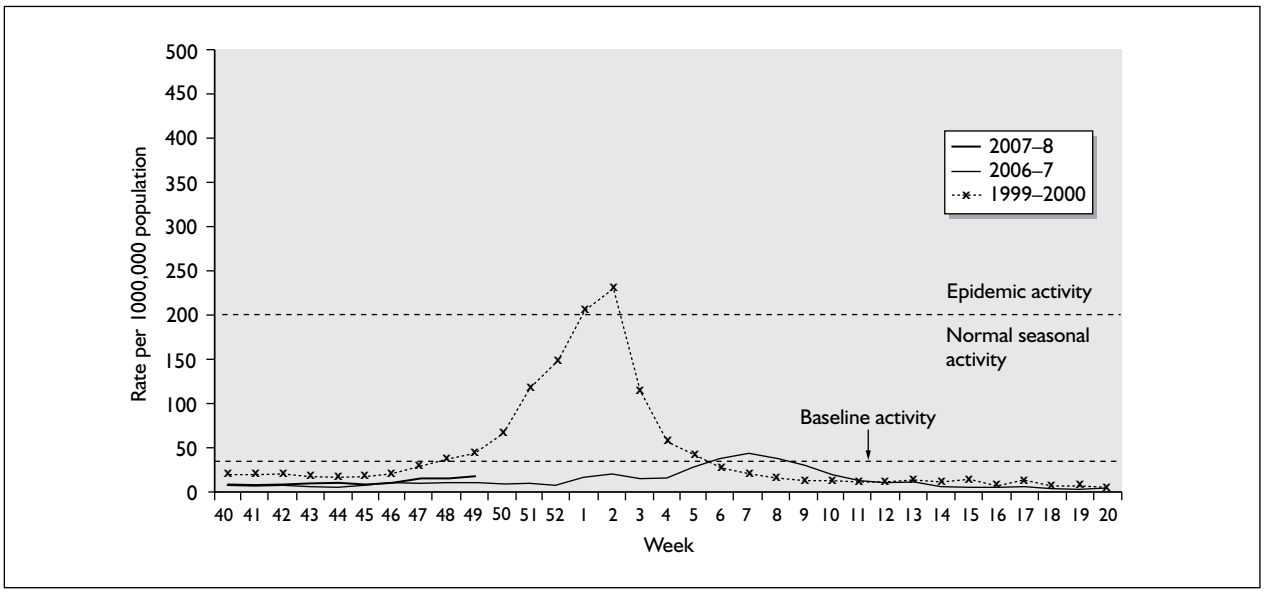

FIGURE 1 *Royal College of General Practitioners (RCGP) weekly consultation rate for influenza-like illness, England: 2007–8, 2006–7 and 1999–2000.*[11]

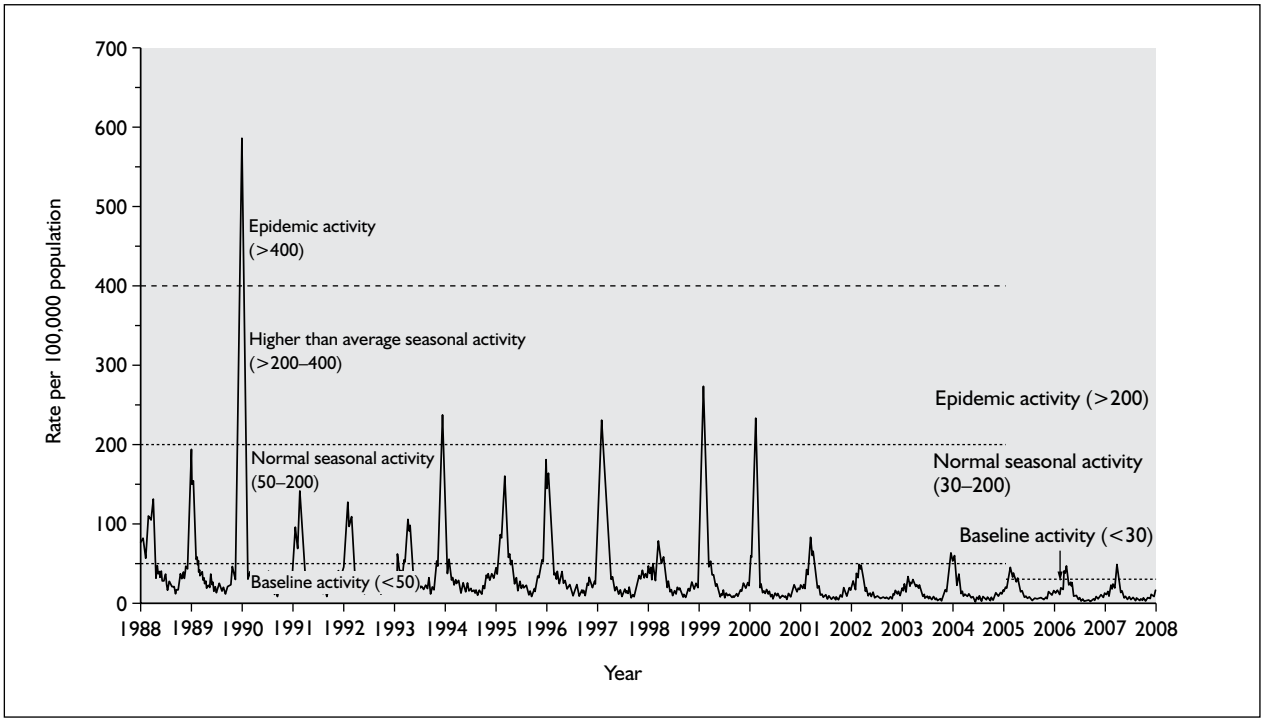

FIGURE 2 *Royal College of General Practitioners (RCGP) weekly consultation rate for influenza-like illness, England, 1988 to 2007–8.*[8]

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: (1) the number of cases of illness attributed to ILI (based on e.g. the number of clinic visits or absences from school/work) and (2) the laboratory-based identification of influenza virus in samples from individuals with ILI.

In 1947, 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 considerable implications for the control of influenza activity. In the UK, the HPA monitors and records the incidence of seasonal influenza and uptake of seasonal influenza vaccine. The Centre for Infections conducts surveillance of influenza activity in the UK, carries out laboratory tests to identify which strains are in circulation and communicates this information to health professionals and the public.[8]

Diagnosis

Influenza-like illness can be defined clinically according to symptoms; the exact definition varies, with different trials of influenza prevention using a range of indicators, often including raised temperature (usually ≥37.8°C) and/or symptoms such as cough, headache, sore throat or myalgia.

To determine whether an individual case of ILI is true influenza, presence of the influenza virus must be determined in a laboratory test. This may consist of isolation of influenza virus from a nose-and-throat swab or nasopharyngeal wash taken from the patient, by means of 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 using a haemagglutination inhibition assay (HAI); influenza infection is usually defined as a fourfold 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, while 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 GP with ILI.[1]

Current service provision

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 COPD)
- 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 defined above, vaccination is recommended for patients with chronic liver disease or chronic neurological disease and also for individuals who live within long-stay residential care facilities, carers, health-care workers and poultry workers.[15,18,19]

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 at 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 as a result of the additional costs of vaccination and the management of secondary complications arising from influenza infection.

Variation in services and/or uncertainty about best practice

There is currently relatively little antiviral usage in the UK, possibly as a result of lower levels of virus activity and/or consultation rates than in previous decades. In contrast, the use of oseltamivir in Japan has increased in recent years.[21]

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 being affected 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 suggest 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.

Relevant national guidelines

NICE has issued guidance relating to the use of amantadine and oseltamivir in prophylaxis[16] and zanamivir, oseltamivir and amantadine in the treatment of influenza.[17] These recommendations are outlined in detail in Current usage in the NHS (see below).

In addition to national policy for influenza vaccination in at-risk groups, vaccination for people aged 65 years and above was 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]

Description of technology under assessment

Summary of interventions

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

Amantadine (Lysovir®, Alliance Pharmaceuticals)

Description of intervention

Amantadine is a symmetrical C-10 primary amine with a cage-like structure, which is water soluble in hydrochloride salt form.[30] Amantadine hydrochloride exerts an antiviral effect on 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.

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).

Dosage and administration

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

Prophylaxis

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

Treatment

Treatment should be initiated within 48 hours of the onset of symptoms.

- Adults: 100 mg/day for 4–5 days
- Children aged 10–15 years: 100 mg/day for 4–5 days
- Children under 10 years of age: dosage not established
- Adults over 65 years of age: owing to the longer elimination half-life and reduced capacity for renal clearance of amantadine in elderly patients, a reduced dose of < 100 mg/day or 100 mg given at intervals of ≥ 1 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:

Creatinine clearance (ml/minute)	Dose
< 15	Lysovir contraindicated
15–35	100 mg every 2–3 days
> 35	100 mg/day

Contraindications

Amantadine hydrochloride is contraindicated in patients who:

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

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 central nervous system (CNS).

Abrupt withdrawal of amantadine therapy should be avoided in patients with Parkinson's disease.

It should be noted that, while resistance to amantadine is well documented,[30] it has been reported that levels of resistance among 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]

Adverse events

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

Oseltamivir (Tamiflu®, Roche)

Description of intervention

Oseltamivir is a neuraminidase inhibitor that exerts an antiviral effect on influenza A and B.[34] The drug inhibits viral release, preventing subsequent infection of adjacent cells. The SPC emphasises 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.

Licensed indications

Oseltamivir is indicated for:

- the post-exposure prophylaxis of influenza in patients aged 1 year and above who have 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 who present with influenza symptoms when influenza is circulating in the community. Treatment is effective when initiated within 48 hours of onset of the first symptoms.

Dosage and administration

Tamiflu is administered orally and is available as grey-yellow capsules containing 75 mg oseltamivir (as phosphate), 45 mg oseltamivir (as phosphate) or 30 mg oseltamivir (as phosphate), and as a powder (as phosphate) for reconstitution with water (12 mg/ml) 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 capsule 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. The SPC recommends that powder for oral suspension should be reconstituted by a pharmacist before it is dispensed 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 for 10 days, for up to 6 weeks during an epidemic

- Children aged 1–13 years: body weight under 15 kg, 30 mg once daily; body weight 15–23 kg, 45 mg once daily; body weight 23–40 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:

Creatinine clearance (ml/minute)	Dose
> 30	75 mg once daily
> 10 to ≤ 30	75 mg every second day *or* 30 mg suspension once daily *or* 30 mg capsules once daily
≤ 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 1–13 years: body weight under 15 kg, 30 mg every 12 hours; body weight 15–23 kg, 45 mg every 12 hours; body weight 23–40 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:

Creatinine clearance (ml/minute)	Dose
> 30	75 mg twice daily
> 10 to ≤ 30	75 mg once daily *or* 30 mg suspension twice daily *or* 30 mg capsule twice daily
≤ 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.

Contraindications

Oseltamivir is contraindicated in patients who have hypersensitivity to oseltamivir or any of its excipients.

Cautions

Oseltamivir should be administered with caution to patients who:

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

The dose should be reduced if creatinine clearance in patients is < 10–30 ml/minute and administration should be avoided if creatinine clearance is < 10 ml/minute.

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.

Zanamivir [Relenza®, GlaxoSmithKline (GSK)]

Description of intervention

Zanamivir is a neuraminidase inhibitor that inhibits the replication of influenza A and B.[34] The SPC states 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 be used only when reliable epidemiological data confirm 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.

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 who present with ILI when influenza is active in the community.

Dosage and administration
Relenza is available in the form of predispensed dry powder for inhalation in blisters containing 5 mg zanamivir per blister, delivered by means of oral inhalation using a *Diskhaler®* device. Each inhalation delivered (quantity released via mouthpiece of the Diskhaler) contains 4 mg zanamivir (the remainder appears to be lost in the inhalation process and is presumably retained within the Diskhaler apparatus).

Prophylaxis

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

- Adults and children aged 5 years and above: 10 mg once daily (i.e. two inhalations) for 10 days.

Seasonal prophylaxis During an epidemic, prophylaxis may be administered.

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

Treatment

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.

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

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

Contraindications
Zanamivir is contraindicated in patients who:

- are pregnant or breastfeeding
- are hypersensitive to any ingredient of the preparation.

Cautions
Zanamivir should be administered with caution to patients who:

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

According to the BNF, zanamivir should be used with caution in pregnancy and is contraindicated in breastfeeding women. However, according to the FDA, pregnancy and breastfeeding are cautions rather than contraindications. Other inhaled drugs, such as asthma medication, should be administered before zanamivir.

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

Identification of important subgroups

A number of important subgroups should be considered in relation to the use of antivirals for influenza prophylaxis. Subgroups viewed to be at risk of developing influenza-associated complications were described earlier in this chapter (see Description of health problem). Within the guidance issued by NICE for the prophylaxis[16] and treatment[17] of influenza, populations viewed to be at risk include individuals who:

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

Current usage in the NHS

Guidance was issued by NICE relating to the use of oseltamivir and amantadine in the prophylaxis

of influenza[16] 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. Guidance issued does not pertain to the circumstances of a pandemic or impending pandemic, or to 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 above.

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 (e.g. individuals who have not received an influenza vaccination for that season, for whom vaccination may be contraindicated or has yet to take effect, or for whom 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 ILI
  - *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 ILI (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 are 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 ILI
  - *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 ILI
  - *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.

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

TABLE 1 *Estimated post-exposure prophylaxis acquisition costs*

Regimen	Age (years)	Prophylaxis days/course	mg/dose	Doses/day	mg/course	Doses/pack	Packs required	Cost/pack	Cost/ course
Amantadine (five-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 (150 ml 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 < 15 kg	< 14	10	30	1	300	30	1	£16.36	£16.36
Oseltamivir (suspension) – children 15–23 kg	< 14	10	45	1	450	20	1	£16.36	£16.36
Oseltamivir (suspension) – children 23–40 kg	< 14	10	60	1	600	15	1	£16.36	£16.36
Oseltamivir (suspension) – children > 40 kg	< 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 (years)	Prophylaxis days/course	mg/dose	Doses/day	mg/course	Doses/pack	Packs required	Cost/pack	Cost/course
Amantadine (five-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 (150 ml syrup, Symmetrel)	> 10	42	100	1	4200	15	3	£5.55	£16.65
Amantadine following vaccination (five-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 (150 ml 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 < 15 kg	< 14	42	30	1	1260	30	2	£16.36	£32.72
Oseltamivir (suspension) – children 15–23 kg	< 14	42	45	1	1890	20	3	£16.36	£49.08
Oseltamivir (suspension) – children 23–40 kg	< 14	42	60	1	2520	15	3	£16.36	£49.08
Oseltamivir (suspension) – children > 40 kg	< 14	42	75	1	3150	12	4	£16.36	£65.44
Zanamivir (powder)	> 5	28	10	1	280	10	3	£24.55	£73.65

suspension form based on body mass. The reader should note that while the BNF lists only 75 mg capsules and suspension, the SPC accessed via the electronic Medicine Compendium[26,27] (www.medicines.org.uk) cites the additional availability of 30 mg and 45 mg capsules of oseltamivir. Amantadine, oseltamivir and zanamivir are self-administered and do not require administration by a health-care 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 (five disks, four blisters per disk); the proposed price for zanamivir is £16.36 (Toni Maslen, Health Outcomes Programme Leader, GSK, 2007, personal communication). This price reduction was approved by the Department of Health with effect from 1 February 2008 but was not listed in the BNF[14] at the time of submission of this report.

Chapter 2

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 given 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.

Decision problem

The decision problem has been defined as described below.

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 with each other and with no prophylaxis (in which subjects received one 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 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 below, 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 were considered. Where evidence was available, vaccination status was also taken into consideration.

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 (HRQoL), 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 with 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 in Chapter 1 and noted above, the remit of this assessment does not include the circumstances of a pandemic, an 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.

Chapter 3

Assessment of clinical effectiveness

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 quality of reporting of meta-analyses (QUOROM) statement.[35] Methods for the review are detailed below.

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).

Sources searched

The electronic databases searched included MEDLINE; MEDLINE In-Process; EMBASE; Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, Biosciences Information Service (BIOSIS), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database (EED) and Health Technology Assessment (HTA) databases; Office of Health Economics Health Economic Evaluations Database (OHE HEED), National Research Register (NNR); Science Citation Index (SCI); Current Controlled Trials (CCT); and ClinicalTrials.gov. Searches were undertaken in July 2007. Sponsor submissions to NICE were also handsearched.

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.

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.

Inclusion and exclusion criteria

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

Populations

The included populations comprised:

- 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

Interventions comprised 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 owing

to their limited external validity. These studies are presented to provide a comprehensive review of the effectiveness of prophylaxis; they were not used to inform the health economic model.

Comparators

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

Outcomes

Outcomes considered included:

- 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
- HRQoL
- mortality
- hospitalisations prevented
- length of influenza illness
- time to return to normal activities
- cost and cost-effectiveness (see Chapter 4).

Study type

The study employed randomised controlled trials (RCTs). Had evidence not been 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 RCTs 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 published only 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.

Data abstraction strategy

Data were extracted with no blinding to authors or journal, and were 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.

Critical appraisal strategy

The quality of included RCTs 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.

Methods of data synthesis

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

Efficacy data are presented as RRs and protective efficacy (PE) (PE = 1 – RR, expressed as a percentage). Where the RR or PE values were not described in the study publication, or where the value differed (usually by only 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 (CI) around the RR or PE, these have been presented. Where no CI was published, it was calculated using the following formula (and marked with †):

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

Lower 95% confidence limit for RR
= exp [ln(RR) – 1.96 × SE ln(RR)]

Upper 95% confidence limit for RR
= exp [ln(RR) + 1.96 × SE ln(RR)].

Results

Quantity and quality of research available

As a result of the searches outlined above, a total of 1010 citations were identified, following removal of duplicates, and were screened for inclusion in the review of clinical effectiveness (*Figure 3*). Two hundred and eighty citations were rejected at the title stage, yielding 730 abstracts for screening, of which 551 were rejected on 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.[37–43] The articles that could not be obtained were unlikely 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]

Quantity of research available

A total of 26 published references presenting findings from 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 reference[45] was a report of a pooled analysis of data relating to post-exposure prophylaxis of influenza using oseltamivir and zanamivir based on included trials.[46–49] No ongoing trials or trials due to report that met the inclusion criteria were identified in searches. All included articles are described below and grouped by intervention.

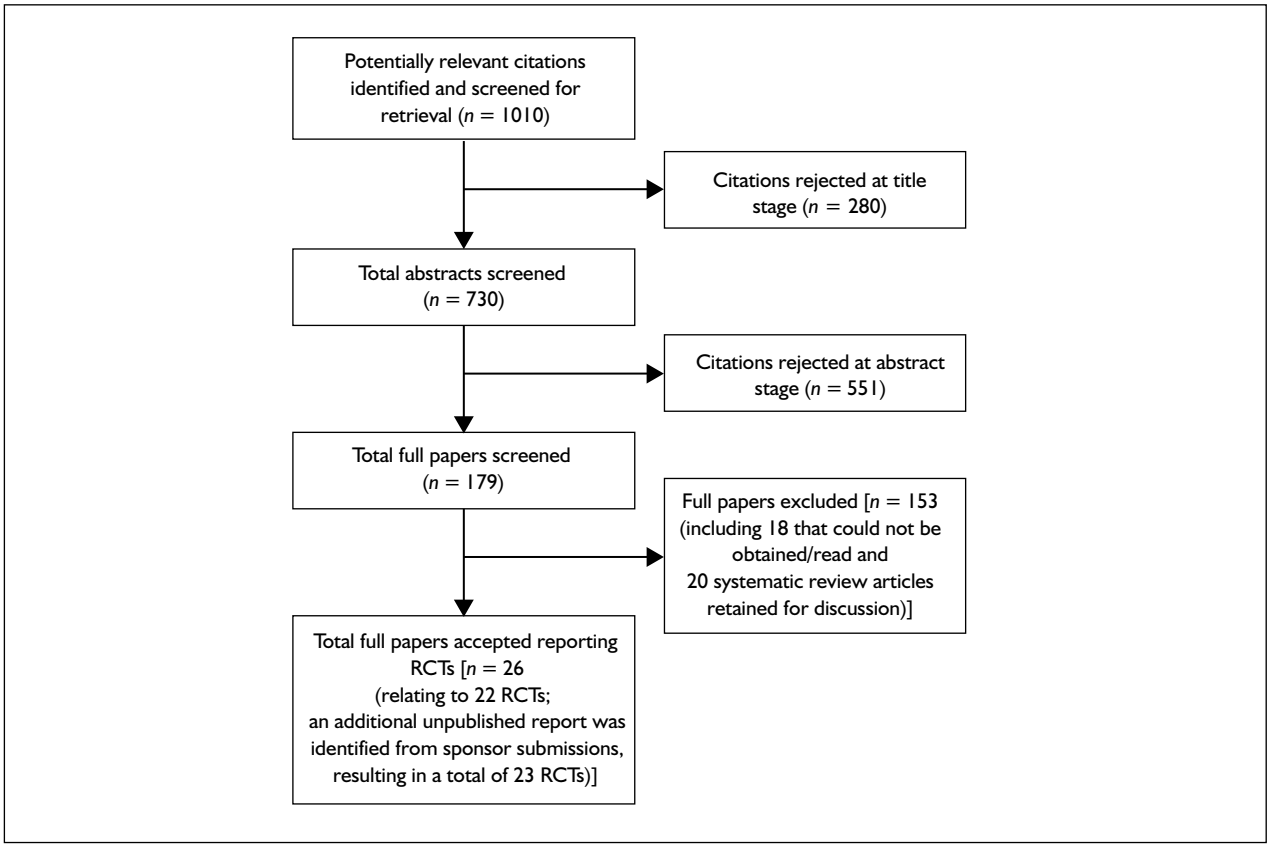

FIGURE 3 *Quality of reporting of meta-analyses (QUOROM) diagram of study inclusion and exclusion in clinical effectiveness review.*

Amantadine

A total of eight full papers reporting eight RCTs that investigated 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 updated[33] and was handsearched to identify any additional citations for inclusion in the current review. Turner *et al.*[10] identified three trials of amantadine prophylaxis undertaken in children.[51–53] However, these studies and an additional trial[54] 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 colleagues[55] are included in this update, while the trial reported by Leeming[56] was excluded, as twice the currently licensed dose was administered to participants.

An additional seven 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 school[59] and in adults in semi-isolated engineering school populations.[60,61] A further three reports of the prophylactic efficacy of amantadine against experimentally-induced influenza were identified.[57,62,63] One of these papers presented results from two 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 adults[33] have been included in our assessment.[55,57,59,61] 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 100 mg/day reduced the incidence of serologically-confirmed infection and was well tolerated. However, as the full text was not available in English, this citation could not be included and is not presented in the review.

Oseltamivir

Nine studies (of which six were reported in full papers and a further three were abstracts) were identified that investigated the use of oseltamivir in prophylaxis against influenza in six 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] WV15697[66] and WV15799.[49] Data for trials WV15673 and WV15697 were reported in the publication by Hayden *et al.*[66] both individually and combined across the two studies. All of these trials are included in the current assessment. An additional publication, by Hayden *et al.*,[47] examining the efficacy of oseltamivir in post-exposure prophylaxis within households present findings of an RCT published subsequent to the HTA review.[10] A further paper describes a trial of experimentally-induced influenza.[67] An additional publication[45] describes a pooled analysis of data from oseltamivir post-exposure prophylaxis trials that are already included in the review.[46–49]

An abstract in English was obtained for the trial by Kashiwagi *et al.*,[41] in which oseltamivir was administered to healthy adults at 75 mg once daily versus placebo for 6 weeks. This trial was previously reviewed by Jefferson *et al.*[68] However, the report was not available in full in English and was therefore excluded from this review.

Zanamivir

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

Turner and colleagues[10] evaluated five zanamivir prevention trials: studies NAIA2010,[69] NAIA3005,[70,71] NAIA30010,[46] NAIA2009[72] and NAIB2009.[72] 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.*,[69] in which the dose of zanamivir used was twice that of current licensed indications.

TABLE 3 *Characteristics of included amantadine prophylaxis RCTs*

Study	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding
Aoki *et al.*, 1986[58]	Healthy adults in a military setting (age not defined) Six to eight individuals in each study year immunised against influenza in previous years	T1: amantadine 100 mg/day: 1980–1, *n* = 74; 1981–2 under 28 years, *n* = 21, over 29 years, *n* = 29; 1982–3, *n* = 46 T2: placebo: 1980–1, *n* = 48; 1981–2 under 28 years, *n* = 16, over 29 years, *n* = 18; 1982–3, *n* = 33	Seasonal	39 days (1980–1), 32 days (1982–3)	National Health Research and Development Program of Canada and the Canadian Foundation for the Advancement of Clinical Pharmacology
Pettersson *et al.*, 1980[55]	Elderly subjects (mean ages T1 = 77.4 years, T2 = 79.0 years) living in a residential home, vaccination status unclear, but discussion states no adequate vaccine available	T1: amantadine 100 mg/day: randomised, *n* = 94; completing study, *n* = 89 T2: placebo: randomised, *n* = 101; completing study, *n* = 99	Seasonal	9 weeks	Medica Ltd and Orion Diagnostica Ltd
Reuman *et al.*, 1989[57]	Healthy unvaccinated adults aged 18–55 years living in the community	T1: amantadine 100 mg/day, *n* = 159 T2: placebo, *n* = 159	Seasonal	Presumed 6 weeks	E.I. DuPont de Nemours and Company, Inc.
Payler and Purdham, 1984[59]	Adolescent males aged 13–19 years in boarding school setting, 87% vaccinated	T1: amantadine 100 mg/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

continued

TABLE 3 *Characteristics of included amantadine prophylaxis RCTs (continued)*

Study	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding
Smorodintsev *et al.*, 1970[60,61]	Male adults (recruitment pool aged 18–30 years), presumed healthy, in semi-isolated engineering school populations	T1: amantadine 100 mg/day (50.7% of 10,053): assigned to group, $n = 5092$; onset of influenza prior to dosing, $n = 441$; regularly or irregularly taking amantadine, $n = 4559$ T2: placebo (31.6% of 10,053): assigned to group, $n = 3175$; onset of influenza prior to dosing, $n = 307$; receiving placebo, $n = 2804$ (3175 – 307 = 2868, 2804 included in analysis) T3: internal control: individuals at same engineering schools as amantadine and placebo groups, but living at home rather than at school; received no prophylaxis (10.0% of 10,053), $n = 1011$ T4: external control: individuals at an eighth engineering school; received no prophylaxis (7.7% of 10,053), assigned to group, $n = 775$	Outbreak control	Five of seven populations dosed for 30 days, two populations dosed for 12 days	Study medication supplied by E.I. DuPont de Nemours and Company, Inc.
Reuman *et al.*, 1989[57]	Healthy unvaccinated adults aged 18–40 years	T1: amantadine 100 mg/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.
Sears and Clements, 1987[63]	Healthy adults aged 18–40 years	T1: amantadine 100 mg/day, $n = 22$ T2: placebo, $n = 22$	Experimentally-induced influenza	8 days	E.I. DuPont de Nemours and Company, Inc.
Smorodintsev *et al.*, 1970[62]	Healthy adults (age not defined)	T1: amantadine 100 mg/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.

DOI: 10.3310/hta13110

TABLE 4 *Characteristics of included oseltamivir prophylaxis trials*

Trial/data source	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding
WV15825 (Peters *et al.*, 2001[64] and De Bock *et al.*, 2000[65])	At-risk elderly subjects living in a residential home (mean age T1 = 81 years, T2 = 82 years), 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
WV15673 (Hayden *et al.*, 1999[66])	Healthy unvaccinated adults aged 18–65 years 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
WV15697 (Hayden *et al.*, 1999[67])	Healthy unvaccinated adults aged 18–65 years 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
WV15799 (Welliver *et al.*, 2001[49])	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 75 mg once daily, *n* = 493 T2: placebo, *n* = 462	Post-exposure prophylaxis	7 days	Hoffman–La Roche
WV16193 (Hayden *et al.*, 2004[48,73,74])	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 75 mg twice daily for 5 days	Oseltamivir: post-exposure prophylaxis vs treatment on influenza onset (expectant treatment); index cases in both groups received treatment T1: oseltamivir prophylaxis 75 mg daily for 10 days, *n* = 400 T2: oseltamivir treatment on influenza onset (expectant treatment) 75 mg twice daily for 5 days (less in children), *n* = 392	Post-exposure prophylaxis	10 days	Hoffman–La Roche
Hayden *et al.*, 2000[67]	Healthy adults aged 18–65 years	T1: oseltamivir 75 mg once daily, *n* = 19 T2: placebo, *n* = 19	Experimentally-induced influenza	7 days (1 day before challenge and 6 days after)	Hoffman La Roche

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 10 mg once daily, *n* = 553 T2: placebo, *n* = 554	Seasonal	28 days	Glaxo Wellcome	Monto *et al.*, 1999a[70,71]
GlaxoSmithKline study 167/101	Health-care workers aged 18 years and above	T1: zanamivir 10 mg once daily, *n* = 161 T2: placebo, *n* = 158	Seasonal	28 days	GlaxoSmithKline	Sponsor submission[44]
NAI30034	At-risk adolescents and adults aged 12 years and above; high-risk defined as aged 65 years and above or chronic disorders of pulmonary or cardiovascular system or diabetes mellitus T1: 67% vaccinated; T2: 68% vaccinated	T1: zanamivir 10 mg once daily: randomised, *n* = 1678; completed study, *n* = 1595 T2: placebo: randomised, *n* = 1685; completed study, *n* = 1594	Seasonal	28 days	GlaxoSmithKline	LaForce *et al.*, 2007[75]
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 Contacts: T1: 11% vaccinated; T2: 10% vaccinated Index cases did not receive treatment	T1: zanamivir 10 mg once daily, *n* = 661 T2: placebo, *n* = 630	Post-exposure prophylaxis	10 days	GlaxoSmithKline	Monto *et al.*, 2002[47]

Trial	Population characteristics	Trial design arms (no. of patients in each arm)	Preventative strategy	Prophylaxis duration	Source of funding	Data source and additional information
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 10 mg daily, *n* = 414 T2: placebo, *n* = 423	Post-exposure prophylaxis	10 days	Glaxo Wellcome	Hayden *et al.*, 2000[46]
NAIA2009/NAIB2009	Subjects of mixed age and health status; unvaccinated adults and children aged 13–65 years (as contacts) Index cases did not receive treatment	T1: zanamivir 10 mg inhaled daily, *n* = 144 T2: placebo, *n* = 144	Post-exposure prophylaxis	5 days	Presumed Glaxo Wellcome	Kaiser *et al.*, 2000[72]
NAIA3004	At-risk elderly subjects in long-term care (mean age T1 = 66.8 years, T2 = 67.2 years); 85% of subjects at randomisation at risk of complications or death due to influenza 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 *et al.*, 2005[76,77]
NAIA3003	At-risk elderly subjects in long-term care (mean age T1 = 76.3 years, T2 = 74.8 years); 96% of subjects at randomisation at risk of complications or death due to influenza 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 *et al.*, 2005[78]

An additional six 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 on the use of zanamivir in post-exposure prophylaxis within households has also been published,[47] while 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.[76–78] An additional paper describes a pooled analysis of data from zanamivir post-exposure prophylaxis trials that are already included in the review.[45]

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 eight RCTs relating to the prophylactic use of amantadine was relatively poor. No new amantadine prevention trials published since the original HTA assessment[10] were identified. A considerable number of the older amantadine trials utilised a dose of 200 mg/day as opposed to the currently licensed adult dose of 100 mg/day[18] and were therefore not considered to be suitable for inclusion in this review (see Inclusion and exclusion criteria, p. 17). Other amantadine prevention trials incorporated the use of doses in line with the current licence alongside inappropriate doses, but did not present data appropriate for inclusion separately and were therefore also excluded. Details of these studies can be found in Appendix 6.

Much of the amantadine prophylaxis evidence was not reported clearly, with a lack of detail on, for example, methods of randomisation of study subjects.[57,59–63] It was unclear in a number of trials whether allocation of treatment group was concealed.[55,57–59,62,63] One study publication failed to state clearly 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 among participants randomised to each trial arm. An additional four publications failed to state the eligibility criteria for participation in the trials.[55,60–62] A number of co-interventions were identified with the potential to affect outcomes, including vaccination,[57–61] intake of medications that may affect study outcomes,[64] 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 while many publications reported that a double-blind design was used, no further details were presented. Although 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 were unclear in the reporting of some studies.[48,49,73–74] All studies stated the number of participants randomised, and only one report failed to describe clearly the baseline characteristics and eligibility criteria,[74] with all others judged to have achieved baseline comparability among subjects. A number of authors identified vaccination status,[48,49,64,66] and recent use of antivirals[48,64] or antibiotics[48] as potentially confounding co-interventions. Clarity of reporting of blinding was variable among studies, and one study was described as being open-label in design.[48,73–78] All studies retained at least 80% of randomised subjects for use in the analysis and all, with the exception of two reports,[64,67] presented reasons for withdrawal, but the analysis of only two studies could be considered to adhere to the intention-to-treat principle.[47,67,73-74]

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[46,47,72] and concealment of allocation.[46,72,76,77] 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[46,47,70,75,76,78] 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.[46,47,70–72,75] However, all studies included more than 80% of randomised subjects in analyses, described reasons for withdrawal and utilised intention-to-treat analysis.

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, HRQoL, mortality, hospitalisations prevented, length of influenza illness, time to return to normal activities, 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 HRQoL 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.[58,60–63] The efficacy of prophylaxis in preventing cases of SLCI was most frequently reported as a protective efficacy statistic (1 – RR, expressed as a percentage). While 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 is presented where available. The majority of trials also presented information on the occurrence of adverse events among 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.

Amantadine

The included evidence focusing on amantadine prophylaxis against influenza was taken from relatively old 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 eight RCTs were identified. The Cochrane review investigating amantadine and rimantadine in influenza A incorporated the use of meta-analysis in their study.[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; 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 published subsequently.

Seasonal prophylaxis with amantadine

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 18–55 years. Although this study also investigated the effects of amantadine at daily doses of 50 mg and 200 mg, only data relating to the use of the drug at the licensed dose of 100 mg 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 100 mg/day dosage group (RR 0.40,† 95% CI 0.08†–2.03†). The authors described

a higher rate of adverse events in the treatment group receiving the higher dose of 200 mg/day but no differences between the arms receiving the licensed dose of 100 mg/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 the 159 in the placebo arm (0.6%) withdrew as a result of adverse events; no withdrawals were described in the amantadine 100 mg/day group. However, adherence to amantadine was relatively poor, with 49% of the amantadine-dosed participants and 58% of the placebo arm taking fewer than the total allotted tablets. This study suggests that the use of amantadine at the lower dose results in fewer adverse effects but that 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 two seasons for 32 days and 39 days respectively was reported by Aoki *et al.*[58] As discussed in Inclusion and exclusion criteria (p. 17), only data comparing effects in treatment arms receiving amantadine at a dose of 100 mg per day or placebo are presented in this review. Reasons for the unequal numbers in each treatment arm are unclear. Six to eight individuals per study season were described as being vaccinated in previous years (proportions not estimable). Primary outcomes that were 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 one subject in the 1980–1 season and two subjects in the 1982–3 season 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 1980–1 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 100 mg/day group. In 1982–3, these rates were described as 1/34 (2.9%) in the placebo group and 1/47 (2.1%) in the amantadine 100 mg/day group. No amantadine-related differences in adverse effects were observed between the placebo and amantadine 100 mg/day groups (no further data were presented).

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. While 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 100 mg/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 to be 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 and placebo arms respectively. Although 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.

Post-exposure prophylaxis with amantadine

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 Purdham[59] 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 100 mg/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 have an impact on 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 ($p < 0.001$, RR 0.17,† 95% CI 0.08†–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% CI 0.66†–0.97†). Of the three subjects developing symptomatic, laboratory-confirmed influenza in the amantadine arm, two were described as being vaccinated, while one subject was reported as unvaccinated. No information was given for the control arm. Urticaria was reported in 1 of 267 participants receiving amantadine (0.4%), while no adverse events were observed in the control group. The authors observed that eight of the nine 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. Subjects in five of seven schools were dosed for 30 days, while subjects in two 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. Regardless of whether subjects received drug medication regularly or irregularly, clinical influenza occurred at rates of 214/4559 (4.7%) and 224/2804 (8.0%) in the amantadine and placebo groups respectively (RR 0.59,† 95% CI 0.49†–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; while 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 criteria for classing symptoms as mild or severe. Mean duration of overall illness was shorter in the amantadine group than in the 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 of a higher rate of adverse effects resulting from amantadine prophylaxis, were presented.

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

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.[57,62,63]

Reuman *et al.*[57] undertook an RCT to determine the efficacy of amantadine in preventing experimentally-induced influenza A. Although the use of doses of amantadine at 50 mg/day and 200 mg/day were also investigated, only data relating to the use of amantadine at 100 mg/day and placebo are presented within this systematic review. Subjects were healthy, unvaccinated adults aged 18–40 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 ($p = 0.012$). Symptomatic, laboratory-confirmed influenza was observed in a smaller proportion of subjects, i.e. 11/19 (58%) in the placebo arm and 3/20 (15%) in the amantadine arm ($p = 0.0055$), resulting in an RR of 0.26 (95% CI 0.09†–0.79†) and a protective efficacy of 74%. Amantadine at all doses was described as suppressing respiratory symptoms on days 2–6 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 100 mg/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 100 mg/day arms.

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

Smorodintsev *et al.*[62] demonstrated the efficacy of amantadine at the lower dose of 100 mg/day versus the previously-used dose of 200 mg/day and placebo in the prevention of experimentally-induced influenza A in healthy medical student volunteers. Only data in which the licensed dose of 100 mg/day and placebo are compared are presented here. A protective efficacy of 42% against clinical influenza was reported for amantadine at 100 mg/day versus placebo (10/19 in the amantadine arm, 28/31 in the placebo arm; RR 0.58, 95% CI 0.37†–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; RR 0.14,† 95% CI 0.02†–0.96†). No data were reported on adverse effects relating to a comparison of amantadine at the licensed dose with placebo; however, no drug-related side effects were reported overall.

Adherence to amantadine prophylaxis

Four trials presented evidence of varying levels of adherence to the study protocols. Payler and Purdham[59] stated that only 2% of their subjects did not take amantadine, while 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 respectively). The study by Aoki *et al.*[58] utilised laboratory testing of samples taken from tested study participants and demonstrated that 10% and 22% of subjects who had been randomised to receipt of amantadine and were tested in different study seasons showed no drug in samples. No amantadine was present in samples from placebo subjects.

Viral resistance to amantadine

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

Discussion

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 control[59] 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 Purdham[59] 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 the amantadine and placebo groups, and 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 Chapter 1, reports of the increasing emergence of amantadine-resistant influenza A strains[31] 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.

Oseltamivir

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

Seasonal prophylaxis with oseltamivir

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

In healthy adults Two RCTs investigating oseltamivir for seasonal prophylaxis were reported by Hayden *et al.*[66] (*Table 6*). The two trials were identically-designed multicentre studies undertaken in healthy, unvaccinated adults aged 18–65 years; the first trial 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% CI 53–96) in trial WV15673 and a non-significant protective efficacy of 50% (95% CI –55 to 94) in trial WV15697. The authors reported a pooled estimate for protective efficacy against SLCI of 76% (95% CI 46–91; RR 0.24). When a meta-analysis of the data reported separately for each trial was undertaken by the Assessment Group, the RR of developing influenza for oseltamivir versus placebo was 0.27 (95% CI 0.09–0.83). 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 75 mg/day group and in 10/519 (1.9%) of the placebo group. Upper GI adverse effects were greater in subjects receiving oseltamivir 75 mg/day (12.1%) than in those receiving placebo (7.1%) (difference 5.0%, 95% CI 1.4–8.6). Vomiting occurred in a higher proportion of subjects receiving the oseltamivir dose (2.5%) than in those receiving placebo (0.8%) (difference 1.7%, 95% CI 0.2–3.3).

In the elderly Peters *et al.*[64] and De Bock *et al.*[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 (*Table 7*). 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 the vaccinated population only 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 occurred at rates of 6.5% (18/276) and 4.0% (11/272) in the oseltamivir and placebo arms respectively. A similar proportion 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 than in the placebo group (8.3% versus 5.5%) and GI adverse events were also more common among individuals receiving oseltamivir (14.9% versus 12.9%).

Post-exposure prophylaxis with oseltamivir

In mixed households Two RCTs, WV15799 reported by Welliver *et al.*[49] and WV16193 reported by Hayden *et al.*,[48,73] and Belshe *et al.*,[74] investigating oseltamivir in the prevention of influenza in household contacts of index cases were identified (*Table 8*).

Welliver *et al.*[49] randomised household contacts of index cases to receive either 75 mg 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 and above

TABLE 6 *Oseltamivir for seasonal prophylaxis in healthy, unvaccinated adults: WV15673 and WV15697 (Hayden* et al.*, 1999[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% CI)
SLCI	WV15673	268	19	268	3	0.16 (0.04–0.47)
SLCI	WV15697	251	6	252	3	0.50 (0.06–1.55)
	Pooled (random effects)					0.27 (0.09– 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% CI)
SLCI	WV15825	272	12	276	1	0.08 (0.01†–0.63†)
SLCI (vaccinated subjects only)	WV15825	218	11	222	1	0.09 (0.01†–0.69†)

TABLE 8 *Oseltamivir for post-exposure prophylaxis in mixed households: WV15799 (Welliver* et al.*, 200149) and WV16193 (Hayden* et al.*, 200448)*

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% CI)
SLCI 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 effects)					0.19 (0.08–0.45) ($p = 0.15$, $I^2 = 52.9\%$)
SLCI 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 effects)					0.21 (0.08–0.58) ($p = 0.13$, $I^2 = 56.3\%$)

received the adult dose of 75 mg once daily, while dosing according to body weight is recommended in subjects aged less than 13 years. Although 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 among individual contacts of all index cases of 89% (95% CI 71–96, $p < 0.001$). For individual contacts of influenza-positive index cases only, the protective efficacy was also 89% (95% CI 67–97, $p < 0.001$). 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, while 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.*[48,73] and Belshe *et al.*[74] investigated the use of oseltamivir (75 mg once daily) in post-exposure prophylaxis in household contacts of index cases for 10 days versus expectant treatment, in which oseltamivir (75 mg twice daily) was administered for 5 days at 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% CI 47–86), 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% CI 35–84). 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 arm ($n = 10$) than in the expectant treatment arm ($n = 33$) [5.5 hours (0–87) versus 39.8 hours (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 4/402 (1.0%) in the expectant treatment arm. Nausea was more common in subjects receiving oseltamivir for post-exposure once daily than treatment twice daily (8% versus 7%). However, vomiting was more frequent in the expectant treatment arm (10% versus 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 RR among household contacts of all index cases was 0.19 (95% CI 0.08–0.45), equating to a protective efficacy of 81%. For contacts of influenza-infected index cases only, the corresponding pooled RR was 0.21 (95% CI 0.08–0.58) and the resulting protective efficacy was 79%. A pooled RR for withdrawals generated by the Assessment Group yielded an RR of 0.85 (95% CI 0.09–7.72), 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% CI 35–94) and an 80% reduction in infectiousness (95% CI 48–72). 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 SLCI divided by the number of contacts with laboratory-confirmed influenza infections (symptomatic or asymptomatic). Pathogenicity was lower among subjects treated with oseltamivir than among control subjects. In the study by Welliver *et al.*,[49] reported pathogenicity in the control group was 34/60 (57%) and in the oseltamivir group it was 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 it was 10/46 (22%); note that for this study, data for contacts with an influenza-positive index case only 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 transmitted not

TABLE 9 *Oseltamivir for post-exposure prophylaxis in paediatric household contacts (1–12 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% CI)
SLCI in contacts of all index cases	WV16193	111	21	104	7	0.36 (0.15–0.84)
SLCI in contacts of influenza-positive index cases	WV16193	74	18	55	6	0.45 (0.18–1.13)

from the index case but from a source external to the household setting.

In paediatric household contacts Clinical outcomes from the trial by Hayden *et al.*[48] were also reported separately for paediatric household contacts aged 1–12 years *(Table 9)*. It should be noted that this study allocated doses according to the child's age banding, rather than body weight, 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% (RR 0.36, 95% CI 16–85). When contacts of influenza-infected index cases only were included in the analysis, the protective efficacy dropped to 55% (RR 0.45, 95% CI –13 to 82). Vomiting was more common in the expectant treatment group (20% versus 10%). No children withdrew as a result of adverse events.

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

Prophylaxis with oseltamivir against experimentally-induced influenza

A single trial by Hayden *et al.*[67] 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 (RR 1.06,† 95% CI 0.83†–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 (RR 0.50,† 95% CI 0.10†–2.41†), while fever was observed in 1/19 (5%) and 2/20 (10%) in the oseltamivir and placebo groups respectively (RR 0.53,† 95% CI 0.05†–5.34†). No serious adverse effects were reported. Adverse effects related to study treatment occurred in 1/19 (5.3%) subjects in each group. No treatment-related adverse effects were observed during the off-treatment follow-up period.

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 subjects in both oseltamivir and placebo arms took 100% of the prescribed doses, 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.

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 below). [48,49,66,67]

Discussion

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 among the frail elderly living in residential care, among 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 trial[48] 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.[67]

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 GI adverse effects were marginally higher among the oseltamivir-treated subjects.[49,66]

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.[82–84] However, additional reports from Japan[85] and Europe[86] (including the UK) have demonstrated the emergence of oseltamivir-resistant strains of influenza A. Recent surveillance data[87] from within the UK have indicated that approximately 5% of influenza A (H1N1) isolates were oseltamivir resistant, but the HPA drew no conclusions with regard to the clinical significance of this finding, stating a requirement for the completion of further research before a judgement could be made. 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.

Zanamivir

Ten published articles presenting the results from eight 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 nine RCTs. The use of inhaled zanamivir only is considered within this assessment, hence trial arms in which doses of intranasal zanamivir were administered were excluded.

Seasonal prophylaxis with zanamivir

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

In healthy adults Study NAIA3005 reported by Monto *et al.*[70,71] evaluated the use of zanamivir in seasonal prophylaxis in healthy adults (*Table 10*) aged 18–64 years and demonstrated a 68%† protective efficacy against SLCI (95% CI 37†–83†). When the unvaccinated subjects were analysed as a subgroup, the protective efficacy was 60% (95% CI 24–80). 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 respectively. Potentially drug-related withdrawals were made in 1.3% of the placebo and 0.7% of the zanamivir groups. A conference abstract[71] presenting further information on the trial stated that significantly less time was lost from work in the zanamivir group (mean hours lost 1.4 hours versus 0.6 hours, $p = 0.001$). Total productive time lost was also less in the zanamivir group (1.8 hours 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 health-care 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 the zanamivir and placebo arms respectively in the 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 subjects and 1.3% in the placebo subjects were considered to be drug related. One serious adverse event, which was not judged to be drug related, occurred in a zanamivir-treated subject.

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] (*Table 11*). High risk was defined as being aged 65 years and above or having chronic pulmonary or cardiovascular disease or diabetes mellitus. For the intention-to-treat (ITT) population assessed for the development of SLCI during days 1–28 of prophylaxis, a protective efficacy of 83% was observed (RR 0.17, 95% CI 0.07–0.44, $p < 0.001$). For the per-protocol

TABLE 10 *Zanamivir for seasonal prophylaxis in healthy adults: NAIA3005 (Monto* et al.*, 1999[70]) and GSK study 167/101[44]*

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% CI, *p*-value if available)
SLCI	NAIA3005	554	34	553	11	0.32 (0.17†–0.63†)
SLCI in unvaccinated subjects only	NAIA3005	No data	No data	No data	No data	0.40 (0.20–0.76, $p = 0.004$)
SLCI in unvaccinated subjects only	GSK study 167/101	156	6	160	3	0.49 (0.12†–1.92,† $p = 0.3314$)

TABLE 11 *Zanamivir for seasonal prophylaxis in at-risk adults and adolescents (67–68% 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% CI, *p*-value if available)
SLCI in all cases	NAI30034	1685	23	1678	4	0.17 (0.07–0.44)
SLCI in vaccinated subjects	NAI30034	1141	6	1116	1	0.17 (0.02†–1.41†)
SLCI in unvaccinated subjects	NAI30034	544	17	562	3	0.17 (0.05†–0.58†)
SLCI in subjects with respiratory disease	NAI30034	695	17	684	3	0.18 (0.05†–0.61†)
SLCI in subjects with cardiovascular disease	NAI30034	307	1	331	0	Not estimable
SLCI in subjects with diabetes	NAI30034	370	3	359	0	Not estimable

population, this value dropped to 75% (RR 0.25, 95% CI 0.09–0.70, $p = 0.014$). Protective efficacies against the development of SLCI during days 2–28 and 3–28 of the prophylactic period were 81% and 80% respectively. Data were also presented by high-risk condition, with RR values calculable for a number of subgroups: subjects with respiratory disease (RR 0.18, 95% CI 0.05†–0.61†), subjects with cardiovascular disease (no events in the zanamivir group) and subjects with diabetes (no events in the zanamivir group). When presented according to age, the incidence of SLCI was lower in the zanamivir group than the 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 RRs of 0.17 (95% CI 0.02†–1.41†) and 0.17 (95% CI 0.05†–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 an RR of 0.12 (95% CI 0.02–0.73). Zanamivir was well tolerated, with no significant differences in total adverse effects between the two groups, with 51% in each group experiencing adverse effects (placebo: 851/1685, 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). In subjects with respiratory disease any adverse event was observed in 59% of each group (405/684 and 412/695 in the zanamivir and placebo arms respectively).[44] Subjects with cardiovascular disease for whom any adverse event was reported comprised 48% (159/331) and 49% (149/307) of the zanamivir and placebo arms respectively.[44] In diabetic subjects any adverse event was 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 commenced: 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 and 3.3 days in zanamivir-treated subjects,[44] mean values 0.4 days and 0.3 days in the placebo and zanamivir groups respectively demonstrating no significant differences between arms.[44] Median time to alleviation of symptoms was shorter in the zanamivir group than in the placebo group (2.5 days versus 4.0 days).

In the elderly Trial NAI30034[75] also evaluated the efficacy of zanamivir in seasonal prophylaxis in subjects aged 65 years and above (*Table 12*). 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 the zanamivir and placebo group subjects respectively, resulting in an RR of 0.20 (0.02†–1.72†). The proportion experiencing any adverse events was 53% in each group (498/946 and 501/950 in the zanamivir and placebo arms respectively).[44]

Post-exposure prophylaxis with zanamivir

In mixed households A total of four 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] and Kaiser *et al.*[72] and a report by Monto and colleagues[47] that was published subsequent to the cut-off date for inclusion of evidence in the original HTA review[10] (*Table 13*).

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 an RR of SLCI of 0.18 (95% CI 0.08†–0.39†). For individual contacts of influenza-positive index cases, the RR was 0.20 (95% CI 0.09†–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. Withdrawals for any reason were made in 5/423 (1.2%) and 3/414 (0.7%) of subjects in the placebo and zanamivir groups. One withdrawal due to adverse effects was made in the zanamivir group while none was made in the placebo group. 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 group and 5.5 days in the zanamivir group. 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, while index cases in the placebo arm received placebo treatment.

Trials NAIA2009 and NAIB2009, performed by Kaiser *et al.*[72] 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 RR for developing SLCI was 0.33 (95% CI 0.09†–1.21†) and during the 10 days after initiation of medication, the RR for SLCI was 0.36 (95% CI 0.12†–1.12†). Length of illness was shorter in the zanamivir group than in the placebo group (mean duration of significant influenza-like symptoms 0.2 days versus 0.6 days, $p = 0.016$).

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% CI, *p*-value if available)
SLCI in subjects aged 65 and above	NAI30034	950	5	946	1	0.20 (0.02†–1.72†)

TABLE 13 *Zanamivir for post-exposure prophylaxis in mixed households: NAI30010 (Hayden* et al.*, 2000[45]), NAIA/B2009 (Kaiser* et al.*, 2000[72]) 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% CI, *p*-values if available)
SLCI 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 effects)					0.21 (0.13–0.33) ($p = 0.72$, $I^2 = 0\%$)
SLCI in contacts of influenza-positive index cases	NAI30010	215	33	195	6	0.20 (0.09†–0.47†)
SLCI in contacts of influenza-positive index cases	NAI30031	398	51	368	9	0.19 (0.10†–0.38†)
	Pooled (random effects)					0.19 (0.11–0.33) ($p = 0.93$, $I^2 = 0\%$)

Potentially drug-related adverse effects occurred in 17% (25/144) of the placebo group and 19% (27/144) of the zanamivir group, and comprised 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,[46] protective efficacy for individual contacts was 79%† (95% CI 62†–89†; RR 0.21) in the ITT population (when calculated by the Assessment Group) and 81%† among individual contacts of influenza-positive index cases (95% CI 62†–90†; RR 0.19). Index cases did not receive treatment. For influenza A, the protective efficacy was 79% (95% CI 55–90; RR 0.21), and for influenza B, the reported protective efficacy was 87% (95% CI 64–95; RR 0.13). However, when calculated by the Assessment Group, the protective efficacy against influenza B was 79%† (95% CI 46†–92†; RR 0.21). The authors observed that, in some cases, there was a 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 group and 42% of the zanamivir group. Adverse events considered by the investigators to be drug related were observed in 7% of placebo subjects and 6% of zanamivir subjects. Total withdrawals were made in 1.7% (11/630) of the placebo subjects and 0.9% (6/661) of the zanamivir subjects. No withdrawals were due to adverse events.

In contacts with SLCI from the zanamivir-treated group, the median time to alleviation of symptoms (5 days) was reduced by 1.5 days, from 6.5 days in the placebo group, demonstrating milder disease.[47] 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

1-day difference in the mean time confined to bed/incapacitated per household between treatment arms (1.8 days versus 2.6 days, $p = 0.053$).

Additional data relating to trial NAI30031 were identified from the sponsor submissions.[43] 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 1 day and another for more than 5 days. The numbers were too low to make a meaningful comparison.

The need for non-prescription medications in households randomised to zanamivir was lower in subjects receiving zanamivir versus placebo (13% zanamivir versus 19% placebo, $p = 0.076$). The number of households requiring prescription medications was also lower (11% of zanamivir subjects versus 17% of placebo subjects, $p = 0.100$). Significantly fewer households receiving zanamivir required additional health-care contacts (20% of zanamivir subjects versus 32% of placebo subjects, $p = 0.004$). Among 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% [RR 0.21, 95% CI 0.13–0.33 (test of heterogeneity: $p = 0.72$, $I^2 = 0$)]. The trial reported by Kaiser *et al.*[72] differed from the trials by Hayden *et al.*[46] and Monto *et al.*[47] 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.*[72] were removed, the RR decreased to 0.20 (95% CI 0.12–0.32), 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 NAI30010[46] and NAI30031[47] were pooled, an RR of 0.19 (95% CI 0.11–0.33) 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% CI 54–86) and a reduction in infectiousness of 19% (95% CI –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 SLCI divided by the number of contacts with laboratory-confirmed influenza infections (symptomatic or asymptomatic). Pathogenicity was lower among subjects treated with zanamivir than among those in the placebo group. In the study reported by Hayden *et al.*,[46] pathogenicity in the control group was reported as 40/66 (61%) while in the zanamivir group it was 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.

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.[76–78]

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 two 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 subjects and 34% of zanamivir subjects. Withdrawals from the study due to adverse events occurred at rates of 0/13 in the placebo arm and 2/238 (0.8%) in the zanamivir arm. 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 (*Table 14*). During influenza A outbreaks, prophylaxis conferred a 32%† protective efficacy against SLCI as calculated by the Assessment Group (95% CI –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% CI 13–89) was observed for laboratory-confirmed febrile illness. When subjects who became ill on days 1 or 2 were excluded, the protective efficacy against SLCI as calculated by

TABLE 14 *Zanamivir in outbreak control in elderly subjects in long-term care: NAIA3004 (Ambrozaitis* et al.*, 2005)[76,77] (9–10% 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% CI)
SLCI	NAIA3004	249	23	240	15	0.68† (0.36†–1.27†)

the Assessment Group was 35%† (95% CI –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 than in the placebo group, although this difference was not statistically significant (5% versus 6%, $p = 0.653$). Respiratory tract infections occurred in fewer subjects in the zanamivir arm (3% versus 6%), as did complications requiring antibiotics (2% versus 3%, $p = 0.445$). Withdrawals from the study due to adverse events were reported as 1/249 (0.4%)in the placebo arm and 2/240 (0.8%) in the zanamivir arm. Early discontinuation of medication due to adverse events occurred in 2/249 (0.8%) and 6/240 (2.5%) of the placebo and zanamivir subjects respectively. The following additional data were identified in the sponsor submissions.[44] Drug-related adverse effects were slightly higher in the zanamivir-treated arm [16/242 (7%)] than in the placebo arm [14/252 (6%)]. Serious adverse events occurred in 6/252 (2.4%) of placebo subjects and 6/242 (2.5%) of zanamivir subjects. There were no serious adverse events that were considered to be related to the study drug. Adverse events during prophylaxis in high-risk subjects were lower in the zanamivir group than in the placebo arm [64/202 (32%) versus 80/215 (37%)]. Subjects with high-risk respiratory conditions also experienced fewer adverse events when receiving zanamivir than did their placebo counterparts [(30/83 (36%) versus 32/80 (40%)].

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.

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 23–28 day period.[70] In another study, 90% of zanamivir subjects and 89% of placebo subjects took at least 24 doses for at least 24 days, with fewer than 1% requiring assistance in 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 the study drug.[46] In the studies by Ambrozaitis *et al.*[76,77] and Gravenstein *et al.*,[78] undertaken in the elderly, subjects who missed two or more consecutive days of medication were considered non-compliant. These proportions were very low, at 1% of total participants[76] and 2% or less of total participants.[77]

Viral resistance to zanamivir

Several trials tested viral isolates for their susceptibility to zanamivir.[46,75,76,77] No evidence of resistance to zanamivir was observed, although rimantadine-resistant variants were reported by Gravenstein *et al.*[78]

Discussion

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; protective efficacy 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 among 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.

TABLE 15 *Summary of efficacy of interventions in prophylaxis against symptomatic, laboratory-confirmed influenza (SCLI)*

	Relative risk of developing SCLI (95% CI)		
Prophylactic strategy	**Amantadine**	**Oseltamivir**	**Zanamivir**
Seasonal prophylaxis			
In healthy children	Dosage not established in children	NDA	NDA
In at-risk children	Dosage not established in children	NDA	NDA
In healthy adults	0.40 (0.08–2.03)[56] (from one trial)	0.27 (0.09–0.83)[66] (pooled estimate from two trials as reported by Assessment Group)	0.32 (0.17–0.63)[70] (from one trial)
In at-risk adults and adolescents	NDA	NDA	0.17 (0.07–0.44)[75] (from one trial)
In healthy elderly subjects	No data reported[55]	NDA	0.20 (0.02–1.72)[75] (from one trial)
In at-risk elderly subjects	No data reported[55]	0.08 (0.01–0.63)[63] (98% subjects with concomitant disease; from one trial)	0.20 (0.02–1.72)[75] (from one trial)
Post-exposure prophylaxis			
In mixed households	NDA	0.19 (0.08–0.45)[48,49] (from two trials)	0.21 (0.13–0.33)[46,47,72] (from three trials)
In healthy children	Dosage not established in children	0.36 (0.15–0.84)[48] (from one trial)	NDA
In at-risk children	Dosage not established in children	NDA (subjects with a number of chronic conditions excluded)[47]	NDA
In healthy adults and adolescents	0.10 (0.03–0.34)[59] (from one trial)	NDA	NDA
In at-risk adults and adolescents	NDA	NDA	NDA
In healthy elderly subjects	NDA	NDA	NDA
In at-risk elderly subjects	NDA	NDA	0.68 (0.36–1.27)[76] (subjects 85% at risk of complications)

NDA, subgroup categories for which no data were available.

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 in mixed households. Zanamivir was also shown to prevent influenza, most notably in seasonal prophylaxis among 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 among trials. However, no clear trends for the higher incidence of adverse events in treatment groups than in 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 or 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. While 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 HRQoL 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 on the use of the interventions in clinical practice.

Chapter 4
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 below. The methods and results of the Assessment Group model are presented in Independent economic assessment (p. 61) and Cost-effectiveness results (p. 84) respectively.

Systematic review of existing cost-effectiveness evidence

Methods

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 3 (see Methods for reviewing effectiveness, p. 17, and Appendix 1). Economic evaluations identified for inclusion in the review were also handsearched to identify other relevant cost-effectiveness studies of influenza prophylaxis that were not identified by the electronic searches. Alongside published economic evaluations, manufacturers' submissions to NICE, where available, were also included in the review of economic evaluations. Appraisal of study quality was undertaken based on checklists for assessing quality in economic evaluations[89] and mathematical models.[90]

Results

Studies included in the review of cost-effectiveness

The systematic searches identified 580 citations of studies relating to the cost-effectiveness of amantadine, oseltamivir and zanamivir in 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 3 (see Inclusion and exclusion criteria, p. 17). 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*.

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

Review of existing economic evaluation studies

Roche submission to NICE

The Roche submission to NICE[20] 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 simulating anti-influenza value and effectiveness (SAVE) 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 with 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 > 12 years), children aged 1–12 years and children aged 1–5 years. 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 licensed only 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

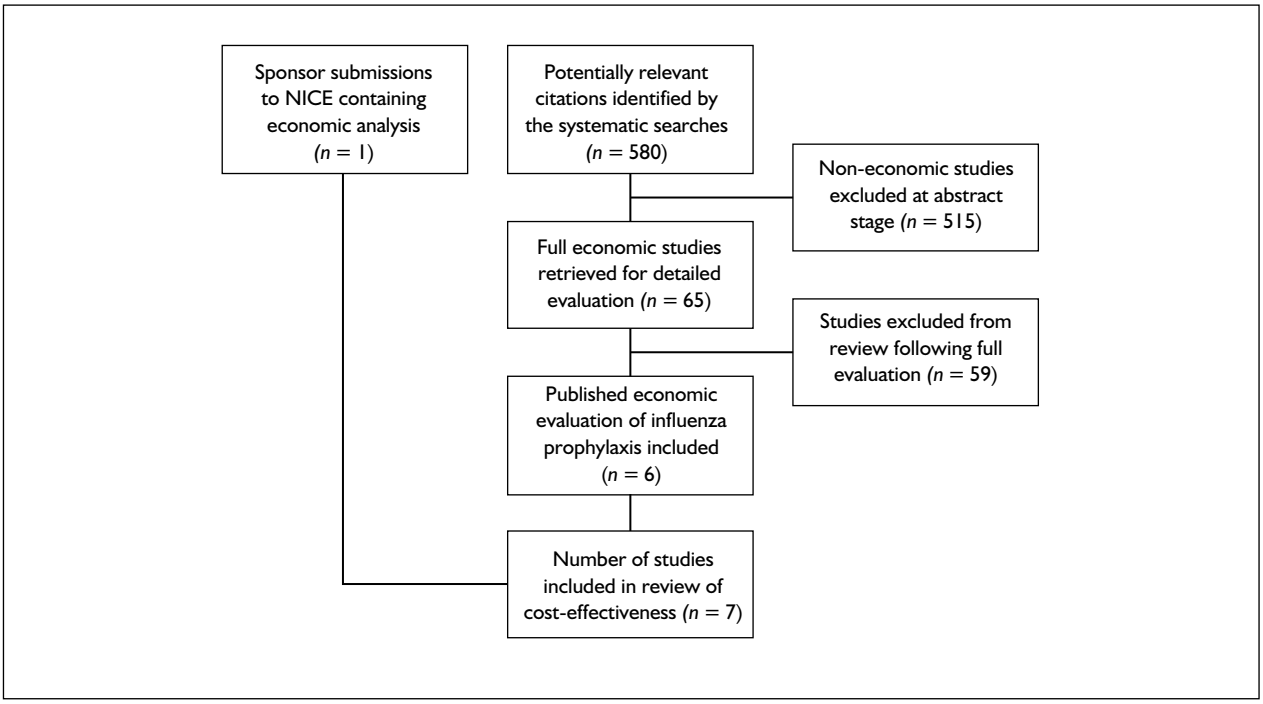

FIGURE 4 *Details of study inclusions and exclusions.*

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 quality-adjusted life-years (QALYs) lost as a result of premature death due to ILI. Cost-effectiveness is expressed in terms of the incremental cost per 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%; owing 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 (i.e. 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 3 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 on 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 some patients who had not been vaccinated.

The model uses a deterministic decision tree approach which is reported to be appropriate as it captures a 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 the impact of both true influenza and other ILI on costs and health outcomes.

DOI: 10.3310/hta13110

TABLE 16 *Characteristics of studies included in the cost-effectiveness review*

	Roche submission, 2007[20]	**Sander *et al.*, 2006[91]**	**Risebrough *et al.*, 2005[92]**	**Turner *et al.*, 2003[10]**	**Scuffham and West, 2002[93]**	**Demicheli *et al.*, 2000[94]**	**Patriarca *et al.*, 1987[95]**
Type of economic analysis	Cost–utility analysis	Cost-effectiveness analysis 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	Health-care 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) rimantadine chemoprophylaxis; (6) oseltamivir treatment; (7) rimantadine 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)

continued

TABLE 16 *Characteristics of studies included in the cost-effectiveness review (continued)*

	Roche submission, 2007[20]	**Sander *et al.*, 2006[91]**	**Risebrough *et al.*, 2005[92]**	**Turner *et al.*, 2003[10]**	**Scuffham and West, 2002[93]**	**Demicheli *et al.*, 2000[94]**	**Patriarca *et al.*, 1987[95]**
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 ≥ 13 years	Elderly vaccinated patients in long-term care facility	Healthy adults, children, residential care elderly, high-risk adults	Elderly patients (age > 65 years 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 ILI case avoided	Incremental cost per QALY gained; incremental cost per 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 ad hoc 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 ad hoc consultant for Hoffman–La Roche	Not reported

ILI, influenza-like illness; NI, neuraminidase inhibitor; QALY, quality-adjusted life-year.

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 his or her GP to receive prophylaxis or may do nothing. For the seasonal prophylaxis model, the individual may or may not have been in contact with an index case when prophylaxis is initiated. The model assumes that one household member can obtain prescriptions for three contacts in the household. Contact cases may or may not go on to develop ILI. Individuals who develop ILI may be treated using oseltamivir (at-risk populations only) or usual care. Individuals who develop ILI may or may not develop complications. 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 may 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 (Gavin Lewis, Head of Health Economics, Roche, personal communication). 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 was 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 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 CIs 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.*[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 200 mg, 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 3). 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 as 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 was sourced from Meier *et al.*[12] However, the submission states that the incidence of otitis media is likely to be under-reported by 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 by 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 the 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 HRQoL 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 visual analogue scale (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 (Gavin Lewis, Head of Health Economics, Roche, personal communication). In addition, the model includes the number of potential QALYs lost due to premature death resulting from 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 Monthly Index of Medical Specialties (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 cost 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, these costs being £68.88 without wastage and £81.80 when wastage is included (see Modelling resource use and costs associated with influenza and other ILI, p. 76). 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 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 intensive therapy unit (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 one-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 pairwise 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 reanalysed the results presented within the Roche submission to generate fully incremental estimates of the cost-effectiveness of each prophylactic option compared with each other and usual care. The results of the reanalyses of the post-exposure models are presented in *Tables 17–20*.

The results 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 that oseltamivir and zanamivir have equivalent preventative efficacy and no differential impact on HRQoL 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

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	£5800

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

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	£7980
Zanamivir	£139.34	108.683	–	–	Dominated by oseltamivir

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

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

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

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	£1955
Zanamivir	£123.60	85.159	–	–	Dominated by oseltamivir

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

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 reanalyses of the seasonal prophylaxis models are presented in *Tables 21–24*.

The reanalysis of the seasonal prophylaxis models presented in *Tables 21–24* suggests that the incremental cost-effectiveness of oseltamivir is expected to be around £46,000 per QALY gained for children aged 1–5 compared with best supportive care, and around £116,000 per QALY gained for children aged 1–12 compared with amantadine. As noted above, amantadine is licensed only in children aged over 10 years, hence this comparison can be considered valid only for children aged 11 or 12 years. Oseltamivir is expected to be dominated by zanamivir for otherwise healthy and at-risk individuals aged over 12 years. The Roche models suggest that prophylaxis using amantadine or zanamivir is likely to have a cost-effectiveness ratio 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 pairwise cost-effectiveness comparisons. The one-way sensitivity analysis was undertaken to explore the 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. Both the seasonal prophylaxis and 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 pairwise comparisons of oseltamivir versus amantadine and oseltamivir versus usual care. This is inappropriate as all options should be compared incrementally. A fully incremental reanalysis of uncertainty was not possible due to the structural limitations of the model (the model was capable of comparing only two prophylaxis options simultaneously). In addition, the submission states that pairwise 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 probabilities that oseltamivir has a cost-effectiveness ratio that is better than £20,000 and £30,000 per QALY gained compared with the next best comparator identified in the incremental reanalysis 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.

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 (i.e. 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 assumed willingness-to-pay threshold.

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

Sander *et al.*[91] present the methods and results of a cost-effectiveness and cost–utility analysis of oseltamivir as post-exposure prophylaxis from the perspective of the 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 by means of comparison with two alternatives: (1) no prophylaxis and no treatment and (2) no prophylaxis followed by treatment of ILI using

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

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

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

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

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

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

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	£6525.00
Zanamivir	£300.78	85.16	£213.85	0.014	£15,275.00
Oseltamivir	£301.21	85.16	–	–	Dominated by zanamivir

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

TABLE 25 *Probability that 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	1.00	1.00

NA, not applicable; QALY, quality-adjusted life-year.

TABLE 26 *Probability that 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 £20,000 per QALY gained	Probability cost-effective at £30,000 per QALY gained
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 in the deterministic analysis	NA	NA
At-risk individuals aged > 12 years	Dominated by zanamivir in the deterministic analysis	NA	NA

NA, not applicable; QALY, quality-adjusted life-year.

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 as a result of 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 because of their high incidence within the model population and 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 attributable 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.[48,49] The GP diagnostic certainty rate (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.[48,49] The model assumes that oseltamivir reduces the number of cases when

used prophylactically and the duration of disease when used as treatment. The model also assumes that while 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 with 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 efficacy rates demonstrated in the trial reported by Hayden *et al.*[48] (62%), which are not used in the base-case health economic analysis.

The model includes HRQoL 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 because of premature death from secondary influenza complications is similar to that reported by Turner *et al.*,[10] but certain underlying assumptions differ between the models. Patient HRQoL 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). Visual analogue scale scores were transformed into TTO index utilities using an algorithm based on econometric work undertaken by researchers at the University of York.[104] 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 (one life-year lost is assumed to equal one QALY lost). As noted above, this assumption is also applied in the Roche submission to NICE.[20] This assumption is highly optimistic, and favours the 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 occurred 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 is 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 health-care service utilisation'.[91] The impact of adverse events of treatment using oseltamivir, however, is 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 NAMCS.[101] This resource use relates to 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 ILI and secondary complications may not reflect those in the UK.

A number of sensitivity analyses were undertaken alongside the underlying probabilistic analysis. These included varying the ILI attack rate for contact cases, varying assumptions regarding health-care 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 post-exposure prophylaxis 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, while 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 were 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 of better than £30,000 is 50% compared with no prophylaxis and 10% compared with oseltamivir treatment.

Risebrough *et al.* – Economic evaluation of oseltamivir phosphate for post-exposure prophylaxis of influenza in long-term care facilities

Risebrough *et al.*[92] 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 because of difficulties in drug administration experienced by elderly patients. The primary health economic outcome for the analysis was reported to be the incremental cost per ILI case avoided compared with 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, while 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, 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 HRQoL 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 RCTs. The precise statistical methods used to derive this baseline attack rate (e.g. 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.[91] 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 rimantadine. Relative risk reductions in ILI incidence of 60% and 63% were assumed for amantadine and oseltamivir respectively. The authors assumed that 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 validity of this assumption. The model includes the possibility of patients withdrawing from therapy as a result of the incidence of adverse events.

The model includes acquisition costs for amantadine and oseltamivir, serum creatinine tests and oral antibiotics, as well as the cost 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, while the cost of oseltamivir was based on the manufacturer's wholesale price. Serum creatinine test costs were taken from the Ministry of Health 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.[106] Higher costs

were assigned to those complications that 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/worst-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 cost of nurse or pharmacist time to review the patient chart and to calculate the creatinine clearance. Finally, the cost-effectiveness of rimantadine was also explored in the sensitivity analysis. Probabilistic sensitivity analysis was not undertaken within this study.

In the base-case analysis, the study suggests that post-exposure prophylaxis using oseltamivir or amantadine is expected to reduce the incidence of ILI cases, hospitalisation and death compared with 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 rimantadine 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 compared with the amantadine and no prophylaxis options.

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

Turner *et al.*[10] 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.[107] The assessment report also evaluated the cost-effectiveness of treatment options for influenza A and B; however, these options are considered separately from 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 ILI. As treatments for influenza are evaluated separately from prophylaxis and vaccination options, the exclusion of ILI may be reasonable because costs and benefits in patients with ILI which is not true influenza are not expected to differ between prophylaxis options (and would therefore cancel each other 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 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 Practitioners (RCGP)[5] 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 in 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 is constant over the year, and is likely to represent the maximum theoretical impact of influenza over a season.[5]

The model includes HRQoL 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 in trials of oseltamivir for the treatment of influenza (studies WV15670, WV15671, WV15730, WV15819, WV15876, WV15978, WV15812 and WV15872). QALYs were derived by recalibrating Likert score data to VAS scores which were then converted into TTO scores.[104] QALY losses due to premature death were estimated on the basis of 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 EuroQol-5D (EQ-5D) profile. Adverse events resulting from the use of oseltamivir and zanamivir were assumed to have no impact on HRQoL. 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 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 Health-care 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 analyses surrounding the base-case model specification. This included varying assumptions in relation to 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 CIs surrounding the cost-effectiveness ratio; CEACs for prophylaxis are not presented in the report.

In the base-case analysis, 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 in the residential care population. The incremental cost-effectiveness ratio (ICER) 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. However, this is 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 less than 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 ICERs 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 less 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 an ICER 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 Europe

Scuffham and West[93] report the use of a decision model to estimate the ICER of six influenza control strategies compared with 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 rimantadine, treatment using oseltamivir and treatment using rimantadine. 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 percentage 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 HRQoL, hence complications appear to be included in the model only 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 a 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 RCGP 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, while 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 (NIs), specifically oseltamivir, reduce the incidence of influenza by 55%, while ion-channel inhibitors, specifically rimantadine, 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 heart failure, vaccination acquisition and administration costs, and antiviral prophylaxis and treatment. Unit costs were derived from the PSSRU,[111] national sources of hospitalisation data,[112] Department of Health publications on prescription costs[113] 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 resulting from 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-week 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 compared with no intervention. The cost per hospitalisation averted for oseltamivir is reported to be €114,774, while the cost per death averted is reported to be €657,544. The cost per morbidity day averted, excluding and including deaths, is reported to be €1198 and €373 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 in 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 healthy adults

Demicheli and colleagues[93] report the use of a 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 three ongoing Cochrane reviews; the results of these reviews led to marked changes in the scope of the 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'. Although the authors justify the exclusion of zanamivir from the analysis because of trials apparently including only 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. a 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 of 5.7 per 1000; while this value appears very low, incidence rates of up to 400 per 1000 were explored within the sensitivity analysis. The model does not include the possibility of a patient with symptomatic influenza presenting to a health-care 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 in 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 £2807, £9458, 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 homes

This study[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 with 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 or will not become ill. Patients who become ill 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. Respiratory complications only 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 1972–85. 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 in the effectiveness aspect of the model.

The model includes costs associated with vaccination, acquisition costs for amantadine prophylaxis and 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 multiway 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 on cost-effectiveness of changing the exposure rate to influenza viruses. 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 programme.[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 include only 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.

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

The economic models included in 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 submission[20] 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[10,20,91] 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 study[93] appears inappropriately to 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 his or her GP and assumptions regarding the treatment of secondary influenza-related complications, each of which has 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 where the impact of influenza on HRQoL has been incorporated into the analysis, this has been drawn consistently 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.

Independent economic assessment

Cost-effectiveness modelling methods

This section details the methods employed 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 modelling work undertaken by Turner *et al.*[10] in the previous assessment of oseltamivir, amantadine and zanamivir for the seasonal prophylaxis of influenza. Key differences between these models include the incorporation of NICE guidance on the use of NIs 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 3) and updated estimates of cost and health outcomes associated with influenza and other ILI-related complications.

Model scope

Interventions and comparators

The model evaluates the incremental costs and health outcomes of seasonal prophylaxis and post-exposure prophylaxis of influenza using amantadine, oseltamivir and zanamivir in comparison with 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. Although 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 in the economic model is the incremental cost per QALY gained. This is calculated for all non-dominated prophylactic options compared with the next most effective option. Options that 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 1 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 lost because of 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 that the duration of prophylaxis is assumed to be in line with licensed indications).

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 with each other and no prophylaxis. The model operates on the basis of ILI which includes true influenza as well as other illnesses that are clinically similar to influenza, e.g. 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 health-care 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 will develop 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 the 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 their HRQoL 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, he or she may seek medical treatment in either primary care (i.e. GP consultation) or secondary care [i.e. presenting at an accident and emergency (A&E) department]. If the patient presents with symptomatic ILI, he or she may be considered appropriate for treatment using oseltamivir or zanamivir (if the patient presents within 48 hours of developing ILI symptoms and is considered to

TABLE 27 *Description of prophylaxis options included in the health economic model of post-exposure prophylaxis*

Prevention strategy	Duration of prophylaxis (seasonal)	Duration of prophylaxis (post-exposure)	Dosage per day
Amantadine	42 days (21 days for patients who have previously been vaccinated)	10 days	100 mg
Oseltamivir[a]	42 days	10 days	75 mg
Zanamivir	28 days	10 days	10mg

a Oseltamivir dosage for children: < 15 kg: 30 mg, 15–23 kg: 45 mg, 23–40 kg: 60 mg, > 40 kg: 75 mg[14]

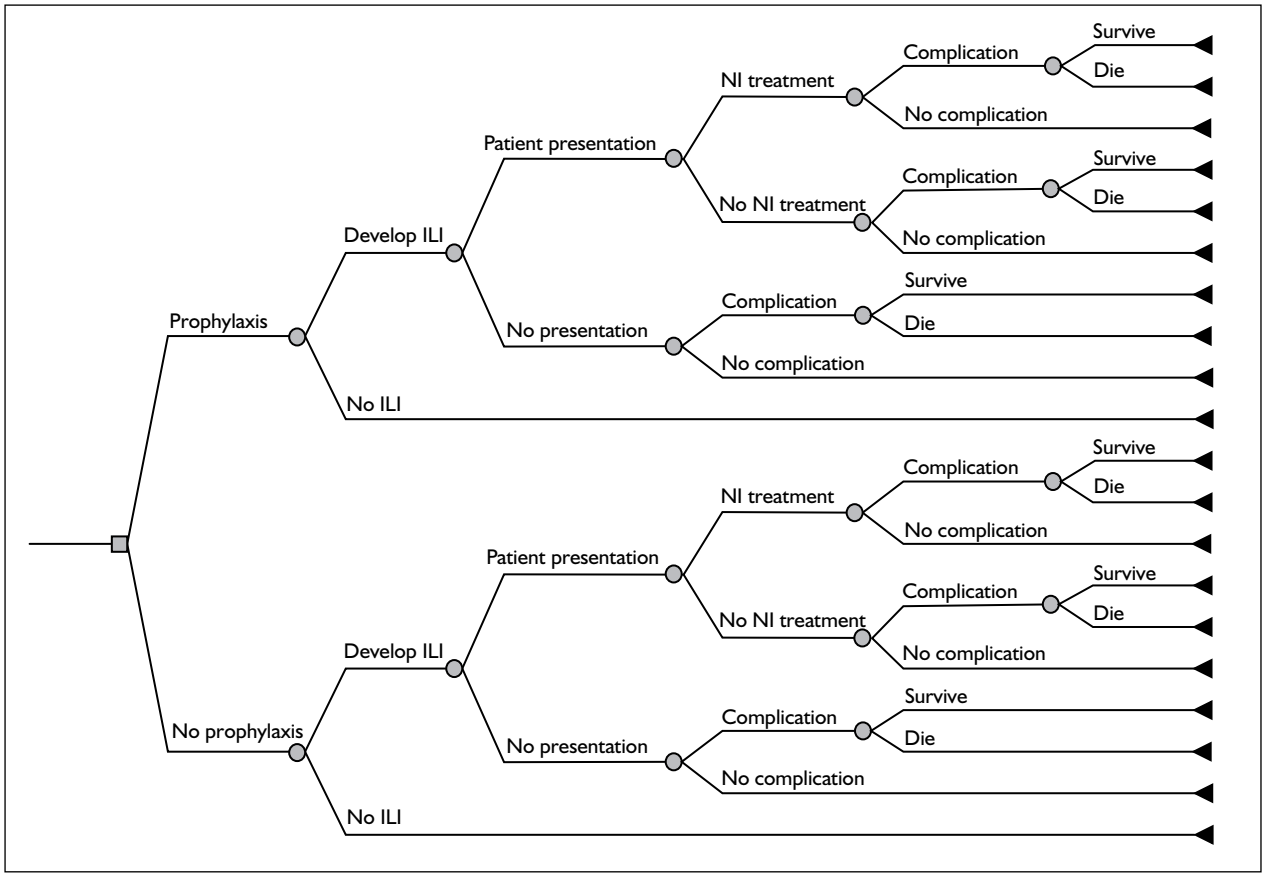

FIGURE 5 *Simplified decision-analytic model structure.*

be at risk of developing secondary complications of influenza).[116]

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, he or she is 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 NIs 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. Quality-adjusted life-year 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 differ in reality from those for other ILI such as RSV (this is a limitation in the use of the data from Meier *et al.*;[12] see Parameters relating to the onset of influenza and other ILI, below). 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 One-way/multiway sensitivity analysis and scenario analysis, p. 90). 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 Systematic review of existing cost-effectiveness evidence (p. 43).

- 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 or not this is due to influenza), 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 while 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 to 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 on a patient's HRQoL. 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 NI 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 health-care 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 One-way/multiway sensitivity analysis and scenario analysis, p. 90).
- The costs of diagnostic tests (blood tests, 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 One-way/multiway sensitivity analysis and scenario analysis, p. 90).
- The model includes only those health benefits accrued by patients receiving influenza prophylaxis; potential benefits accrued through decreased transmission of influenza as a result of the use of prophylaxis are not considered in the health economic model.
- A proportion of influenza cases are assumed to be resistant to amantadine. Although there is some evidence of resistance for the NIs, 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 One-way/multiway sensitivity analysis and scenario analysis, p. 90).

Model parameters

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

Event probabilities

Baseline influenza attack rate

The baseline influenza attack rate describes the probability that an individual will develop influenza over the influenza season. The model assumes that the probability of developing influenza differs among 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 3). 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.[46–49,72] 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*.

Probability that an ILI is influenza

The probability of developing ILI during the influenza season was not available from the literature. Instead, the model uses data provided by the 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 ILIs). 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 2003–4 to 2006–7 (Dr Alex Elliott, RCGP, personal communication). 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] they are shown in *Table 29*.

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 that influenza is influenza A

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

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 2002–3 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

TABLE 28 *Attack rates assumed within the model*

Type of prophylaxis	Age group	Number of 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

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

Season	Week	ILI consultation rate	Number of swabs	Number influenza A	Number influenza B	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
	52	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

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.

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
2006–7	168	2	170
2005–6	28	85	113
2004–5	76	29	105
2003–4	124	0	124
2002–3	20	20	40
2001–2	39	1	40
2000–1	35	93	128
1999–2000	77	0	77
1998–9	49	17	66
1997–8	58	1	59
1996–7	74	69	143
1995–6	75	0	75

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 1987–8 to 2006–7 were made available to the assessment team by the RCGP (Dr Alex Elliot, RCGP, personal communication). These data are shown in *Table 31*.

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 One-way/multiway sensitivity analysis and scenario analysis, p. 90). 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

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.[117–119] The model assumes that influenza vaccination and prophylaxis are effective against true influenza but not ILI and that inactive parenteral vaccines represent the mainstay of vaccination use in England and Wales.

The Cochrane reviews report the RR of experiencing influenza for vaccination versus placebo to be 0.36 (95% CI 0.28–0.48) in healthy children, 0.35 (95% CI 0.25–0.49) in healthy adults and 0.42 (95% CI 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 RRs 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 end points appear to relate to pneumonias, hospitalisations and deaths in 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 overestimate of the

TABLE 31 *Duration of influenza epidemic period*

Winter	Epidemic weeks	Consultation rate threshold used to estimate duration
1987–8	21	50 per 100,000 population
1988–9	10	50 per 100,000 population
1989–90	9	50 per 100,000 population
1990–1	11	50 per 100,000 population
1991–2	10	50 per 100,000 population
1992–3	10	50 per 100,000 population
1993–4	11	50 per 100,000 population
1994–5	12	50 per 100,000 population
1995–6	11	50 per 100,000 population
1996–7	13	50 per 100,000 population
1997–8	7	50 per 100,000 population
1998–9	8	50 per 100,000 population
1999–2000	7	50 per 100,000 population
2000–1	11	30 per 100,000 population
2001–2	7	30 per 100,000 population
2002–3	1	30 per 100,000 population
2003–4	9	30 per 100,000 population
2004–5	6	30 per 100,000 population
2005–6	3	30 per 100,000 population
2006–7	3	30 per 100,000 population

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 also be noted that vaccination status is incorporated 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 1 minus the RR 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

Estimates of the preventative efficacy of amantadine, oseltamivir and zanamivir in reducing SLCI were derived from evidence included in the systematic review of clinical effectiveness presented in Chapter 3. The model 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 prophylaxis using amantadine

The systematic review of clinical effectiveness presented in Chapter 3 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;[57,58] data relating to the relative protective benefit of amantadine compared with placebo was available only from the study reported by Reuman *et al.*[57] This study included healthy adults who had not been vaccinated; a mean RR of 0.40 (95% CI 0.08–2.03) 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 3); 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 3). 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 (as a result of 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 a duration of 10 days). Based on the event data reported in the clinical trial publication, the RR of amantadine versus placebo was estimated to be 0.10 (95% CI 0.03–0.34). Owing to a lack of any alternative evidence, this RR 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 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 2004–7. Resistance may occur in either strain; recent data suggest that amantadine resistance is considerably higher in the H3N2 strain. Based on the data for the 2006–7 influenza season, the model assumes that 37% of influenza A cases are resistant to amantadine. This proportion is a crude estimate based on the experience over a single influenza season and may vary considerably as resistance levels and the ratio of H3N2 and H1N1 strains vary from year to year.

Preventative efficacy of prophylaxis using oseltamivir

The systematic review of clinical effectiveness presented in Chapter 3 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;[64,66] one study[66] recruited healthy adults (unvaccinated), while the other trial recruited at-risk elderly subjects in a residential home (> 80% of 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, while 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 RR of developing influenza was estimated to be 0.24 (95% CI 0.10–0.58). Analysis of event data reported by Peters *et al.*[64] suggested an RR of developing influenza of 0.08 (95% CI 0.01–0.63). 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 RR used in the model was estimated to be 0.19 (95% CI 0.08–0.45). Importantly, within the two trials included in the meta-analysis one trial included paediatric and adult subjects[48] while the other included only adult subjects.[49] Owing to a paucity of alternative evidence, this RR was applied to all otherwise healthy and at-risk adult populations. In the paediatric population, the RR of developing influenza following oseltamivir post-exposure prophylaxis was modelled on the subgroup analysis reported by Hayden *et al.*;[48] the mean RR of developing influenza for children was 0.36 (95%

CI 0.16–0.80). This RR 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.[70,75] The study reported by Monto *et al.*[70] recruited healthy adults, the majority of whom were unvaccinated. The study reported by La Force *et al.*[74] 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 RR of developing influenza in healthy adults was estimated to be 0.32 (95% CI 0.17–0.63).[70] This estimate was applied to the otherwise healthy and at-risk children subgroups as well as to the healthy adult subgroup. Similarly, the RR of developing influenza in at-risk adults was estimated to be 0.17 (95% CI 0.06–0.50); this RR was applied to the at-risk adult working age subgroup.[75] The RR for the elderly populations was based on a subgroup analysis reported by LaForce *et al.*;[75] this RR was estimated to be 0.20 (95% CI 0.02–1.72).

The review identified three trials which reported the clinical efficacy of zanamivir versus placebo for the post-exposure prophylaxis of influenza in adults[72] and children and adults.[46,47] The RR of developing influenza in all subgroups receiving zanamivir was estimated using a random-effects meta-analysis of these three trials; the RR was estimated to be 0.21 (95% CI 0.13–0.33). 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 because of 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% CIs (shown in parentheses) used in the model are summarised in *Table 32*. The footnotes detail whether each RR is based on trial evidence relating exclusively to the model subgroup, trial evidence that includes the subgroup or trial evidence relating to other subgroups.

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 end-point 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 RRs of developing influenza for vaccination and prophylaxis was modelled using lognormal distributions; estimates of preventative efficacy were sampled from a normal distribution characterised by the logmean RR and the standard error of the log of the RR. 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.*,[76] sourced from an observational study of a 2-day work absence per 100 healthy adults as a result of influenza vaccination.[121] Although larger surveillance data sources are available [e.g. the vaccine adverse event reporting system (VAERS)], these tend to be insensitive in the identification of minor adverse events. Adverse events due to vaccination are assumed to be self-limiting, to require no treatment and to have no impact on HRQoL. However, the model does 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, while in other instances, rates were higher in the intervention groups (see Chapter 3). 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 event rates between amantadine, oseltamivir and zanamivir. In the absence of more robust

TABLE 32 *Summary of relative risk (RR) estimates and 95% confidence intervals used in the model*

Intervention	Healthy children	At-risk children	Healthy adults	At-risk adults	Healthy elderly	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 RR based on clinical trial evidence relating exclusively to model subgroup.
b RR based on clinical trial evidence which includes model subgroup and other subgroups.
c RR based on clinical trial evidence from other model subgroups (equal effectiveness assumed).
NB It is unclear whether elderly individuals were represented within the trials included in the meta-analysis of zanamivir post-exposure prophylaxis.

estimates from the trials included in the systematic review (see Chapter 3), 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 NIs are self-limiting, incur no treatment cost and have no impact on HRQoL. There is evidence, however, that amantadine can result in severe neuropsychiatric adverse events 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 5 days, based on the analysis reported by Turner *et al.*[10] The model assumes that 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, while 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 3), 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.

Parameters relating to the onset of influenza and other influenza-like illnesses

Probability of an individual with ILI presenting symptomatically

There is considerable uncertainty surrounding the probability that an individual with ILI will consult a health-care 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.[112] The use of these data implies the assumption that all excess GP consultations over the influenza season compared with the baseline rate are due to influenza. The validity of this assumption is questionable,[122] as other ILIs 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 will present 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 One-way/multiway sensitivity analysis and scenario analysis, p. 90).

Probability of an individual presenting 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 of an individual presenting 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 was modelled using beta distributions based on the empirical data reported by Ross *et al.*[123]

Probability that an individual presenting within 48 hours is prescribed an NI for the treatment of ILI

In line with current recommendations from NICE concerning the use of NIs 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% of patients receive oseltamivir, based on data reported within the 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 is not reported in detail within clinical trials of influenza prophylaxis (see Chapter 3). 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 in the GPRD in the period 1991–6. A total of 141,293 patients in 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*.

Data concerning complication rates for the predisposed group were assumed to represent the at-risk populations within the model. Complication rates among 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, while 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 compounded further 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 NIs 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 reappraisal 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 NIs 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 lead to a modest reduction in the impact of influenza on quality of life compared with best symptomatic care alone. The model assumes an odds ratio for all complications for zanamivir versus no treatment of 0.49 (95% CI 0.23–1.04) in all at-risk populations, while the odds ratio for complications for oseltamivir versus no treatment is assumed to be 0.65 (95% CI 0.43, 0.97) in the at-risk paediatric population and 0.40 (95% CI 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; owing 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 is shown in *Table 34*.

As noted in Model structure (above), 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.

TABLE 33 *Incidence of influenza-like illness 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	1697	520	4530	1337	1106	604	819	754
Bronchitis	113	21	748	203	309	167	273	256
Pneumonia	29	9	185	35	52	27	106	97
URTI	1470	302	3502	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	2311	650	5185	1472	1252	670	981	936
Total complications	2417	676	5270	1502	1274	680	1049	1019
Complications per patient	1.05	1.04	1.02	1.02	1.02	1.01	1.07	1.09
Number in group	17,201	3695	69,231	12,195	16,017	5402	10,145	7407
Total cases in age group	20,896		81,426		21,419		17,552	

CNS, central nervous system; GI, gastrointestinal; URTI, upper respiratory tract infection.

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

	Odds ratios (and 95% CIs) for reduction in complications	
Population	**Odds ratio for zanamivir**	**Odds ratio for oseltamivir**
Healthy children	0.70 (0.52–0.96)	0.65 (0.43–0.97)
At-risk children	0.49 (0.23–1.04)	0.65 (0.43–0.97)
Healthy adults	0.70 (0.52–0.96)	0.40 (0.16–0.93)
At-risk adults	0.49 (0.23–1.04)	0.40 (0.16–0.93)
Healthy elderly	0.70 (0.52–0.96)	0.40 (0.16–0.93)
At-risk elderly	0.49 (0.23–1.04)	0.40 (0.16–0.93)

Probability of receiving antibiotics

The model assumes that antibiotics may be prescribed for both 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, 0.42 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 healthy 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*.

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 RTIs reported within a meta-analysis of 10 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 10 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 subdivided further 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.

TABLE 35 *Probability of antibiotic use for influenza-like illness-related complications[12]*

	Patients without complications		Patients with complications	
Age group	**Number receiving antibiotics**	**Number in group**	**Number receiving antibiotics**	**Number in group**
1–14 years	2183	3093	4997	17,910
15–64 years	6983	8726	39,622	94,338
> 65 years	1527	2068	8544	15,620

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 with 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*.

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 is assumed to be 100 mg and 10 mg respectively for all populations. The cost of prophylaxis and treatment using oseltamivir for children assumes a mean body mass of between 23 kg and 40 kg. 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 (Dr Andrew Ross, RCGP, personal communication). 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*.

In the base-case analysis, the model assumes that each prescription of prophylaxis requires a GP consultation. The model assumes also 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 One-way/multiway sensitivity analysis and scenario analysis, p. 90).

TABLE 36 *Probability of death due to influenza and ILI-related complications*[12]

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

TABLE 37 *Acquisition cost per course of antiviral prophylaxis and treatment*

	Seasonal prophylaxis		Post-exposure prophylaxis		Treatment	
Drug	**Adults**	**Children**	**Adults**	**Children**	**Adults**	**Children**
Amantadine prophylaxis (unvaccinated)	£14.40	£14.40	£4.80	£4.80	NA	NA
Amantadine prophylaxis (previously vaccinated)	£9.60	£9.60	£4.80	£4.80	NA	NA
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

NA, not applicable.

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 (*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 Curtis and Netten.[102] A GP visit is assumed to cost £25. As these costs are common to all patients receiving vaccination, these parameters have no impact on the incremental cost-effectiveness of influenza prophylaxis.

Cost of ILI presentation

The model assumes that patients present with symptomatic ILI either to their GP (in the surgery or at home) or at an A&E 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 patients aged under 75 and those 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 (Dr Andrew Ross, RCGP, personal communication). The proportion of home visits was low in the paediatric and adult populations (5% and 8% respectively); the proportion was considerably higher in the elderly

TABLE 38 *Unit costs of inactivated influenza vaccines*[14]

Product	Type of vaccine	Unit cost
Inactivated influenza vaccine[a]	Suspension of formaldehyde-inactivated influenza virus (split virion)	£6.29
Inactivated influenza vaccine[a]	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 subunit®	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

a Non-proprietary vaccine product.

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 A&E departments was based on clinical opinion (Professor Robert Read, University of Sheffield, personal communication); the model assumes that 3% of patients present to A&E (range 1–5%). 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 PSSRU[102] while the cost of an A&E consultation was derived from the NHS reference costs.[125] The model assumes that a GP surgery consultation costs £25,[102] a home visit costs £69[102] 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]

Cost 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.

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

The cost of hospitalisation for serious complications 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 interquartile 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 lengths 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*.

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 intensive care unit (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 £1345.39 (Critical care level 2 code TCCS CC1L2).

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

TABLE 39 *Mean length of hospital stay assumed for patients experiencing ILI-related complications*

Population	Mean length of stay (days)	Assumed standard error
Healthy children	2.3	3
At-risk children	2.3	3
Healthy adults	11.9	3
At-risk adults	11.9	3
Healthy elderly	15	3
At-risk elderly	15	3

(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 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 direct evaluation of the impact of the prophylaxis or disease on 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 HRQoL employed within the model should be treated 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-5D[127] or the Health Utilities Index, mark III (HUI3)[128] 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[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 Review of exisiting economic evaluation studies, p. 43). The expected QALY loss due to an episode of influenza was estimated using data collected in 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 employed was similar to a VAS, using a lower anchor which had a score of 0 describing 'worst possible health' and an upper anchor which had a score of 10 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 Measurement and Valuation of Health (MVH) study.[105] The VAS equivalent data were then converted into TTO utility scores based on a VAS–TTO transformation algorithm reported by the MVH group.[105] Turner *et al.*[10] assumed that missing values resulted from 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 loss 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 HRQoL is equivalent to that for oseltamivir. Data were not available for the paediatric population; therefore, the model assumes the same QALY loss as in 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.

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 7 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 HRQoL.

Systematic searches were undertaken to identify studies reporting preference-based valuations of the impact of influenza, ILI and related complications on HRQoL (see Appendix 1). The searches did not identify any published studies that reported preference-based valuations of the impact of the range of ILI complications associated with influenza and ILI (bronchitis, pneumonia, otitis media and exacerbation of an underlying

TABLE 40 *Mean quality-adjusted life-year (QALY) gains over 21-day period*

Population	Oseltamivir mean QALY	Placebo mean QALY
Healthy children	0.042	0.041
At-risk children	0.030	0.028
Healthy adults	0.042	0.041
At-risk adults	0.030	0.028
Healthy elderly	0.030	0.028
At-risk elderly	0.030	0.028

TABLE 41 *Utility scores associated with ILI-related complications*

Parameter	Committee HUI values	Mean decrement from baseline	Assumed lower 95% CI	Assumed upper 95% CI
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

HUI, Health Utilities Index.

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 HUI (mark II) scores were derived for a number of health states associated with influenza and ILI (*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.

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 simply by calculating the number of days between the onset of the complication and its resolution (Gavin Lewis, Roche, personal communication). 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 was 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 is assumed to be the same as that for respiratory complications. *Table 42* shows the assumed durations for these reductions in HRQoL.

QALYs lost due to premature death resulting from ILI complications

The expected number of QALYs lost due to premature death resulting from secondary complications of ILI was 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 (ONS; 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 lost were discounted at a rate of 3.5%. It should be noted that while 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 be biased 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]

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.

TABLE 42 *Assumed duration of utility reductions*

	Respiratory and other complications		Otitis media	
Population	**Mean duration (days)**	**Assumed standard error**	**Mean duration (days)**	**Assumed standard error**
Healthy children	7.89	3.00	9.36	3.00
At-risk children	8.07	3.00	9.36	3.00
Healthy adults	9.23	3.00	9.36	3.00
At-risk adults	10.65	3.00	9.36	3.00
Healthy elderly	10.88	3.00	9.36	3.00
At-risk elderly	10.87	3.00	9.36	3.00

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

QALY, quality-adjusted life-year.

Uncertainty analysis

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 One-way/multiway sensitivity analysis and scenario analysis, p. 90). 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 (five disks, four blisters per disk); the new proposed price for zanamivir is £16.36 (Toni Maslen, Health Outcomes Programme Leader, GSK, personal communication). This proposed price reduction for zanamivir was approved by the Department of Health with effect from 1 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 in this analysis are the same as those in the base-case analysis presented in Central estimates of cost-effectiveness (see below). 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 on 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 10×75 mg tablets providing 750 mg of the drug (10 doses) while a 75 ml bottle (60 mg/5 ml) of oseltamivir in suspension form provides a total of 900 mg of the drug (12 doses of 75 mg). While 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 four prescriptions may be obtained per individual, 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 an RR for vaccination of 0.50, while scenario 6 assumes an RR 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 that 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 0.

Sensitivity analyses 12–16: resistance against oseltamivir

The base-case model assumes that resistance to oseltamivir is 0. 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 in each model subgroup.

Sensitivity analysis 18: higher attack rates

This scenario assumes that the attack rate is double that of the base case 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 ILI consults a health-care 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 losses 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. 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.

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 (5000 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 Probabilistic sensitivity analysis results (p.102), Appendix 10 and Appendix 11].

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 was reviewed by clinical experts and compared with assumptions used in 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.

Cost-effectiveness results

This section presents the results of the cost-effectiveness analysis of amantadine, oseltamivir and zanamivir for the prevention of influenza. The central estimates of cost-effectiveness for each of the six model subgroups with and without previous influenza vaccination are presented below. As noted in Calculation of cost-effectiveness (see above), all central estimates of cost-effectiveness are based on expected costs and health outcomes generated by the stochastic model. The next section, One-way/multiway sensitivity analysis and scenario analysis (see p. 90), 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. The subsequent section, Probabilistic sensitivity analysis results, presents the results of the probabilistic sensitivity analysis using CEACs.

Central estimates of cost-effectiveness

Seasonal prophylaxis model results

Tables 44–49 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

The model results presented in *Table 44* suggest 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 QALY losses avoided compared with 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 by 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

TABLE 44 *Cost-effectiveness of seasonal prophylaxis – healthy children*

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

TABLE 45 *Cost-effectiveness of seasonal prophylaxis – at-risk children*

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

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 compared with no prophylaxis is estimated to be approximately £129,000 per QALY gained.

Group 2: at-risk children

The model results presented in *Table 45* suggest that the most effective seasonal prophylaxis option for at-risk children is oseltamivir irrespective of whether or not they have been previously vaccinated. Again, zanamivir is expected to be less effective and more expensive than oseltamivir, hence it is ruled out of the analysis by simple dominance. Amantadine is expected to be ruled out of the analysis by extended dominance (again oseltamivir has a more favourable cost-effectiveness ratio). The incremental cost-effectiveness of oseltamivir compared with 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.

TABLE 46 *Cost-effectiveness of seasonal prophylaxis – healthy adults*

Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Unvaccinated individuals					
No prophylaxis	£6.63	0.0020	–	–	–
Amantadine	£46.49	0.0019	–	–	Extendedly dominated
Zanamivir	£103.70	0.0015	–	–	Extendedly dominated
Oseltamivir	£111.09	0.0013	£104.45	0.0007	£147,505
Previously vaccinated individuals					
Amantadine	£71.34	0.0014	–	–	Dominated
No prophylaxis	£35.64	0.0014	–	–	Dominates
Zanamivir	£133.74	0.0012	–	–	Extendedly dominated
Oseltamivir	£141.6	0.0011	£105.9	0.0002	£427,184

TABLE 47 *Cost-effectiveness of seasonal prophylaxis – at-risk adults*

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

Group 3: healthy adults

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 by extended dominance, while for vaccinated healthy adults amantadine is expected to be dominated by no prophylaxis. The incremental cost-effectiveness of oseltamivir compared with 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

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 by extended dominance, while 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 compared with 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.

TABLE 48 *Cost-effectiveness of seasonal prophylaxis – healthy elderly*

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

TABLE 49 *Cost-effectiveness of seasonal prophylaxis – at-risk elderly*

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

Group 5: healthy elderly

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 by extended dominance for unvaccinated individuals, and is dominated by no prophylaxis in vaccinated populations. The incremental cost-effectiveness of oseltamivir compared with 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

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 with 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.

Post-exposure prophylaxis model results

Tables 50–55 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

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

The cost-effectiveness results presented in *Table 51* suggest that zanamivir is expected to be the most

TABLE 50 *Cost-effectiveness of post-exposure prophylaxis – healthy children*

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

TABLE 51 *Cost-effectiveness of post-exposure prophylaxis – at-risk children*

Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Unvaccinated individuals					
No prophylaxis	£32.56	0.0118	–	–	–
Amantadine	£57.55	0.0097	–	–	Extendedly dominated
Oseltamivir	£63.97	0.0082	–	–	Extendedly dominated
Zanamivir	£69.76	0.0073	£37.20	0.0045	£8233
Previously vaccinated individuals					
No prophylaxis	£53.57	0.0081	–	–	–
Amantadine	£82.44	0.0074	–	–	Extendedly dominated
Oseltamivir	£91.35	0.0068	–	–	Extendedly dominated
Zanamivir	£98.67	0.0065	£45.10	0.0016	£27,684

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 by extended dominance for unvaccinated and vaccinated subgroups. The incremental cost-effectiveness of zanamivir versus no prophylaxis is estimated to be around £8000 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 £9000 per QALY gained for unvaccinated at-risk children and around £29,000 per QALY gained for vaccinated at-risk children.

Group 3: healthy adults

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 by 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

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 by 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

Table 54 suggests 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 by 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

TABLE 52 *Cost-effectiveness of post-exposure prophylaxis – healthy adults*

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

TABLE 53 *Cost-effectiveness of post-exposure prophylaxis – at-risk adults*

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

gained for at-risk elderly who have previously been vaccinated against influenza.

Group 6: at-risk elderly

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 by extended dominance. The incremental cost-effectiveness of oseltamivir versus no prophylaxis is estimated to be around £8000 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.

One-way/multiway sensitivity analysis and scenario analysis

This section presents one-way and multiway sensitivity analysis to explore the impact of changing parameter assumptions on the incremental cost-effectiveness of amantadine,

TABLE 54 *Cost-effectiveness of post-exposure prophylaxis – healthy elderly*

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

TABLE 55 *Cost-effectiveness of post-exposure prophylaxis – at-risk elderly*

Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Unvaccinated individuals					
No prophylaxis	£22.88	0.0106	–	–	–
Amantadine	£50.05	0.0089	–	–	Extendedly dominated
Zanamivir	£63.68	0.0065	–	–	Dominated
Oseltamivir	£55.33	0.0065	£32.45	0.0041	£7866
Previously vaccinated individuals					
No prophylaxis	£47.50	0.0076	–	–	–
Amantadine	£76.92	0.0070	–	–	Extendedly dominated
Zanamivir	£93.37	0.0059	–	–	Dominated
Oseltamivir	£85.11	0.0058	£37.60	0.0017	£21,608

oseltamivir and zanamivir for the prevention of influenza. Descriptions of these scenarios are presented in Uncertainty analysis (p. 82).

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

Tables 56–67 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

Results for seasonal prophylaxis are presented in *Tables 56–61*.

Post-exposure prophylaxis

Results for post-exposure prophylaxis are presented in *Tables 62–67*.

TABLE 56 *Cost-effectiveness of seasonal prophylaxis – healthy children*

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

TABLE 57 *Cost-effectiveness of seasonal prophylaxis – at-risk children*

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

Table 68 summarises the ICERs presented in the base-case analysis and those including the proposed reduction in the price of zanamivir.

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 by 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-

TABLE 58 *Cost-effectiveness of seasonal prophylaxis – healthy adults*

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

TABLE 59 *Cost-effectiveness of seasonal prophylaxis – at-risk adults*

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

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 £8000 per QALY gained to £6000 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.

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*.

The simple sensitivity analysis results presented in *Table 69* suggest that the base-case seasonal prophylaxis cost-effectiveness estimates are

TABLE 60 *Cost-effectiveness of seasonal prophylaxis – healthy elderly*

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

TABLE 61 *Cost-effectiveness of seasonal prophylaxis – at-risk elderly*

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

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 in the majority of the scenarios presented for healthy children.

TABLE 62 *Cost-effectiveness of post-exposure prophylaxis – healthy children*

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

TABLE 63 *Cost-effectiveness of post-exposure prophylaxis – at-risk children*

Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Unvaccinated individuals					
No prophylaxis	£32.38	0.0119	–	–	–
Amantadine	£57.38	0.0098	–	–	Extendedly dominated
Oseltamivir	£63.82	0.0082	–	–	Dominated
Zanamivir	£61.45	0.0073	£29.07	0.0045	£6390
Previously vaccinated individuals					
No prophylaxis	£53.42	0.0081	–	–	–
Amantadine	£82.29	0.0075	–	–	Extendedly dominated
Oseltamivir	£91.22	0.0068	–	–	Dominated
Zanamivir	£90.37	0.0065	£36.96	0.0016	£22,663

At-risk children

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

The simple sensitivity analysis results presented in *Table 70* suggest that the base-case seasonal prophylaxis cost-effectiveness estimates for at-risk children are also 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 in 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

TABLE 64 *Cost-effectiveness of post-exposure prophylaxis – healthy adults*

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

TABLE 65 *Cost-effectiveness of post-exposure prophylaxis – at-risk adults*

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

dominated by zanamivir within the at-risk children subgroup.

Healthy adults

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

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.

At-risk adults

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

TABLE 66 *Cost-effectiveness of post-exposure prophylaxis – healthy elderly*

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

TABLE 67 *Cost-effectiveness of post-exposure prophylaxis – at-risk elderly*

Option	Costs	QALYs lost	Incremental cost	Incremental QALYs	Incremental cost per QALY gained
Unvaccinated individuals					
No prophylaxis	£22.75	0.0106	–	–	–
Amantadine	£49.95	0.0089	–	–	Extendedly dominated
Zanamivir	£55.39	0.0065	–	–	Dominated
Oseltamivir	£55.24	0.0064	£32.49	0.0041	£7892
Previously vaccinated individuals					
No prophylaxis	£47.41	0.0075	–	–	–
Amantadine	£76.84	0.0069	–	–	Extendedly dominated
Zanamivir	£85.10	0.0058	–	–	Dominated
Oseltamivir	£85.04	0.0058	£37.63	0.0017	£21,749

The results presented in *Table 72* suggest that the cost-effectiveness estimates for seasonal prophylaxis in at-risk adults again 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 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.

Healthy elderly

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

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

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

	Base case (incremental cost per QALY gained)			Price reduction for zanamivir (incremental cost per QALY gained)		
Population	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
Seasonal prophylaxis						
Healthy children						
Unvaccinated	Ext dom	Dom	£44,007	Ext dom	Dom	£43,870
Vaccinated	Dom	Dom	£129,357	Dom	Dom	£129,888
At-risk children						
Unvaccinated	Ext dom	Dom	£16,630	Ext dom	Dom	£16,598
Vaccinated	Ext dom	Dom	£51,069	Ext dom	Dom	£50,902
Healthy adults						
Unvaccinated	Ext dom	Ext dom	£147,505	Ext dom	Ext dom	£147,083
Vaccinated	Dom	Ext dom	£427,184	Dom	Ext dom	£427,802
At-risk adults						
Unvaccinated	Ext dom	Ext dom	£63,552	Ext dom	£53,159	£108,379
Vaccinated	Dom	Ext dom	£186,651	Dom	£157,216	£313,592
Healthy elderly						
Unvaccinated	Ext dom	Ext dom	£49,742	Ext dom	Ext dom	£49,590
Vaccinated	Dom	Ext dom	£121,728	Dom	Ext dom	£120,292
At-risk elderly						
Unvaccinated	Ext dom	Ext dom	£38,098	Ext dom	Ext dom	£37,968
Vaccinated	Ext dom	Ext dom	£93,763	Ext dom	Ext dom	£93,581
Post-exposure prophylaxis						
Healthy children						
Unvaccinated	Ext dom	£23,225	Ext dom	Ext dom	£18,717	Dom
Vaccinated	Ext dom	£71,648	Ext dom	Ext dom	£59,412	Dom
At-risk children						
Unvaccinated	Ext dom	£8233	Ext dom	Ext dom	£6390	Dom
Vaccinated	Ext dom	£27,684	Ext dom	Ext dom	£22,663	Dom
Healthy adults						
Unvaccinated	Ext dom	Dom	£34,181	Ext dom	Dom	£34,099
Vaccinated	Ext dom	Dom	£103,706	Ext dom	Dom	£103,573
At-risk adults						
Unvaccinated	Ext dom	Dom	£13,459	Ext dom	Dom	£13,539
Vaccinated	Ext dom	Dom	£43,970	Ext dom	Dom	£44,163
Healthy elderly						
Unvaccinated	Ext dom	Dom	£10,716	Ext dom	Dom	£10,734
Vaccinated	Ext dom	Dom	£28,473	Ext dom	Dom	£28,608
At-risk elderly						
Unvaccinated	Ext dom	Dom	£7866	Ext dom	Dom	£7892
Vaccinated	Ext dom	Dom	£21,608	Ext dom	Dom	£21,749

Dom, dominated; Ext dom, extendedly dominated.

DOI: 10.3310/hta13110

TABLE 69 *Sensitivity analysis – healthy children*

	Unvaccinated			Vaccinated		
Scenario	**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 influenza 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

continued

TABLE 69 *Sensitivity analysis – healthy children (continued)*

	Unvaccinated			Vaccinated		
Scenario	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
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
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 influenza season	Ext dom	£23,217	Ext dom	Ext dom	£71,668	Ext dom

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
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	£9590	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	£3485	Dom	Ext dom	£51,937	Ext dom
26. Undiscounted	Ext dom	£19,296	Ext dom	Ext dom	£59,566	Ext dom

Dom, dominated; EQ-5D, EuroQol-5D; Ext dom, extendedly dominated; GP, general practitioner; NI, neuraminidase inhibitor; QALY, quality-adjusted life-year; VAS, visual analogue scale.

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.

Healthy elderly

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

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.

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. Cost-effectiveness acceptability curves 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.

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 net benefit is highlighted in bold for each comparison.

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 net benefit is highlighted in bold for each comparison.

Budget impact analysis

This section presents estimates of the budget impact of a positive recommendation for each prophylactic option within each model subgroup in the light of 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 ILIs. Separate budget impact analyses are presented for seasonal prophylaxis and post-exposure prophylaxis. NICE currently recommends the use of oseltamivir as post-exposure prophylaxis in at-risk individuals aged over 13 years; 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 ONS. Of this figure, 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 respectively 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 suggest 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 (*Table 77*).

For the seasonal prophylaxis budget impact model, *any* individual within each subgroup could be potentially eligible to receive prophylaxis provided he or she is 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

DOI: 10.3310/hta13110

TABLE 70 *Sensitivity analysis – at-risk children*

	Unvaccinated			Vaccinated		
Scenario	**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 influenza 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	£6583	Ext dom	Dom	£23,114

continued

TABLE 70 *Sensitivity analysis – at-risk children (continued)*

	Unvaccinated			Vaccinated		
Scenario	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
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	£8341	Ext dom	Dom	£41,402
26. Undiscounted	Ext dom	Dom	£11,658	Ext dom	Dom	£35,925
Post-exposure prophylaxis						
Base case (stochastic model)	Ext dom	£8233	Ext dom	Ext dom	£27,684	Ext dom
1. Price reduction zanamivir	Ext dom	£6390	Dom	Ext dom	£22,663	Dom
2. Base-case deterministic model	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom
3. Oseltamivir as suspension	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom
4. Multiple prescriptions	£2991	£6797	£4075	Ext dom	£23,706	£14,428
5. Vaccine efficacy = 50%	Ext dom	£8236	Ext dom	Ext dom	£19,187	Ext dom
6. Vaccine efficacy = 25%	Ext dom	£8236	Ext dom	Ext dom	£11,887	Ext dom
7. 100% protection over influenza season	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom
8. No antiviral treatment	Ext dom	£8073	Ext dom	Ext dom	£27,226	Ext dom
9. Best-case efficacy for NIs	Ext dom	£252,401	£6491	Ext dom	£705,940	£22,858
10. No adverse events	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
11. No withdrawals	Ext dom	£8094	Ext dom	Ext dom	£27,310	Ext dom
12. 10% resistance for oseltamivir	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom
13. 20% resistance for oseltamivir	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom
14. 30% resistance for oseltamivir	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom
15. 40% resistance for oseltamivir	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom
16. 50% resistance for oseltamivir	Ext dom	£8236	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	£2761	Ext dom	Ext dom	£12,495	Ext dom
19. Higher influenza threshold	Ext dom	£8236	Ext dom	Ext dom	£27,705	Ext dom
20. GP consultation rates halved	Ext dom	£8280	Ext dom	Ext dom	£27,589	Ext dom
21. GP consultation rates doubled	Ext dom	£8147	Ext dom	Ext dom	£27,943	Ext dom
22. VAS to EQ-5D mapping function	Ext dom	£8781	Ext dom	Ext dom	£29,537	Ext dom
23. QALY loss for at-risk halved	Ext dom	£9242	Ext dom	Ext dom	£31,088	Ext dom
24. Complication disutilities halved	Ext dom	£8319	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	£6045	Ext dom	Ext dom	£20,336	Ext dom

Dom, dominated; EQ-5D, EuroQol-5D; Ext dom, extendedly dominated; GP, general practitioner; NI, neuraminidase inhibitor; QALY, quality-adjusted life-year; VAS, visual analogue scale.

TABLE 71 *Sensitivity analysis – healthy adults*

	Unvaccinated			Vaccinated		
Scenario	**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 influenza 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

Scenario	Unvaccinated			Vaccinated		
	Amantadine	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
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
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 influenza 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

continued

TABLE 71 *Sensitivity analysis – healthy adults (continued)*

	Unvaccinated			Vaccinated		
Scenario	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
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	£2920	Ext dom	Dom	£72,366
26. Undiscounted	Ext dom	Dom	£28,849	Ext dom	Dom	£87,579

Dom, dominated; EQ-5D, EuroQol-5D; Ext dom, extendedly dominated; GP, general practitioner; NI, neuraminidase inhibitor; QALY, quality-adjusted life-year; VAS, visual analogue scale.

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TABLE 72 *Sensitivity analysis – at-risk adults*

	Unvaccinated			Vaccinated		
Scenario	**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 influenza 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

continued

TABLE 72 *Sensitivity analysis – at-risk adults (continued)*

	Unvaccinated			Vaccinated		
Scenario	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
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
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	£6017	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 influenza 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

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	Unvaccinated			Vaccinated		
Scenario	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
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	£5250	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; EQ-5D, EuroQol-5D; ext dom, extendedly dominated; GP, general practitioner; NI, neuraminidase inhibitor; QALY, quality-adjusted life-year; VAS, visual analogue scale.

TABLE 73 *Sensitivity analysis – healthy elderly*

	Unvaccinated			Vaccinated		
Scenario	**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 influenza 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

Scenario	Unvaccinated			Vaccinated		
	Amantadine	Zanamivir	Oseltamivir	Amantadine	Zanamivir	Oseltamivir
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
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	£4897	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 influenza 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

continued

TABLE 73 *Sensitivity analysis – healthy elderly (continued)*

	Unvaccinated			Vaccinated		
Scenario	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
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	£4294	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	Dom	Dom	Dom	£16,207
26. Undiscounted	Ext dom	Dom	£10,020	Ext dom	Dom	£26,645

Dom, dominated; EQ-5D, EuroQol-5D; Ext dom, extendedly dominated; GP, general practitioner; NI, neuraminidase inhibitor; QALY, quality-adjusted life-year; VAS, visual analogue scale.

DOI: 10.3310/hta13110

TABLE 74 *Sensitivity analysis – at-risk elderly*

	Unvaccinated			Vaccinated		
Scenario	**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 influenza 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

continued

TABLE 74 *Sensitivity analysis – at-risk elderly (continued)*

	Unvaccinated			Vaccinated		
Scenario	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
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
Post-exposure prophylaxis						
Base case (stochastic model)	Ext dom	Dom	£7866	Ext dom	Dom	£21,608
1. Price reduction zanamivir	Ext dom	Dom	£7892	Ext dom	Dom	£21,749
2. Base-case deterministic model	Ext dom	Dom	£7871	Ext dom	Dom	£21,712
3. Oseltamivir as suspension	Ext dom	Dom	£7871	Ext dom	Dom	£21,712
4. Multiple prescriptions	Ext dom	Dom	£3327	Ext dom	Dom	£10,894
5. Vaccine efficacy = 50%	Ext dom	Dom	£7871	Ext dom	Dom	£17,894
6. Vaccine efficacy = 25%	Ext dom	Dom	£7871	Ext dom	Dom	£11,212
7. 100% protection over influenza season	Ext dom	Dom	£7871	Ext dom	Dom	£21,712
8. No antiviral treatment	Ext dom	Dom	£7750	Ext dom	Dom	£21,419

	Unvaccinated			Vaccinated		
Scenario	**Amantadine**	**Zanamivir**	**Oseltamivir**	**Amantadine**	**Zanamivir**	**Oseltamivir**
9. Best-case efficacy for NIs	Ext dom	£275,589	£7871	Ext dom	£659,137	£21,712
10. No adverse events	Ext dom	Dom	£7871	Ext dom	Dom	£21,712
11. No withdrawals	Ext dom	Dom	£7671	Ext dom	Dom	£21,235
12. 10% resistance for oseltamivir	Ext dom	£21,970	£8985	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	£2860	Ext dom	Dom	£9780
19. Higher influenza threshold	Ext dom	Dom	£7871	Ext dom	Dom	£21,712
20. GP consultation rates halved	Ext dom	Dom	£7908	Ext dom	Dom	£21,662
21. GP consultation rates doubled	Ext dom	Dom	£7796	Ext dom	Dom	£21,814
22. VAS to EQ-5D mapping function	Ext dom	Dom	£8141	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	£7915	Ext dom	Dom	£21,835
25. 10% uncomplicated hospitalised	Dom	Dom	Dom	Dom	Dom	£12,411
26. Undiscounted	Ext dom	Dom	£7278	Ext dom	Dom	£20,076

Dom, dominated; EQ-5D, EuroQol-5D; Ext dom, extendedly dominated; GP, general practitioner; NI, neuraminidase inhibitor; QALY, quality-adjusted life-year; VAS, visual analogue scale.

TABLE 75 *Uncertainty analysis results: probability of being optimal at willingness-to-pay thresholds (base-case scenario)*

	Probability optimal at £20,000/QALY				Probability optimal at £30,000/QALY			
Population	**No prophylaxis**	**Amantadine**	**Oseltamivir**	**Zanamivir**	**No prophylaxis**	**Amantadine**	**Oseltamivir**	**Zanamivir**
Seasonal prophylaxis								
Healthy children								
Unvaccinated	1.00	0.00	0.00	0.00	0.97	0.00	0.03	0.00
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk children								
Unvaccinated	0.27	0.03	0.70	0.00	0.02	0.03	0.94	0.01
Vaccinated	1.00	0.00	0.00	0.00	0.97	0.00	0.03	0.00
Healthy adults								
Unvaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults								
Unvaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Healthy elderly								
Unvaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk elderly								
Unvaccinated	1.00	0.00	0.00	0.00	0.89	0.02	0.08	0.01
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00

Population	Probability optimal at £20,000/QALY				Probability optimal at £30,000/QALY			
	No prophylaxis	Amantadine	Oseltamivir	Zanamivir	No prophylaxis	Amantadine	Oseltamivir	Zanamivir
Post-exposure prophylaxis								
Healthy children								
Unvaccinated	0.63	0.00	0.22	0.15	0.15	0.00	0.40	0.45
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk children								
Unvaccinated	0.00	0.00	0.33	0.67	0.00	0.00	0.27	0.73
Vaccinated	0.81	0.00	0.11	0.08	0.39	0.00	0.29	0.31
Healthy adults								
Unvaccinated	1.00	0.00	0.00	0.00	0.81	0.00	0.19	0.00
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults								
Unvaccinated	0.02	0.00	0.89	0.10	0.00	0.00	0.84	0.16
Vaccinated	1.00	0.00	0.00	0.00	0.96	0.00	0.04	0.00
Healthy elderly								
Unvaccinated	0.00	0.00	0.87	0.13	0.00	0.00	0.82	0.18
Vaccinated	0.91	0.00	0.09	0.00	0.47	0.00	0.50	0.03
At-risk elderly								
Unvaccinated	0.00	0.00	0.83	0.17	0.00	0.00	0.77	0.23
Vaccinated	0.64	0.00	0.35	0.01	0.15	0.00	0.78	0.07

QALY, quality-adjusted life-year.

TABLE 76 *Uncertainty analysis results: probability of being optimal at willingness-to-pay thresholds (incorporating proposed reduction in price of zanamivir)*

	Probability optimal at £20,000/QALY				Probability optimal at £30,000/QALY			
Population	**No prophylaxis**	**Amantadine**	**Oseltamivir**	**Zanamivir**	**No prophylaxis**	**Amantadine**	**Oseltamivir**	**Zanamivir**
Seasonal prophylaxis								
Healthy children								
Unvaccinated	1.00	0.00	0.00	0.00	0.97	0.00	0.03	0.00
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk children								
Unvaccinated	0.25	0.03	0.70	0.03	0.01	0.02	0.91	0.05
Vaccinated	1.00	0.00	0.00	0.00	0.97	0.00	0.03	0.00
Healthy adults								
Unvaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults								
Unvaccinated	1.00	0.00	0.00	0.00	0.99	0.00	0.00	0.01
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
Healthy elderly								
Unvaccinated	1.00	0.00	0.00	0.00	0.97	0.00	0.00	0.03
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk elderly								
Unvaccinated	0.99	0.00	0.00	0.00	0.77	0.02	0.05	0.16
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00

Population	Probability optimal at £20,000/QALY				Probability optimal at £30,000/QALY			
	No prophylaxis	Amantadine	Oseltamivir	Zanamivir	No prophylaxis	Amantadine	Oseltamivir	Zanamivir
Post-exposure prophylaxis								
Healthy children								
Unvaccinated	0.44	0.00	0.09	0.47	0.06	0.00	0.15	0.79
Vaccinated	1.00	0.00	0.00	0.00	0.99	0.00	0.00	0.01
At-risk children								
Unvaccinated	0.00	0.00	0.15	0.85	0.00	0.00	0.15	0.85
Vaccinated	0.70	0.00	0.04	0.26	0.24	0.00	0.12	0.65
Healthy adults								
Unvaccinated	1.00	0.00	0.00	0.00	0.76	0.00	0.18	0.06
Vaccinated	1.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00
At-risk adults								
Unvaccinated	0.00	0.00	0.59	0.40	0.00	0.00	0.59	0.41
Vaccinated	1.00	0.00	0.00	0.00	0.95	0.00	0.04	0.01
Healthy elderly								
Unvaccinated	0.00	0.00	0.62	0.38	0.00	0.00	0.62	0.38
Vaccinated	0.90	0.00	0.07	0.03	0.42	0.00	0.38	0.20
At-risk elderly								
Unvaccinated	0.00	0.00	0.60	0.40	0.00	0.00	0.60	0.40
Vaccinated	0.60	0.00	0.25	0.15	0.11	0.00	0.54	0.34

QALY, quality-adjusted life-year.

TABLE 77 *Number of individuals in each model subgroup*

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

ONS. The estimated budget impact for seasonal prophylaxis options is 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 in 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 in the light of the existing NICE guidance (the 'current policy cost' column details the expected cost per patient of prophylaxis according to current NICE guidance). The budget impact for the residential care home population was based on an assumed ILI attack rate of 41%.[132] The estimated budget impact for post-exposure prophylaxis options is presented in *Tables 79* and *80*.

DOI: 10.3310/hta13110

TABLE 78 *Seasonal prophylaxis budget impact estimates*

Population group	No. of individuals	Current policy	Expected cost per patient				Current cost	Additional budget impact over eligible population		
			NP	Amantadine	Zanamivir	Oseltamivir		Amantadine	Zanamivir	Oseltamivir
Healthy children										
Unvaccinated	10,240,912	NP	£17.72	£56.23	£112.15	£85.51	£17.72	£183,952,396	£343,735,708	£655,247,656
Vaccinated	–	NP	£43.23	£78.64	£140.36	£115.05	£43.23	£0	£0	£0
At-risk children										
Unvaccinated	808,567	NP	£29.89	£66.92	£121.56	£93.57	£29.89	£13,970,266	£26,347,333	£48,599,333
Vaccinated	587,921	NP	£51.71	£86.84	£147.86	£122.06	£51.71	£9,632,657	£20,090,863	£39,033,738
Healthy adults										
Unvaccinated	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
Vaccinated	–	NP	£35.64	£71.34	£133.74	£141.62	£35.64	£0	£0	£0
At-risk adults										
Unvaccinated	4,846,375	NP	£13.57	£52.74	£108.33	£115.63	£13.57	£189,831,470	£459,262,856	£494,635,028
Vaccinated	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										
Unvaccinated	1,033,813	NP	£10.43	£49.93	£106.16	£112.80	£10.43	£40,836,559	£98,974,490	£105,837,889
Vaccinated	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										
Unvaccinated	748,623	NP	£13.45	£52.63	£108.39	£114.54	£13.45	£29,333,408	£71,075,149	£75,678,598
Vaccinated	2,867,913	NP	£40.75	£76.25	£137.84	£145.15	£40.75	£101,827,060	£278,453,842	£299,415,220

NP, no prophylaxis

TABLE 79 *Post-exposure prophylaxis budget impact estimates (including community-dwelling elderly)*

Population group	No. of individuals	Current policy	Expected cost per patient				Current cost	Additional budget impact over eligible population		
			NP	Amantadine	Zanamivir	Oseltamivir		Amantadine	Zanamivir	Oseltamivir
Healthy children										
Unvaccinated	2,067,940	NP	£18.96	£46.40	£61.18	£54.35	£18.96	£31,971,071	£16,526,348	£35,963,481
Vaccinated	–	NP	£44.09	£73.84	£91.00	£83.30	£44.09	£0	£0	£0
At-risk children										
Unvaccinated	163,273	Ose/NP	£32.56	£57.55	£69.76	£63.97	£47.99	–£254,503	–£1,873,897	£0
Vaccinated	118,719	Ose/NP	£53.57	£82.44	£98.67	£91.35	£72.13	–£256,859	–£1,966,380	£0
Healthy adults										
Unvaccinated	5,070,595	NP	£9.17	£38.48	£55.19	£46.94	£9.17	£23,136,834	£36,323,410	£29,814,690
Vaccinated	–	NP	£37.36	£67.80	£85.67	£77.46	£37.36	£0	£0	£0
At-risk adults										
Unvaccinated	978,625	Ose	£19.34	£47.10	£61.49	£53.18	£24.61	–£927,521	£1,265,252	£0
Vaccinated	711,574	Ose	£44.32	£74.21	£91.27	£83.04	£50.35	–£978,796	£911,673	£0
Healthy elderly										
Unvaccinated	195,544	Ose	£17.75	£45.76	£60.50	£52.17	£21.63	–£141,505	£183,604	£0
Vaccinated	749,114	Ose	£43.82	£73.59	£90.52	£82.27	£48.16	–£733,300	£696,777	£0
At-risk elderly										
Unvaccinated	141,601	Ose	£22.88	£50.05	£63.68	£55.33	£26.54	–£84,394	£133,358	£0
Vaccinated	542,462	Ose	£47.50	£76.92	£93.37	£85.11	£51.75	–£500,882	£505,397	£0

NP, no prophylaxis; Ose, oseltamivir.

TABLE 80 *Post-exposure prophylaxis budget impact estimates: residential care elderly*

Population group	No. of individuals	Current policy	Expected cost per patient				Current cost	Additional budget impact over eligible population		
			NP	Amantadine	Zanamivir	Oseltamivir		Amantadine	Zanamivir	Oseltamivir
Healthy elderly										
Unvaccinated	26,827	Ose	£17.75	£45.76	£60.50	£52.17	£21.63	–£19,413.59	£25,189	£0.00
Vaccinated	102,774	Ose	£43.82	£73.59	£90.52	£82.27	£48.16	–£100,603.99	£4,352,991	£0.00
At-risk elderly										
Unvaccinated	19,427	Ose	£22.88	£50.05	£63.68	£55.33	£26.54	–£11,578.37	£721,445	£0.00
Vaccinated	74,422	Ose	£47.50	£76.92	£93.37	£85.11	£51.75	–£68,717.81	£3,097,413	£0.00

NP, no prophylaxis; Ose, oseltamivir.

Chapter 5

Assessment of factors relevant to the NHS and other parties

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.

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 as a result of vaccination and/or influenza prophylaxis, unprotected individuals are less likely to become exposed to infection and are thus indirectly protected. Although this concept has not been modelled in this assessment, it should be considered that influenza prophylaxis in at-risk groups may result in herd immunity effects in the population with which they are in contact. Additional studies that examine the degree of viral shedding among subjects receiving prophylaxis versus placebo may provide further information with regard to this effect.

An additional issue relating to immunity against influenza was raised by study authors, who proposed that, while antivirals may be effective in preventing the development of SLCI, asymptomatic individuals may in fact have subclinical influenza infection, which may have the potential to confer immunity to the circulating strain on the exposed individual.

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; these are discussed in Chapter 6. It was noted that in some studies, subjects who had lower levels of cognitive function and/or manual dexterity were excluded from participation. Therefore, it is possible that the reported levels of adherence and acceptability of the use of the Diskhaler device for delivery of zanamivir, and the ability of subjects to take oral antivirals independently, may not accurately reflect the scenario in 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.

Prescribing patterns for influenza prophylaxis

It was typically stipulated in the study inclusion criteria in the clinical trials of the use of oseltamivir and zanamivir in post-exposure prophylaxis that the administration of antivirals should be commenced within 48 hours of exposure to the ILI index case for oseltamivir and within 36 hours for zanamivir. In clinical practice, this requirement may be problematic, as it relies on both the identification of 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 affect the speed with which prophylaxis may be implemented.

A GP can usually prescribe medication only for individuals who present 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.

Impact on primary care

Raised awareness of the availability of antiviral prophylaxis among the general population may lead to increased workloads for GPs and other primary health-care 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 (e.g. the use of post-exposure prophylaxis to manage opportunistically outbreaks in residential care homes) while for other settings the infrastructure may be of greater concern (e.g. introducing routine prophylaxis in schools).

Involvement of pharmacist in use of powder for oral suspension

As noted in Chapter 1, the summary of product characteristics for oseltamivir recommends that powder for oral suspension should be reconstituted by a pharmacist before being dispensed to the patient.

Chapter 6
Discussion

Statement of principal findings

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 among 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 in 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 and in healthy and at-risk elderly subjects and in post-exposure prophylaxis in mixed households. Interventions appeared to be tolerated reasonably well 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 minimising length of illness and time to return to normal activities. No data could be identified for HRQoL 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.

Cost-effectiveness review

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

In 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.

In 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 that 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 (p = 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 0.97 or higher.

In 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 more 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.

In 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.

In healthy elderly individuals
In this subgroup, 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).

In at-risk elderly individuals
In this subgroup, 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.

Cost-effectiveness of amantadine, zanamivir and oseltamivir as post-exposure prophylaxis
In 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 ($p = 0.99$ 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.

In 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 £8000 per QALY gained at the current list price, and around £6000 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 £9000 per QALY gained for unvaccinated at-risk children and around £29,000 per QALY gained for vaccinated at-risk children.

In 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 0 at a willingness-to-pay threshold of £30,000 per QALY gained.

In 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

(p = 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 (p = 0.95 when the proposed price reduction for zanamivir is included).

In healthy elderly individuals
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 (p = 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 (p = 0.07 and 0.38 when the proposed price reduction for zanamivir is included in the analysis).

In at-risk elderly individuals
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 £8000 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 (p = 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.

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, owing 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 4 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 Chapter 4, Systematic review of existing cost-effectiveness data); 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 below).

Uncertainties

Although 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 and hospitalisations, and on 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 among those population groups considered to be 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 among elderly subjects, particularly in long-term care settings, as subjects over 65 years of age were not well represented in the post-exposure prophylaxis trials. Further research to investigate the use of zanamivir by patients with low cognitive function is warranted. Randomised controlled trials to investigate the use of oseltamivir in seasonal prophylaxis in healthy and at-risk children, at-risk adults and healthy elderly subjects, and the representation of a range of risk and age subgroups in post-exposure prophylaxis studies would be of value. Although the report by LaForce *et al.*[75] presented considerable evidence since the last HTA review[10] 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 healthy and at-risk children and healthy elderly subjects, and a more comprehensive representation of age and risk subgroups in 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 explored further are recommended. Research to assess the impact of seasonal prophylaxis in certain groups, such as children, on the transmission and circulation of influenza in 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] while 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 amantadine[134] 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[62,67] to 4 days[63] before viral challenge. In the post-exposure prophylaxis studies based in households, prophylaxis in contact cases with oseltamivir began within 48 hours of the onset of symptoms in the index case;[48,49] however, in the zanamivir trials prophylaxis was initiated within 36 hours of the onset of symptoms in the index case in two studies[46,47] and where contacts had been exposed to an index case with ILI of no longer than 4 days' duration.[72] Considerable variation was also present in the timing of the initiation of prophylaxis in trials of amantadine[59–61] 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 on 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[58,70] described the rationale for the length of prophylaxis administered, typically as a result of 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, as the risk of developing SLCI following antiviral prophylaxis is considered to be ongoing, with an apparent drop-off in efficacy on 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 2–4 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 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 subclinical 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 have an impact on 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, while 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 12 studies giving a specific value for a raised temperature, eight used ≥37.8°C, while three used ≥37.2°C and one used ≥37.3 °C. The study by Ambrozaitis *et al.*[76] defined SLCI as the presence of a new influenza-like sign or symptom, but also reported separately cases of 'febrile SLCI', which was defined as a new symptom plus a temperature of ≥37.8°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 depending on 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, by means of which zanamivir is administered by oral inhalation, and suggested that such practical difficulties posed a barrier to use among 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] while 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 caused by NIs, in order to reflect the effects of these interventions on patients in clinical practice. Although a higher incidence of severe adverse events in oseltamivir and zanamivir was not apparent in the RCTs identified in this review, the occurrence of serious neuropsychiatric events among a minority of patients treated with NIs has been described;[20,137] these circumstances should be monitored and taken into account during the interpretation of this evidence. Indeed, the assumptions made in the economic analysis reflect the current uncertainties regarding the incidence, duration and quality of life impact of adverse events caused by 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. Although 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 Chapter 1 and Chapter 3, the emergence of strains of influenza resistant to amantadine, in particular, 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 among influenza isolates was taken into account in the cost-effectiveness analysis. Although the base case assumes oseltamivir resistance to be 0 (as 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 among 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 are 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 on 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 of key importance that the results of the economic analysis are interpreted in the light of current levels of influenza activity and resistance.

A further problem, noted in Chapter 4, is the complete absence of preference-based estimates of the impact of influenza and influenza prophylaxis on HRQoL. In addition, systematic searches were unable to identify robust estimates of the impact of influenza complications on quality of life. Consequently, 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.

Chapter 7
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 and hospitalisations and in minimising 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 among 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

In 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.

In 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.

In 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.

In 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.

In healthy elderly individuals

In this subgroup, 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.

In at-risk elderly individuals

In this subgroup, 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

In 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.

In 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 £8000 per QALY gained at the current list price, and around £6000 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 £9000 per QALY gained for unvaccinated at-risk children and around £29,000 per QALY gained for vaccinated at-risk children.

In 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.

In 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.

In healthy elderly individuals

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.

In at-risk elderly individuals

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 £8000 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.

Recommendations for research

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 effectiveness 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:

- Additional RCTs in subgroups for which data are currently lacking (as described in Chapter 6 and including assessments of oseltamivir in seasonal prophylaxis in children, at-risk adults and healthy elderly subjects; zanamivir in seasonal prophylaxis in children and healthy elderly subjects; and post-exposure prophylaxis trials of the interventions in elderly subjects and individuals with low cognitive function and/or manual dexterity)
- RCTs in which the follow-up period extends beyond the duration of prophylaxis
- head-to-head RCTs in which the clinical effectiveness of amantadine, oseltamivir and/or zanamivir in different subgroups is directly compared
- quality of life studies to inform future economic decision modelling
- further research concerning the incidence and management of complications caused by influenza.

Acknowledgements

We would like to thank Piers Mook, Joanna Ellis and Maria Zambon at the Health Protection Agency for providing advice and data for the model. We would also like to thank Alex Elliot, Andrew Ross and Douglas Fleming (Director) at the Royal College of General Practitioners for providing expert input and data for the modelling process. We would like to acknowledge Allan Wailoo, David Turner, John Brazier and Jim Chilcott for providing further methodological advice within the model development process. Myfanwy Lloyd-Jones provided methodological suggestions for the systematic review of clinical effectiveness. We would like to thank Hazel Pilgrim for her comments and validation of the model. Finally, we would like to thank Dr Rod Taylor (Peninsula Technology Assessment Group), Dr Martin Wiselka (University Hospitals of Leicester NHS Trust) and Dr Wei Shen Lim (Nottingham City Hospital) for commenting on this report.

Contribution of authors

Paul Tappenden (Senior Cost-effectiveness Modeller/Research Fellow) was the Assessment Group lead, undertook the cost-effectiveness review and developed the cost-effectiveness model. Rachel Jackson (Research Associate) and Katy Cooper (Research Associate) undertook the clinical effectiveness review. Emma Simpson (Research Fellow) was involved in the preparation of the scope and protocol and advised on the clinical effectiveness review. Angie Rees (Information Officer) performed the literature searches. Robert Read (Honorary Consultant Physician in Infectious Diseases) and Karl Nicholson (Consultant Physician and Professor of Infectious Diseases) provided clinical input to both the systematic review and health economic modelling throughout the assessment. Andrea Shippam helped in the retrieval of papers and in preparing and formatting the report. Jim Chilcott and Eva Kaltenthaler are guarantors.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Research and Development Support Unit (RDSU), which is funded by NIHR to facilitate high-quality health services research and capacity development.

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References

1. Wiselka M. Influenza: diagnosis, management and prophylaxis. *BMJ* 1994;**308**:1341–5.
2. Nicholson KG. Human influenza. In Nicholson KG, Webster RG, Hay AJ, editors. *Textbook of influenza*. Oxford: Blackwell Science; 1998, pp. 219–64.
3. Tillett HE, Smith JWG, Gooch CD. Excess deaths attributable to influenza in England and Wales: age at death and certified cause. *Int J Epidemiol* 1983;**12**:344–52.
4. Nicholson KG. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. *Epidemiol Infect* 1996;**116**:51–63.
5. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions and deaths in winter. *Commun Dis Publ Health* 2000;**3**:32–8.
6. Ruigrok RWH. Structure of influenza A, B and C viruses. In Nicholson KG, Webster RG, Hay AJ, editors. *Textbook of influenza*. Oxford: Blackwell Science; 1998, pp. 29–42.
7. Jefferson T, Demicheli V. Socioeconomics of influenza. In Nicholson KG, Webster RG, Hay AJ, editors. *Textbook of influenza*. Oxford: Blackwell Science; 1998, pp. 541–7.
8. Health Protection Agency (HPA). www.hpa.org.uk/infections/topics_az/influenza/seasonal/default.htm. 2007.
9. Douglas RG. Prophylaxis and treatment of influenza. *New Engl J Med* 1990;**322**:443–50.
10. Turner D, Wailoo A, Nicholson K, Cooper N, Sutton, A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. *Health Technol Assess* 2003;**7**:1–170.
11. Health Protection Agency (HPA) Centre for Infections (CfI). *HPA national influenza season summary 2006/2007*. 2007.
12. Meier CR, Napalkov PN, Wegmuller Y, Jefferson T, Jick H. Population-based study on incidence, risk factors, clinical complications and drug utilisation associated with influenza in the United Kingdom. *Eur J Clin Microbiol Infect Dis* 2000;**19**:834–42.
13. Nicholson KG, Wood JM, Zambon M. Influenza. *Lancet* 2003;**362**:1733–45.
14. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary*. No. 54, 2007.
15. Department of Health Immunisation programme for poultry workers. *Guidance on the implementation of a seasonal flu vaccination programme for poultry workers*. 2007.
16. National Institute for Clinical Excellence. *Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza*. Technology Appraisal Guidance 67. 2003.
17. NHS and National Institute for Clinical Excellence. *Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza*. Technology Appraisal 58. 2003.
18. Joint Formulary Committee. *British national formulary*. No. 53, 2007.
19. Department of Health. *The influenza immunisation programme 2007/2008*. 2007.
20. Roche. *Tamiflu (oseltamivir) influenza prophylaxis: achieving clinical excellence in influenza prophylaxis*. Roche submission to the National Institute for Health and Clinical Excellence. 2007. pp. 1–197.
21. Monto AS, McKimm-Breschkin JL, Macken C, Hampson AW, Hay A, Klimov A, *et al*. Detection of influenza viruses resistant to neuraminidase inhibitors in global surveillance during the first 3 years of their use. *Antimicrob Agents Chemother* 2006;**50**:2395–402.
22. Department of Health. *National Service Framework for Older People*. 2001.
23. Department of Health. *National Service Framework for Coronary Heart Disease*. 2000.
24. Alliance Pharmaceuticals. Lysovir 100 mg capsules. *Summary of product characteristics*. 2005.
25. Roche. Tamiflu 12 mg/ml powder for oral suspension. *Summary of product characteristics*. 2007.
26. Roche. Tamiflu 30 mg hard capsules. *Summary of product characteristics*. 2007.

27. Roche. Tamiflu 45 mg hard capsules. *Summary of product characteristics*. 2007.

28. Roche. Tamiflu 75 mg hard capsules. *Summary of Product Characteristics*. 2007.

29. GlaxoSmithKline. Relenza 5 mg/dose inhalation powder. *Summary of product characteristics*. 2006.

30. Aoki F. Amantadine and rimantadine. In KG Nicholson, RG Webster, AJ Hay, editors. *Textbook of influenza*. Oxford: Blackwell Science; 1998, pp. 457–476.

31. Hayden FG. Antiviral resistance in influenza viruses – implications for management and pandemic response. *New Engl J Med* 2006;**354**:785–8.

32. Schilling M, Gravenstein S, Drinka P, Cox N, Krause P, Povinelli L, *et al*. Emergence and transmission of amantadine-resistant influenza A in a nursing home. *J Am Geriatr Soc* 2004;**52**:2069–73.

33. Jefferson T, Demicheli V, Di Pietrantonj C, Rivetti D. *Amantadine and rimantadine for influenza A in adults*. [Update of Cochrane Database System Review 2004;(3):CD001169; PMID: 15266442]. Cochrane Database of Systematic Reviews 2006.

34. Penn C. Inhibitors of influenza virus neuraminidase. In KG Nicholson, RG Webster, AJ Hay, editors. *Textbook of influenza*. Oxford: Blackwell Science; 1998, pp. 477–487.

35. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF and for the QUOROM Group. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1999;**354**:1896–1900.

36. NHS Centre for Reviews and Dissemination. *Report 4: undertaking systematic reviews on effectiveness; CRDs guidance for those carrying out or commissioning reviews*. 2001.

37. Hess P. Amantadine and rimantadine in the prophylaxis of influenza A. *Med Hygiene* 1982;**40**:3496.

38. Plesnik V, Heinz F, Bindas B, Cechova D, Eliasova J, Galetkova A, *et al*. Controlled study of influenza prophylaxis by VUFB amantadin. *Cesk Epidemiol Mikrobiol Imunol* 1977;**26**:216–26.

39. Quilligan Jr JJ, Hirayama M, Baernstein Jr HD. [The prevention of A2-influenza in children by chemoprophylaxis with amantadine hydrochloride]. [German]. Schweizerische Medizinische Wochenschrift, 17 December 1966. *J Suisse Med* 1966;**96**:1689–92.

40. Smorodintsev AA, Romanov YA, Rumovski VI, Zlydniko DM. Effectiveness of hydrochloric amantadine (midantane) in prevention of artificially induced influenza infection. *Vopr Virusol* 1972;152–6.

41. Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. [Efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir for prophylaxis against influenza – placebo-controlled double-blind multicenter phase III trial]. *Kansenshogaku zasshi* (Journal of the Japanese Association for Infectious Diseases) 2000;**74**:1062–76.

42. Shinjoh M, Sato S, Sugaya N, Mitamura K, Takeuchi Y, Kosaki K, *et al*. Effect of post-exposure prophylaxis with oseltamivir for those in contacts with influenza patients in pediatric wards. *Kansenshogaku Zasshi* (Journal of the Japanese Association for Infectious Diseases) 2004;**78**:262–9.

43. Diaz-Pedroche C, Lizasoain M, Lopez-Medrano F, Escalante F, Lumbreras C, Folgueira D, *et al*. [Nosocomial outbreak of influenza in high-risk hematological patients. Efficacy of control measures and the use of zanamivir]. [Spanish]. *Enferm Infecc Microbiol Clin* 2006;**24**:10–13.

44. GlaxoSmithKline Pharmaceuticals. *Drugs for the prophylaxis of influenza – review of zanamivir*. Submission to the National Institute for Health and Clinical Excellence. 2007

45. Halloran M, Hayden FG., Yang Y, Longini IM, Monto AS. Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. *Am J Epidemiol* 2007;**165**:212–21.

46. Hayden FG, Gubareva LV, Monto AS, Klein TC, Elliott MJ, Hammond JM, *et al*. Inhaled zanamivir for the prevention of influenza in families. *New Engl J Med* 2000;**343**:1282–9.

47. Monto AS, Pichichero ME, Blanckenberg SJ, Ruuskanen O, Cooper C, Fleming DM, *et al*. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis* 2002;**186**:1582–8.

48. Hayden FG, Belshe R, Villanueva C, Lanno R, Hughes C, Small I, *et al*. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. *J Infect Dis* 2004;**189**:440–9.

49. Welliver R, Monto AS, Carewicz O, Schatteman E, Hassman M, Hedrick J, *et al*. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA 2001;**285**:748–54.

50. Jefferson TO, Demicheli V, Deeks JJ, Rivetti D. *Amantadine and rimantadine for preventing and treating influenza A in adults*. Cochrane Database of Systematic Reviews 2000;**2**.

51. Finklea JF, Hennessy AV, Davenport FM. A field trial of amantadine prophylaxis in naturally-occurring acute respiratory illness. *Am J Epidemiol* 1967;**85**:403–12.

52. Quilligan JJ, Hirayama M, Baernstein HD. The suppression of A2 influenza in children by the chemoprophylactic use of amantadine. *J Pediatr* 1966;**69**:572–5.

53. Leung P, McIntosh K, Chai H. Amantadine prophylaxis against influenza A/USSR in children with chronic asthma. *J Allergy Clin Immunol* 1979;**63**:140.

54. Wright PF, Khaw KT, Oxman MN, Shwachman H. Evaluation of the safety of amantadine-HC1 and the role of respiratory viral infections in children with cystic fibrosis. *J Infect Dis* 1976;**134**:144–9.

55. Pettersson RF, Hellström PE, Penttinen K, Pyhälä R, Tokola O, Vartio T, *et al*. Evaluation of amantadine in the prophylaxis of influenza A (H1N1) virus infection: a controlled field trial among young adults and high-risk patients. *J Infect Dis* 1980;**142**:377–83.

56. Leeming JT. Amantidine hydrochloride and the elderly. *BMJ* 1969;**1**:313–14.

57. Reuman PD, Bernstein DI, Keefer MC, Young EC, Sherwood JR., Schiff GM. Efficacy and safety of low dosage amantadine hydrochloride as prophylaxis for influenza A. *Antiviral Res* 1989;**11**:27–40.

58. Aoki FY, Stiver HG, Sitar DS, Hammond GW, Milley EV, Vermeersch C, *et al*. Potential of influenza vaccine and amantadine to prevent influenza A illness in Canadian forces personnel 1980–1983. *Mil Med* 1986;**151**:459–65.

59. Payler DK, Purdham PA. Influenza A prophylaxis with amantadine in a boarding school. *Lancet* 1984;**1**:502–4.

60. Smorodintsev A, Karpuchin G, Zlydnikov D. The prospect of amantadine for prevention of influenza A in humans (effectiveness of amantadine during influenza A2/Hong Kong epidemics in January–February 1969 in Leningrad). *Ann N Y Acad Sci* 1970;**173**:44–73.

61. Smorodintsev AA, Karapuhi GI, Zlydniko DM, Malyseva AM, Svecova EG, Burov SA, *et al*. Prophylactic effectiveness of amantadine hydrochloride in an epidemic of Hong-Kong influenza in Leningrad in 1969. *Bull World Health Organ* 1970;**42**:865–72.

62. Smorodintsev AA, Zlydnikov DM, Kiseleva AM, Romanov JA, Kazantsev AP, Rumovsky VI. Evaluation of amantadine in artificially induced A2 and B influenza. *JAMA* 1970;**213**:1448–54.

63. Sears SD, Clements ML. Protective efficacy of low-dose amantadine in adults challenged with wild-type influenza A virus. *Antimicrob Agents Chemother* 1987;**31**:1470–3.

64. Peters PH, Gravenstein S, Norwood P, De Bock V, Van Couter A, Gibbens M, *et al*. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc* 2001;**49**:1025–31.

65. De Bock V, Peters P, Von Planta T-A, Gibbens M, Ward P. Oral oseltamivir for prevention of influenza in the frail elderly. *Clin Microbiol Infect* 2000;**6**:140.

66. Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, *et al*. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *New Engl J Med* 1999;**341**:1336–43.

67. Hayden FG, Jennings L, Robson R, Schiff G, Jackson H, Rana B, *et al*. Oral oseltamivir in human experimental influenza B infection. *Antiviral Ther* 2000;**5**:205–13.

68. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. *Neuraminidase inhibitors for preventing and treating influenza in healthy adults*. Cochrane Database of Systematic Reviews 2006.

69. Schilling M, Povinelli L, Krause P, Gravenstein M, Ambrozaitis A, Jones H, *et al*. Efficacy of zanamivir for chemoprophylaxis of nursing home influenza outbreaks. *Vaccine* 1998;**16**:1771–4.

70. Monto AS, Robinson DP, Louise M, James H, Hinson M, Elliott MJ, *et al*. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 1999;**282**:31–5.

71. Monto AS, Robinson D, Griffin AD, Edmundson S. The effects of zanamivir on productivity in the prevention of influenza among healthy adults. *J Antimicrob Chemother* 1999;**44**.

72. Kaiser L, Henry D, Flack NP, Keene O, Hayden FG. Short-term treatment with zanamivir to prevent influenza: results of a placebo-controlled study. *Clin Infect Dis* 2000;**30**:587–9.

73. Hayden F, Belshe R, Villanueva C, Lanno R, Small I, Hughes C, *et al*. Oral oseltamivir prevents the spread of influenza between children in households.

Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 2002;**42**.

74. Belshe R, Hayden F, Carewicz O, Lanno R, Martin C, Hughes C, *et al*. Effectiveness of oral oseltamivir in preventing spread of influenza-like illness in households with proven influenza. Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 2001;**41**.

75. LaForce C, Man CY, Henderson FW, McElhaney JE, Hampel Jr FC, Bettis R, *et al*. Efficacy and safety of inhaled zanamivir in the prevention of influenza in community-dwelling, high-risk adult and adolescent subjects: a 28-day, multicenter, randomized, double-blind, placebo-controlled trial. *Clin Ther* 2007;**29**:1579–90.

76. Ambrozaitis, A., Gravenstein, S., Van Essen, G. A., Rubinstein, E., Balciuniene, L., Stikleryte, A., Crawford, C., Elliott, M., and Shult, P. Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population. J of the American Medical Directors Association 2005;**6** 367–374.

77. Ambrozaitis, A, Van Essen G, Rubinstein E, Balciuniene L, Stikleryte A, Gravenstein S, *et al*. Inhaled zanamivir versus placebo for the prevention of influenza outbreaks in an unvaccinated long-term care population (NAIA3004). *J Am Geriatr Soc* 2001;**49**:S130–1.

78. Gravenstein S, Drinka P, Osterweil D, Schilling M, Krause P, Elliott M, *et al*. Inhaled zanamivir versus rimantadine for the control of influenza in a highly vaccinated long-term care population. *J Am Med Dir Assoc* 2005;**6**:359–66.

79. Jefferson T, Deeks JJ, Demicheli V, Rivetti D, Rudin M *Amantadine and rimantadine for preventing and treating influenza A in adults*. [Update in Cochrane Database Syst Rev. 2006;(2):CD001169; PMID: 16625539][update of Cochrane Database Syst Rev. 2002;(3):CD001169; PMID: 12137620]. Cochrane Database of Systematic Reviews 2004.

80. European Medicines Agency Scientific discussion. *Tamiflu-H-402-II-20*. 2006.

81. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M. *Neuraminidase inhibitors for preventing and treating influenza in children*. [Update of Cochrane Database Syst Rev. 2003;(3):CD002744; PMID: 12917931]. Cochrane Database of Systematic Reviews 2007.

82. Aoki FY, Boivin G, Roberts N. Influenza virus susceptibility and resistance to oseltamivir. *Antiviral Ther* 2007;**12**:603–16.

83. Hatakeyama S, Sugaya N, Ito M, Yamazaki M, Ichikawa M, Kimura K, Kiso M, *et al*. Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. *JAMA* 2007;**297**:1435–42.

84. Escuret V, Frobert E, Bouscambert-Duchamp M, Sabatier M, Grog I, Valette M, *et al*. Detection of human influenza A (H1N1) and B strains with reduced sensitivity to neuraminidase inhibitors. *J Clin Virol* 2007;**41**:25–8.

85. Kiso M, Mitamura K, Sakai-Tagawa Y, Shiraishi K, Kawakami C, Kimura K, *et al*. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 2004;**364**:759–65.

86. European Centre for Disease Prevention and Control. *Emergence of seasonal influenza viruses type A/H1N1 with oseltamivir resistance in some European Countries at the start of the 2007–8 influenza season*. 2008.

87. Health Protection Agency. *Oseltamivir resistance in European influenza viruses – update*. 2008.

88. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner DA, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003;**326**:1235–9.

89. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd edn. New York: Oxford University Press; 2007.

90. Eddy DM. Technology assessment: the role of mathematical modeling. In Institute of Medicine, editor. *Assessing medical technology*. Washington, DC: National Academy Press; 1985, pp. 144–153.

91. Sander B, Hayden FG, Gyldmark M, Garrison Jr LP. Post-exposure influenza prophylaxis with oseltamivir: cost effectiveness and cost utility in families in the UK. *Pharmacoeconomics* 2006;**24**:373–86.

92. Risebrough NA, Bowles SK, Simor AE, McGeer A, Oh PI. Economic evaluation of oseltamivir phosphate for postexposure prophylaxis of influenza in long-term care facilities. *J Am Geriatr Soc* 2005;**53**:444–51.

93. Scuffham P, West P. Economic evaluation of strategies for the control and management of influenza in Europe. *Vaccine* 2002; 20:2562–78.

94. Demicheli V, Jefferson T, Rivetti D, Deeks J. Prevention and early treatment of influenza in healthy adults. *Vaccine* 2000;**18**:957–1030.

95. Patriarca PA, Arden NH, Koplan JP, Goodman RA. Prevention and control of type A influenza infections in nursing homes: benefits and costs of four approaches using vaccination and amantadine. *Ann Intern Med* 1987;**107**:732–40.

96. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. 2004.

97. Monto AS, Gunn RA, Bandyk MG, King CL. Prevention of Russian influenza by amantadine. *JAMA* 1979;**241**:1003–7.

98. Cox NJ, Subbarao K. Global epidemiology of influenza: past and present. *Annu Rev Med* 2000;**51**:407–21.

99. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Oseltamivir prevents complications from influenza-related lower respiratory tract infections. *ACOG Clin Rev* 2003;**8**:12.

100. Stouthard M, Essink-Bot M, Bonsel G, et al. *Disability weights for diseases in the Netherlands*. Rotterdam, Netherlands: Department of Public Health, Erasmus University Rotterdam; 1997.

101. Department of Health and Human Services. *National ambulatory medical care survey (NACMS)*. National Centre for Health Statistics; 1997.

102. Curtis L, Netten A. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit (PSSRU); 2006.

103. MIMS. *The prescribing reference for general practice*. September 2007.

104. van Noort SP. Gripenet: an internet-based system to monitor influenza-like illness uniformly across Europe. *Euro Surveill* 2007; 12

105. MVH Group. *The measurement and valuation of health*. First report on the main survey. 1994.

106. Ontario Ministry of Health and Long Term Care. *Ontario Ministry of Health Schedule of Benefits and Fees*. 2007.

107. Ontario Case Cost Initiative. *Average costs per case mix group (CMG) 2000–2001*. 2001.

108. Wailoo A, Abrams K., Turner D, Sutton AJ, Cooper NJ, Nicholson KG. *Review of influenza post-exposure prophylaxis*. DSU report to the National Institute for Clinical Excellence. 2003.

109. Murray CJ, Lopez AD. *The global burden of disease: a comprehensive assessment of mortality and disabilities from diseases, injuries and risk factors in 1990 and projected to 2020*. Global burden of disease and injury series, volume 1. Cambridge, MA: Harvard School of Public Health;1996.

110. Fleming DM. The contribution of influenza to combined acute respiratory infections, hospital admissions and deaths in winter. *Comm Dis Publ Health* 2000;**3**:32–8.

111. Netten A, Curtis L. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit (PSSRU); 2000.

112. CHKS Ltd. *Hospitalisation data for England and Wales 1995–1999*. 2000.

113. Department of Health. *Prescription cost analysis*. 2000.

114. Department of Health. *Drug Tariff National Health Service, England and Wales*. 1999.

115. Patriarca PA, Weber JA, Parker RA, Orenstein WA, Hall WN, Kendal AP, *et al*. Risk factors for outbreaks of influenza in nursing homes. *Am J Epidemiol* 1986;**124**(1):114–119.

116. National Institute for Clinical Excellence. *Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza*. Technology appraisal guidance no. 58. 2003.

117. Smith S, Demicheli V, Pietrantonj C, Harnden AR, Jefferson T, Matheson NJ, *et al*. *Vaccines for preventing influenza in healthy children (review)*. The Cochrane Library: 2007.

118. Jefferson TO, Rivetti D, Pietrantonj C, Rivetti A, Demicheli V. *Vaccines for preventing influenza in healthy adults (review)*. The Cochrane Library; 2007.

119. Rivetti D, Jefferson TO, Thomas R, Rudin M, Rivetti A, Pietrantonj C, *et al*. *Vaccines for preventing influenza in the elderly (review)*. The Cochrane Library; 2007.

120. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. *Ann Intern Med* 1995;**123**:518–27.

121. Nichol KL, Margolis KL, Lind A, Murdoch M, McFadden R, Hauge M, *et al*. Side effects associated with influenza vaccination in healthy working adults. A randomized, placebo-controlled trial. *Ann Intern Med* 1996;**156**:1546–50.

122. Pitman R, Melegaro A, Gelb D, Siddiqui M, Gay N, Edmunds W. Assessing the burden of influenza and other respiratory infections in England and Wales. *J Infect* 2007;**54**:530–8.

123. Ross AM, Kai J, Salter R, Ross J, Fleming DM. Presentation with influenza-like illness in general practice: implications for use of neuraminidase inhibitors. *Commun Dis Publ Health* 2000;**3**:256–60.

124. Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Med Decis Making* 2003;**23**:341–50.

125. Department of Health. *NHS Reference Costs 2005–2006*. 2007.

126. Oliveira EC, Marik PE, Colice G. Influenza pneumonia: a descriptive study. *Chest* 2001;**119**:1723.

127. Griffin ADP. Cost-effectiveness analysis of inhaled zanamivir in the treatment of influenza A and B in high-risk patients. *Pharmacoeconomics* 2001;**19**:293–301.

128. Rothberg MBH. Management of influenza symptoms in healthy adults: cost-effectiveness of rapid testing and antiviral therapy. *J Gen Intern Med* 2003;**18**:808–15.

129. Stratton KR, Durch JS, Lawrence RS. Vaccines for the 21st century: a tool for decisionmaking. Washington, DC: National Academy Press; 2007.

130. Office for National Statistics. *Mortality statistics: cause*. Review of the Registrar General on deaths by cause, sex and age in England and Wales, 2005. 2006;DH2 no.32

131. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*. Centre for Health Economics Discussion Paper Series; 1999.

132. Gupta RK, Zhao H, Cooke M, Harling R, Regan M, Bailey L, *et al*. Public health responses to influenza in care homes: a questionnaire-based study of local health protection units. *J Publ Health* 2007;**29**:88–90.

133. Quarles JM, Couch RB, Cate TR, Goswick CB. Comparison of amantadine and rimantadine for prevention of type A (Russian) influenza. *Antiviral Res* 1981;**1**:149–55.

134. Dolin R, Reichman RC, Madore HP, Maynard R, Linton PN, Webber-Jones J. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *New Engl J Med* 1982;**307**:580–4.

135. Cohen A, Togo Y, Khakoo R, Waldman R, Sigel M. Comparative clinical and laboratory evaluation of the prophylactic capacity of ribavirin, amantadine hydrochloride and placebo in induced human influenza type A. *J Infect Dis* 1976;**133**(Suppl):A114–20.

136. Diggory P, Fernandez C, Humphrey A, Jones V, Murphy M. Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial. *BMJ* 2001;**322**:577–9.

137. Pocock N. *US FDA staff recommend additional neuropsychiatric warnings for oseltamivir and zanamivir*. NHS National Electronic Library for Medicines; 2007

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

These quality assessment criteria were based on those proposed by the NHS Centre for Reviews and Dissemination.[35]

	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

Quality criterion	Reuman et *al.*, 1989[57] (1)[a]	Reuman et *al.*, 1989[57] (2)[a]	Aoki et *al.*, 1986[58]	Pettersson et *al.*, 1980[55]	Payler and Purdham, 1984[59]	Smorodintsev et *al.*, 1970[60,61]	Sears and Clements, 1987[63]	Smorodintsev et *al.*, 1970[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 For nurses classifying illness: U	U For self-recorded symptoms and adverse effects: Y	U	For adverse effect and morbidity assessment: Y	U	U

Quality criterion	Reuman et *al.*, 1989[57] (1)[a]	Reuman et *al.*, 1989[57] (2)[a]	Aoki et *al.*, 1986[58]	Pettersson et *al.*, 1980[55]	Payler and Purdham, 1984[59]	Smorodintsev et *al.*, 1970[60,61]	Sears and Clements, 1987[63]	Smorodintsev et *al.*, 1970[62]
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	NA
Was intention-to-treat analysis included?	Y	Y	N	Mixed For efficacy analysis: N For adverse event analysis: Y	N	N	Y	Y

HAI, haemagglutination inhibition assay; NA, not applicable.
a (1) Seasonal influenza study; (2) experimentally induced influenza study.
Y, N and U are used to denote positive, negative and unclear decisions with respect to each quality criterion.

Appendix 4

Study quality characteristics for oseltamivir prophylaxis trials

	Peters et *al.*, 2001[64]	Hayden et *al.*, 1999[66]	Welliver et *al.*, 2001[49]	Hayden et *al.*, 2004[48,73,74]	Hayden et *al.*, 2000[67]
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	U	U	U	U
	For self-recording of data: Y	For self-recording of data: Y	For self-recording of data: Y	For self-recording of data: Y	
Were the individuals who administered the intervention blinded to allocation?	U	Y	U	N	U
	Described as double blind but no further details	Double-blind labelling	Described as double blind but no further details	Open-label	Described as double blind but no further details
Were the participants receiving intervention blinded to allocation?	Y	Y	U	N	U
		Double-blind labelling	Described as double blind but no further details	Open-label	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

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

Appendix 5

Study quality characteristics for zanamivir prophylaxis trials

Quality criterion	Monto et *al.*, 1999[72,73]	LaForce et *al.*, 2007[75]	Monto et *al.*, 2002[47]	Hayden et *al.*, 2000[46]	Kaiser et *al.*, 2000[72]	Ambrozaitis et *al.*, 2005[76,77]	Gravenstein et *al.*, 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

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

Appendix 6

Studies excluded after close scrutiny with rationale

Study	Reason for exclusion
Aoki *et al.*, 1985	Not in line with licensed indications
Bowles *et al.*, 1999	Not a randomised controlled trial
Bowles *et al.*, 2002	Not a randomised controlled trial
Bryson *et al.*, 1980	Not in line with licensed indications
Bush *et al.*, 2004	Not a randomised controlled trial
Calfee *et al.*, 1999a	Not in line with licensed indications
Calfee *et al.*, 1999b	Not in line with licensed indications
Callmander *et al.*, 1968	Not in line with licensed indications
Cass *et al.*, 2000	Not in line with licensed indications
Cohen *et al.*, 1976	Not in line with licensed indications
Davies *et al.*, 1988	Not a randomised controlled trial
Dawkins *et al.*, 1968	Analogue of amantadine hydrochloride. Not in line with licensed indications
Degelau *et al.*, 1990	Not a randomised controlled trial
Diaz-Pedroche *et al.*, 2006	Not available to read in English
Dolin *et al.*, 1982	Not in line with licensed indications
Drinka *et al.*, 1998	Comparison of short and long-term amantadine prophylaxis protocols
Finklea *et al.*, 1967	Not in line with licensed indications – dosage not established in children
Galbraith *et al.*, 1969a	Data for subgroup in line with licensed indications not presented
Galbraith *et al.*, 1969b	Data for subgroup in line with licensed indications not presented
Galbraith *et al.*, 1971	Data for subgroup in line with licensed indications not presented
Hayden *et al.*, 1981	Not in line with licensed indications
Hayden *et al.*, 1996	Not in line with licensed indications
Hayden *et al.*, 1999b	Not in line with licensed indications
Hayden, 2001	Abstract only. Insufficient data
Hess, 1982	Not available to read in English
Hirji *et al.*, 2001	Not a randomised controlled trial
Hirji *et al.*, 2002	Not a randomised controlled trial
Jackson *et al.*, 1963	Not in line with licensed indications
Kantor *et al.*, 1980	Not in line with licensed indications
Kashiwagi *et al.*, 2000	Not available to read in English
Lee *et al.*, 2000	Not a randomised controlled trial
Leeming *et al.*, 1969	Not in line with licensed indications
Leung *et al.*, 1979	Not in line with licensed indications
Libow *et al.*, 1996	Not a randomised controlled trial
Mate *et al.*, 1970	Not in line with licensed indications

continued

Study	Reason for exclusion
McLeod & Lau, 2001	Not a randomised controlled trial
Millet *et al.*, 1982	Not in line with licensed indications
Monto *et al.*, 1979	Not in line with licensed indications
Monto *et al.*, 2004	Not a randomised controlled trial
Muldoon *et al.*, 1976	Not in line with licensed indications
Nafta *et al.*, 1970	Not in line with licensed indications
O'Donoghue *et al.*, 1973	Not in line with licensed indications
Oker-Blom *et al.*, 1970	Not in line with licensed indications
Peckinpaugh *et al.*, 1970	Not in line with licensed indications
Peters *et al.*, 1989	Not a randomised controlled trial
Plesnik *et al.*, 1977	Not available to read in English
Quarles *et al.*, 1981	Not in line with licensed indications
Quilligan *et al.*, 1966a	Not in line with licensed indications – dosage not established in children
Quilligan *et al.*, 1966	Not available to read in English
Schapira *et al.*, 1971	Not in line with licensed indications
Schilling *et al.*, 1998	Not in line with licensed indications
Shinjoh *et al.*, 2004	Not available to read in English
Smorodintsev *et al.*, 1972	Not available to read in English
Somani *et al.*, 1991	Not a randomised controlled trial
Stanley *et al.*, 1965	Not in line with licensed indications
Togo *et al.*, 1968	Not in line with licensed indications
Tyrrell *et al.*, 1965	Not in line with licensed indications
Vogel, 2002	Not a randomised controlled trial
Walker *et al.*, 1997	Not in line with licensed indications
Wendel *et al.*, 1966	Not in line with licensed indications
Wright *et al.*, 1974	Not in line with licensed indications
Wright *et al.*, 1976	Not in line with licensed indications – dosage not established in children

Appendix 7

List of all model parameters

The following abbreviations are used in this appendix:

A&E, accident and emergency; CNS, central nervous system; GP, general practitioner; ICU, intensive care unit; ILI, influenza-like illness; ITU, intensive therapy unit; LOS, length of stay; NA, not applicable; QALY, quality-adjusted life-year; RR, relative risk; SE, standard error.

Distribution parameter key

Distribution type	Parameter 1	Parameter 2
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

TABLE 81 *Seasonal prophylaxis: healthy children*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.36	–1.02	0.14
9	RR for influenza – amantadine prophylaxis	Lognormal	0.40	–0.92	0.83
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.24	–1.43	0.45
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.32	–1.13	0.34
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	0.53	0.53	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	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

DOI: 10.3310/hta13110

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 Treatment | presents < 48 hours	NA	0	0	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	1	1	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	0	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 treatment	Beta	0.14	2417	17,201
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	1	2423
35	Probability complication is CNS	Dirichlet	0.01	18	2423
36	Probability complication is renal	Dirichlet	0	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	17,910
41	Probability patient receives antibiotics | complication	Beta	0.74	2183	2962
42	Probability of influenza death | complication	Beta	0	1	2311
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (without vaccine)	NA	£14.40	£14.40	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£9.60	£9.60	–
45	Cost of oseltamivir prophylaxis course	NA	£49.08	£49.08	–
46	Cost of zanamivir prophylaxis course	NA	£73.65	£73.65	–

continued

TABLE 81 *Seasonal prophylaxis: healthy children (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£42	£42	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	21	21	–
51	Days per course – oseltamivir prophylaxis	NA	42	42	–
52	Days per course – zanamivir prophylaxis	NA	28	28	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.05	4	73
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.05	4	73
64	Cost of uncomplicated influenza presentation	NA	£29.52	£29.52	–
65	Cost of complicated influenza presentation	NA	£29.52	£29.52	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.11	5	46
72	Probability ICU care | complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	2.30	1	4

DOI: 10.3310/hta13110

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
74	Cost of ITU day	Normal	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£2430.18	£2430.18	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.04	4146	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.04	4247	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.04	4247	100,000
80	QALY loss for influenza case – no treatment	NA	0.01	0.01	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.01	0.01	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

continued

TABLE 81 *Seasonal prophylaxis: healthy children (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	24.74	24.74	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

DOI: 10.3310/hta13110

TABLE 82 *Seasonal prophylaxis: at-risk children*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.36	–1.02	0.14
9	RR for influenza – amantadine prophylaxis	Lognormal	0.40	–0.92	0.83
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.24	–1.43	0.45
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.32	–1.13	0.34
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	0.53	0.53	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	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

continued

TABLE 82 *Seasonal prophylaxis: at-risk children (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	1	1	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	1	1	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	0	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 treatment	Beta	0.18	675	3695
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	1	681
35	Probability complication is CNS	Dirichlet	0	1	681
36	Probability complication is renal	Dirichlet	0	1	681
37	Probability complication is otitis media	Dirichlet	0.23	154	681
38	Probability complication is other	Dirichlet	0	3	681
39	Probability respiratory complication is pneumonia	Beta	0.02	9	520
40	Probability patient receives antibiotics | no complication	Beta	0.28	4997	17,910
41	Probability patient receives antibiotics | complication	Beta	0.74	2183	2962
42	Probability of influenza death | complication	Beta	0	1	650
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (without vaccine)	NA	£14.40	£14.40	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£9.60	£9.60	–
45	Cost of oseltamivir prophylaxis course	NA	£49.08	£49.08	–

DOI: 10.3310/hta13110

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
46	Cost of zanamivir prophylaxis course	NA	£73.65	£73.65	–
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£42	£42	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	21	21	–
51	Days per course – oseltamivir prophylaxis	NA	42	42	–
52	Days per course – zanamivir prophylaxis	NA	28	28	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.05	4	73
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.05	4	73
64	Cost of uncomplicated influenza presentation	NA	£29.52	£29.52	–
65	Cost of complicated influenza presentation	NA	£29.52	£29.52	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.16	15	95

continued

TABLE 82 *Seasonal prophylaxis: at-risk children (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£2430.18	£2430.18	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.03	2820	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.03	2977	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.03	2977	100,000
80	QALY loss for influenza case – no treatment	NA	0.02	0.02	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.02	0.02	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	24.74	24.74	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

TABLE 83 *Seasonal prophylaxis: healthy adults*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.35	–1.05	0.17
9	RR for influenza – amantadine prophylaxis	Lognormal	0.40	–0.92	0.83
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.24	–1.43	0.45
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.32	–1.13	0.34
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	0.53	0.53	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	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

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	0	0	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	0.89	0.89	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	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 treatment	Beta	0.08	6509	85,248
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	12	6515
35	Probability complication is CNS	Dirichlet	0.02	102	6515
36	Probability complication is renal	Dirichlet	0	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	47,169
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 (without vaccine)	NA	£14.40	£14.40	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£9.60	£9.60	–
45	Cost of oseltamivir prophylaxis course	NA	£81.80	£81.80	–
46	Cost of zanamivir prophylaxis course	NA	£73.65	£73.65	–
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–

continued

TABLE 83 *Seasonal prophylaxis: healthy adults (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£42	£42	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	21	21	–
51	Days per course – oseltamivir prophylaxis	NA	42	42	–
52	Days per course – zanamivir prophylaxis	NA	28	28	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.08	56	674
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.08	56	674
64	Cost of uncomplicated influenza presentation	NA	£30.73	£30.73	–
65	Cost of complicated influenza presentation	NA	£30.73	£30.73	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.11	5	46
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	£1345.39	£1345.39	£31.95

DOI: 10.3310/hta13110

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£4937.39	£4937.39	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.04	4146	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.04	4247	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.04	4247	100,000
80	QALY loss for influenza case – no treatment	NA	0.01	0.01	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.01	0.01	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

continued

TABLE 83 *Seasonal prophylaxis: healthy adults (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	13.37	13.37	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

DOI: 10.3310/hta13110

TABLE 84 *Seasonal prophylaxis: at-risk adults*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.35	–1.05	0.17
9	RR for influenza – amantadine prophylaxis	Lognormal	0.40	–0.92	0.83
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.24	–1.43	0.45
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.17	–1.75	0.54
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	0.53	0.53	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	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

continued

TABLE 84 *Seasonal prophylaxis: at-risk adults (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	1	1	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	0.89	0.89	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	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 treatment	Beta	0.12	2166	17,597
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	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	47,169
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 (without vaccine)	NA	£14.40	£14.40	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£9.60	£9.60	–
45	Cost of oseltamivir prophylaxis course	NA	£81.80	£81.80	–
46	Cost of zanamivir prophylaxis course	NA	£73.65	£73.65	–

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£42	£42	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	21	21	–
51	Days per course – oseltamivir prophylaxis	NA	42	42	–
52	Days per course – zanamivir prophylaxis	NA	28	28	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.08	56	674
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.08	56	674
64	Cost of uncomplicated influenza presentation	NA	£30.73	£30.73	–
65	Cost of complicated influenza presentation	NA	£30.73	£30.73	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.16	15	95
72	Probability ICU care | complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	11.90	16	1

continued

TABLE 84 *Seasonal prophylaxis: at-risk adults (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
74	Cost of ITU day	Normal	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£4937.39	£4937.39	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.03	2820	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.03	2977	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.03	2977	100,000
80	QALY loss for influenza case – no treatment	NA	0.02	0.02	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.02	0.02	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	13.37	13.37	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

TABLE 85 *Seasonal prophylaxis: healthy elderly*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.42	–0.87	0.23
9	RR for influenza – amantadine prophylaxis	Lognormal	0.40	–0.92	0.83
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.08	–2.50	1.04
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.20	–1.61	1.09
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	0.53	0.53	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	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

DOI: 10.3310/hta13110

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	1	1	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	0.89	0.89	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	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 treatment	Beta	0.09	942	10,145
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	15,620
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 (without vaccine)	NA	£14.40	£14.40	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£9.60	£9.60	–
45	Cost of oseltamivir prophylaxis course	NA	£81.80	£81.80	–
46	Cost of zanamivir prophylaxis course	NA	£73.65	£73.65	–
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–

continued

TABLE 85 *Seasonal prophylaxis: healthy elderly (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£42	£42	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	21	21	–
51	Days per course – oseltamivir prophylaxis	NA	42	42	–
52	Days per course – zanamivir prophylaxis	NA	28	28	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.38	62	165
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.38	62	165
64	Cost of uncomplicated influenza presentation	NA	£43.20	£43.20	–
65	Cost of complicated influenza presentation	NA	£43.20	£43.20	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.16	15	95
72	Probability ICU care | complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	15	25	1

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
74	Cost of ITU day	Normal	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£5747.01	£5747.01	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.03	2820	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.03	2977	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.03	2977	100,000
80	QALY loss for influenza case – no treatment	NA	0.02	0.02	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.01	0.01	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

continued

TABLE 85 *Seasonal prophylaxis: healthy elderly (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	2.95	2.95	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

DOI: 10.3310/hta13110

TABLE 86 *Seasonal prophylaxis: at-risk elderly*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.42	–0.87	0.23
9	RR for influenza – amantadine prophylaxis	Lognormal	0.40	–0.92	0.83
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.08	–2.50	1.04
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.20	–1.61	1.09
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	0.53	0.53	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	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

continued

TABLE 86 *Seasonal prophylaxis: at-risk elderly (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	1	1	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	0.89	0.89	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	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 treatment	Beta	0.12	908	7407
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	15,620
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 (without vaccine)	NA	£14.40	£14.40	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£9.60	£9.60	–
45	Cost of oseltamivir prophylaxis course	NA	£81.80	£81.80	–
46	Cost of zanamivir prophylaxis course	NA	£73.65	£73.65	–

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£42	£42	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	21	21	–
51	Days per course – oseltamivir prophylaxis	NA	42	42	–
52	Days per course – zanamivir prophylaxis	NA	28	28	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.38	62	165
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.38	62	165
64	Cost of uncomplicated influenza presentation	NA	£43.20	£43.20	–
65	Cost of complicated influenza presentation	NA	£43.20	£43.20	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.16	15	95
72	Probability ICU care | complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	15	25	1

continued

TABLE 86 *Seasonal prophylaxis: at-risk elderly (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
74	Cost of ITU day	Normal	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£5747.01	£5747.01	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.03	2820	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.03	2977	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.03	2977	100,000
80	QALY loss for influenza case – no treatment	NA	0.02	0.02	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.01	0.01	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	2.95	2.95	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

List of model parameters – post-exposure prophylaxis

TABLE 87 *Post-exposure: healthy children*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.36	–1.02	0.14
9	RR for influenza – amantadine prophylaxis	Lognormal	0.10	–2.26	0.60
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.36	–1.03	0.41
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.21	–1.56	0.24
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	1	1	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	1	1	–
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

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	0	0	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	1	1	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	0	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 treatment	Beta	0.14	2417	17,201
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	1	2423
35	Probability complication is CNS	Dirichlet	0.01	18	2423
36	Probability complication is renal	Dirichlet	0	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	17,910
41	Probability patient receives antibiotics | complication	Beta	0.74	2183	2962
42	Probability of influenza death | complication	Beta	0	1	2311
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (without vaccine)	NA	£4.80	£4.80	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£4.80	£4.80	–
45	Cost of oseltamivir prophylaxis course	NA	£16.36	£16.36	–
46	Cost of zanamivir prophylaxis course	NA	£24.55	£24.55	–
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–

continued

TABLE 87 *Post-exposure: healthy children (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£10	£10	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	10	10	–
51	Days per course – oseltamivir prophylaxis	NA	10	10	–
52	Days per course – zanamivir prophylaxis	NA	10	10	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.05	4	73
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.05	4	73
64	Cost of uncomplicated influenza presentation	NA	£29.52	£29.52	–
65	Cost of complicated influenza presentation	NA	£29.52	£29.52	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.11	5	46
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	£1345.39	£1345.39	£31.95

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£2430.18	£2430.18	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.04	4146	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.04	4247	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.04	4247	100,000
80	QALY loss for influenza case – no treatment	NA	0.01	0.01	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.01	0.01	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

continued

TABLE 87 *Post-exposure: healthy children (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	24.74	24.74	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

DOI: 10.3310/hta13110

TABLE 88 *Post-exposure: at-risk children*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.36	–1.02	0.14
9	RR for influenza – amantadine prophylaxis	Lognormal	0.10	–2.26	0.60
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.36	–1.03	0.41
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.21	–1.56	0.24
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	1	1	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	1	1	–
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

continued

TABLE 88 *Post-exposure: at-risk children (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	1	1	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	1	1	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	0	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 treatment	Beta	0.18	675	3695
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	1	681
35	Probability complication is CNS	Dirichlet	0	1	681
36	Probability complication is renal	Dirichlet	0	1	681
37	Probability complication is otitis media	Dirichlet	0.23	154	681
38	Probability complication is other	Dirichlet	0	3	681
39	Probability respiratory complication is pneumonia	Beta	0.02	9	520
40	Probability patient receives antibiotics | no complication	Beta	0.28	4997	17,910
41	Probability patient receives antibiotics | complication	Beta	0.74	2183	2962
42	Probability of influenza death | complication	Beta	0	1	650
Cost/resource parameters					
43	Cost of amantadine prophylaxis course (without vaccine)	NA	£4.80	£4.80	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£4.80	£4.80	–
45	Cost of oseltamivir prophylaxis course	NA	£16.36	£16.36	–
46	Cost of zanamivir prophylaxis course	NA	£24.55	£24.55	–

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£10	£10	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	10	10	–
51	Days per course – oseltamivir prophylaxis	NA	10	10	–
52	Days per course – zanamivir prophylaxis	NA	10	10	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.05	4	73
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.05	4	73
64	Cost of uncomplicated influenza presentation	NA	£29.52	£29.52	–
65	Cost of complicated influenza presentation	NA	£29.52	£29.52	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.16	15	95
72	Probability ICU care | complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	2.30	1	4

continued

TABLE 88 *Post-exposure: at-risk children (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
74	Cost of ITU day	Normal	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£2430.18	£2430.18	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.03	2820	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.03	2977	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.03	2977	100,000
80	QALY loss for influenza case – no treatment	NA	0.02	0.02	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.02	0.02	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	24.74	24.74	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

TABLE 89 *Healthy adults*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.35	–1.05	0.17
9	RR for influenza – amantadine prophylaxis	Lognormal	0.10	–2.26	0.60
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.19	–1.66	0.44
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.21	–1.56	0.24
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	1	1	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	1	1	–
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

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
24	Probability patient presents within 48 hours of ILI onset	Beta	0.16	104	668
25	Probability patient given antiviral treatment | presents < 48 hours	NA	0	0	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	0.89	0.89	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	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 treatment	Beta	0.08	6509	85,248
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	12	6515
35	Probability complication is CNS	Dirichlet	0.02	102	6515
36	Probability complication is renal	Dirichlet	0	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	47,169
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 (without vaccine)	NA	£4.80	£4.80	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£4.80	£4.80	–
45	Cost of oseltamivir prophylaxis course	NA	£16.36	£16.36	–
46	Cost of zanamivir prophylaxis course	NA	£24.55	£24.55	–
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£10	£10	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	10	10	–

continued

TABLE 89 *Healthy adults (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
51	Days per course – oseltamivir prophylaxis	NA	10	10	–
52	Days per course – zanamivir prophylaxis	NA	10	10	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.08	56	674
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.08	56	674
64	Cost of uncomplicated influenza presentation	NA	£30.73	£30.73	–
65	Cost of complicated influenza presentation	NA	£30.73	£30.73	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.11	5	46
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	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£4937.39	£4937.39	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.04	4146	100,000

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.04	4247	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.04	4247	100,000
80	QALY loss for influenza case – no treatment	NA	0.01	0.01	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.01	0.01	–
82	QALY loss for influenza case – zanamivir treatment	NA	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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	13.37	13.37	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

TABLE 90 *Post-exposure prophylaxis: at-risk adults*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.35	–1.05	0.17
9	RR for influenza – amantadine prophylaxis	Lognormal	0.10	–2.26	0.60
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.19	–1.66	0.44
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.21	–1.56	0.24
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	1	1	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	1	1	–
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

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
24	Probability patient presents within 48 hours of ILI onset	Beta	0.16	104	668
25	Probability patient given antiviral treatment | presents < 48 hours	NA	1	1	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	0.89	0.89	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	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 treatment	Beta	0.12	2166	17,597
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	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	47,169
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 (without vaccine)	NA	£4.80	£4.80	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£4.80	£4.80	–
45	Cost of oseltamivir prophylaxis course	NA	£16.36	£16.36	–
46	Cost of zanamivir prophylaxis course	NA	£24.55	£24.55	–
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£10	£10	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	10	10	–

continued

TABLE 90 *Post-exposure prophylaxis: at-risk adults (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
51	Days per course – oseltamivir prophylaxis	NA	10	10	–
52	Days per course – zanamivir prophylaxis	NA	10	10	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.08	56	674
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.08	56	674
64	Cost of uncomplicated influenza presentation	NA	£30.73	£30.73	–
65	Cost of complicated influenza presentation	NA	£30.73	£30.73	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.16	15	95
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	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£4937.39	£4937.39	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.03	2820	100,000

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.03	2977	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.03	2977	100,000
80	QALY loss for influenza case – no treatment	NA	0.02	0.02	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.02	0.02	–
82	QALY loss for influenza case – zanamivir treatment	NA	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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	13.37	13.37	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

TABLE 91 *Post-exposure prophylaxis: healthy elderly*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.42	–0.87	0.23
9	RR for influenza – amantadine prophylaxis	Lognormal	0.10	–2.26	0.60
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.19	–1.66	0.44
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.21	–1.56	0.24
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	1	1	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	1	1	–
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

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	1	1	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	0.89	0.89	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	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 treatment	Beta	0.09	942	10,145
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	15,620
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 (without vaccine)	NA	£4.80	£4.80	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£4.80	£4.80	–
45	Cost of oseltamivir prophylaxis course	NA	£16.36	£16.36	–
46	Cost of zanamivir prophylaxis course	NA	£24.55	£24.55	–

continued

TABLE 91 *Post-exposure prophylaxis: healthy elderly (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£10	£10	–
50	Days per course – amantadine prophylaxis (prior vaccination)	NA	10	10	–
51	Days per course – oseltamivir prophylaxis	NA	10	10	–
52	Days per course – zanamivir prophylaxis	NA	10	10	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.38	62	165
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.38	62	165
64	Cost of uncomplicated influenza presentation	NA	£43.20	£43.20	–
65	Cost of complicated influenza presentation	NA	£43.20	£43.20	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7-day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.16	15	95
72	Probability ICU care | complication	Beta	0.05	22	453

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
73	Inpatient LOS (days)	Gamma	15	25	1
74	Cost of ITU day	Normal	£1345.39	£1345.39	£31.95
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£5747.01	£5747.01	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.03	2820	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.03	2977	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.03	2977	100,000
80	QALY loss for influenza case – no treatment	NA	0.02	0.02	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.01	0.01	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

continued

TABLE 91 *Post-exposure prophylaxis: healthy elderly (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	2.95	2.95	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

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TABLE 92 *Post-exposure prophylaxis: at-risk elderly*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 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 influenza is influenza A in influenza A dominant seasons	Beta	0.86	740	859
5	Probability influenza is influenza A in influenza B dominant years	Beta	0.30	83	281
6	Probability influenza is influenza A	NA	0.72	0.72	–
7	Duration of influenza epidemic (days)	Gamma	40	32.65	1.23
Effectiveness parameters (prevention)					
8	RR for influenza – vaccine	Lognormal	0.42	–0.87	0.23
9	RR for influenza – amantadine prophylaxis	Lognormal	0.10	–2.26	0.60
10	RR for influenza – oseltamivir prophylaxis	Lognormal	0.19	–1.66	0.44
11	RR for influenza – zanamivir prophylaxis	Lognormal	0.21	–1.56	0.24
12	Probability of amantadine resistance	Beta	0.37	73.40	199
13	Probability influenza case occurs within epidemic	Beta	1	1	1125
14	Probability influenza case avoidable – amantadine	NA	1	1	–
15	Probability influenza case avoidable – amantadine (vaccination)	NA	1	1	–
16	Probability influenza case avoidable – oseltamivir	NA	1	1	–
17	Percentage of influenza cases avoidable – zanamivir	NA	1	1	–
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

continued

TABLE 92 *Post-exposure prophylaxis: at-risk elderly (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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 treatment | presents < 48 hours	NA	1	1	–
26	Probability patient receives oseltamivir | prescribed antiviral	NA	0.89	0.89	–
27	Probability patient receives zanamivir | prescribed antiviral	NA	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 treatment	Beta	0.12	908	7407
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	15,620
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 (without vaccine)	NA	£4.80	£4.80	–
44	Cost of amantadine prophylaxis course (with vaccine)	NA	£4.80	£4.80	–
45	Cost of oseltamivir prophylaxis course	NA	£16.36	£16.36	–
46	Cost of zanamivir prophylaxis course	NA	£24.55	£24.55	–
47	Cost of oseltamivir treatment course	NA	£16.36	£16.36	–

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No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
48	Cost of zanamivir treatment course	NA	£24.55	£24.55	–
49	Days per course – amantadine prophylaxis	NA	£10	£10	–
50	Days per course – amantadine prophylaxis (prior vac)	NA	10	10	–
51	Days per course – oseltamivir prophylaxis	NA	10	10	–
52	Days per course – zanamivir prophylaxis	NA	10	10	–
53	Acquisition cost for vaccination	NA	£5.63	£5.63	–
54	Administration cost for vaccination	NA	£25	£25	–
55	Cost of attendance at GP surgery consultation	NA	£25	£25	–
56	Cost of attendance at GP home visit	NA	£69	£69	–
57	Cost of attendance at A&E	NA	£95.56	£95.56	–
58	Probability A&E attendance | patient presents (no complication)	Beta	0.03	8.35	270.11
59	Probability GP attendance | patient presents (no complication)	NA	0.97	0.97	–
60	Probability home GP visit | GP presentation (no complication)	Beta	0.38	62	165
61	Probability A&E attendance | patient presents (complication)	Beta	0.03	8.35	270.11
62	Probability GP attendance | patient presents (complication)	NA	0.97	0.97	–
63	Probability home GP visit | GP presentation (complication)	Beta	0.38	62	165
64	Cost of uncomplicated influenza presentation	NA	£43.20	£43.20	–
65	Cost of complicated influenza presentation	NA	£43.20	£43.20	–
66	Cost of antibiotics course	NA	£6.80	£6.80	–
67	Cost of anti-emetics course (metaclopramide 7 day course)	NA	£1.69	£1.69	–
68	Cost of managing adverse events – vaccination	NA	£25	£25	–
69	Cost of managing adverse events – amantadine prophylaxis	NA	£25	£25	–
70	Cost of inpatient episode	Gamma	£261.17	£261.17	5.16
71	Probability hospitalisation no treatment | complication	Beta	0.16	15	95
72	Probability ICU care | complication	Beta	0.05	22	453
73	Inpatient LOS (days)	Gamma	15	25	1
74	Cost of ITU day	Normal	£1345.39	£1345.39	£31.95

continued

TABLE 92 *Post-exposure prophylaxis: at-risk elderly (continued)*

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
75	ITU LOS (days)	Gamma	28	11.60	2.41
76	Expected cost of hospitalisation	NA	£5747.01	£5747.01	–
HRQoL parameters					
77	21-day QALYs for influenza case – no treatment	Beta	0.03	2820	100,000
78	21-day QALYs for influenza case – oseltamivir treatment	Beta	0.03	2977	100,000
79	21-day QALYs for influenza case – zanamivir treatment	Beta	0.03	2977	100,000
80	QALY loss for influenza case – no treatment	NA	0.02	0.02	–
81	QALY loss for influenza case – oseltamivir treatment	NA	0.01	0.01	–
82	QALY loss for influenza case – zanamivir treatment	NA	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

No.	Parameter description	Distribution	Mean	Parameter 1	Parameter 2
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	NA	0.51	0.51	–
105	QALY loss for premature death	NA	2.95	2.95	–
106	Discount rate for QALYs	NA	3.50%	3.50%	–

Appendix 8

Cost-effectiveness acceptability curves (base-case analysis)

Cost-effectiveness acceptability curves for seasonal prophylaxis

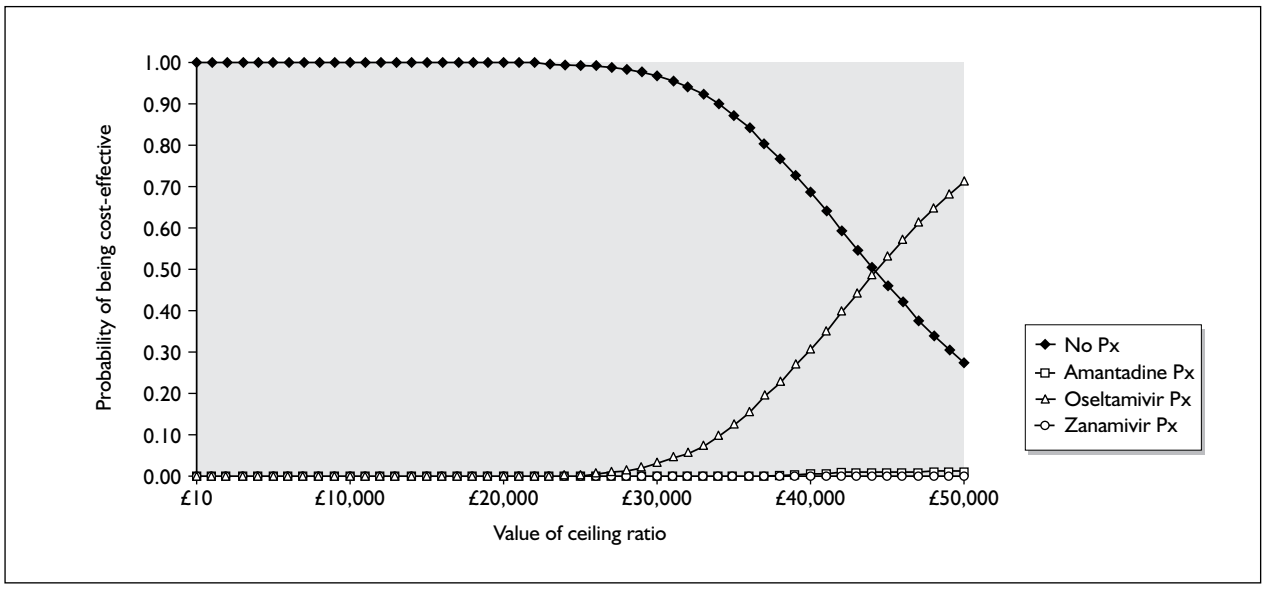

FIGURE 6 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy children (no vaccination). Px, prophylaxis.*

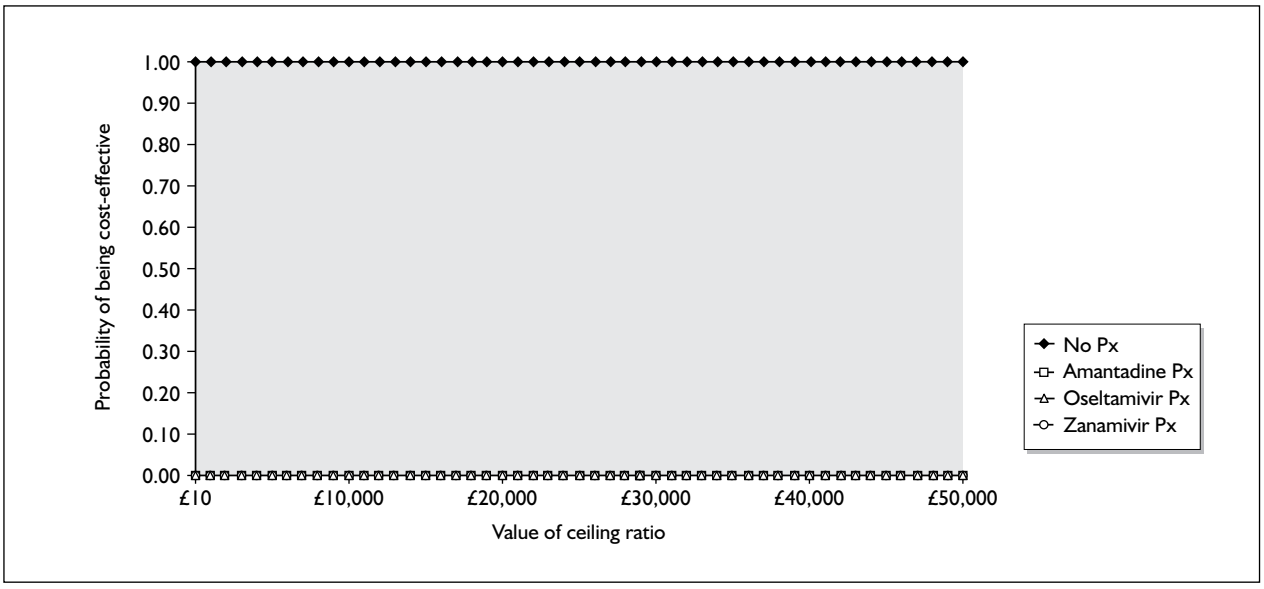

FIGURE 7 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy children (prior vaccination). Px, prophylaxis.*

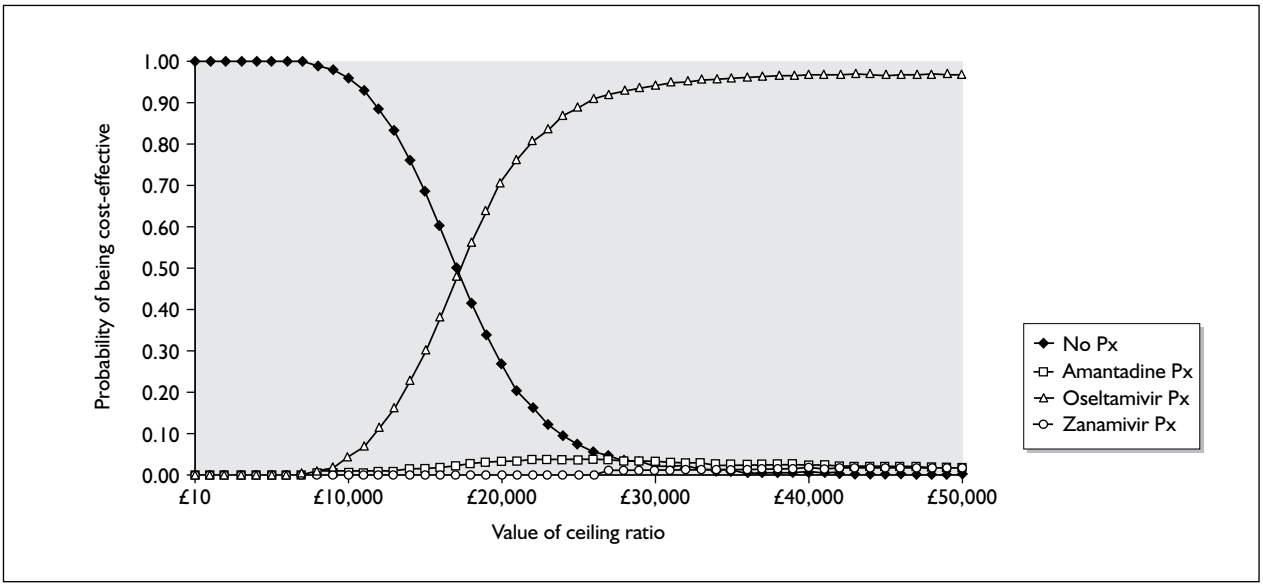

FIGURE 8 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk children (no vaccination). Px, prophylaxis.*

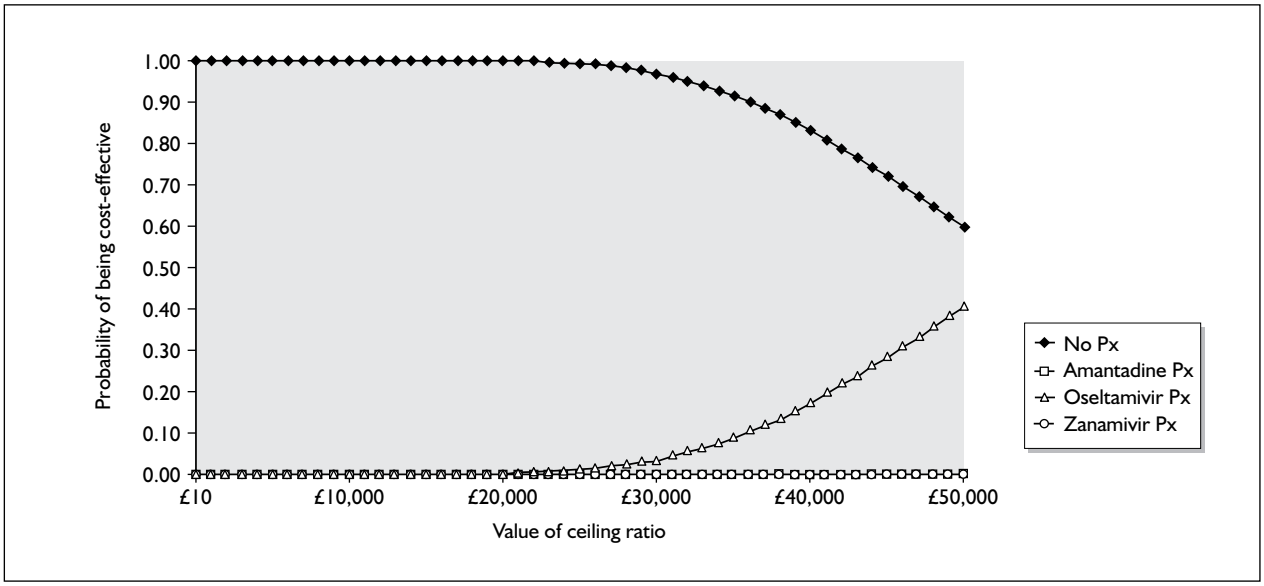

FIGURE 9 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk children (prior vaccination). Px, prophylaxis.*

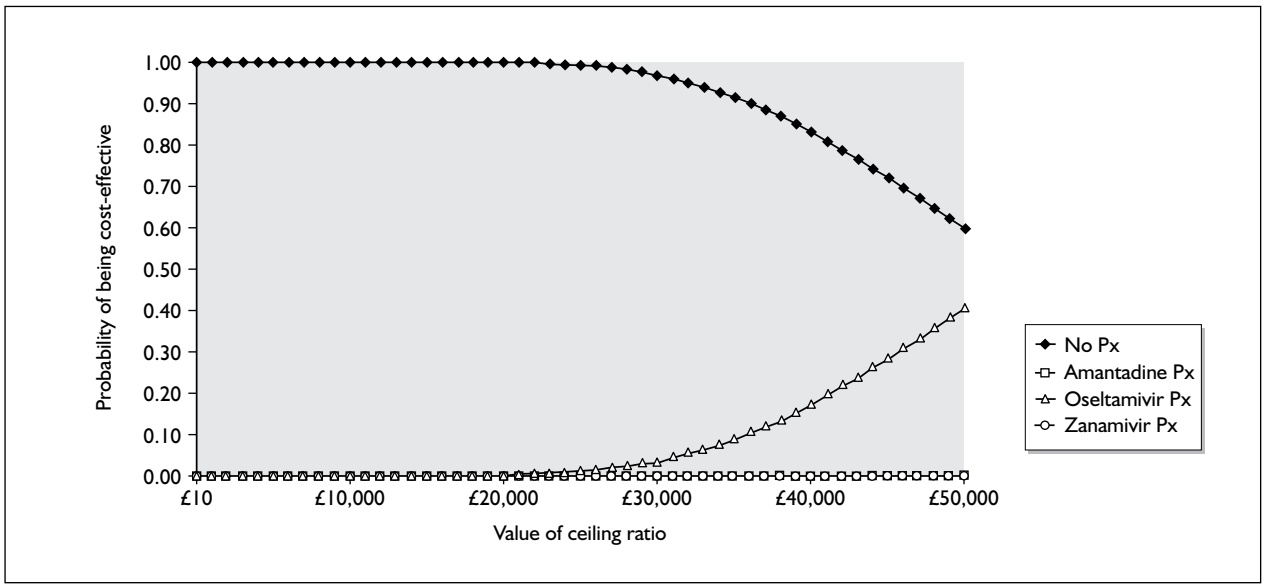

FIGURE 10 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy adults (no vaccination). Px, prophylaxis.*

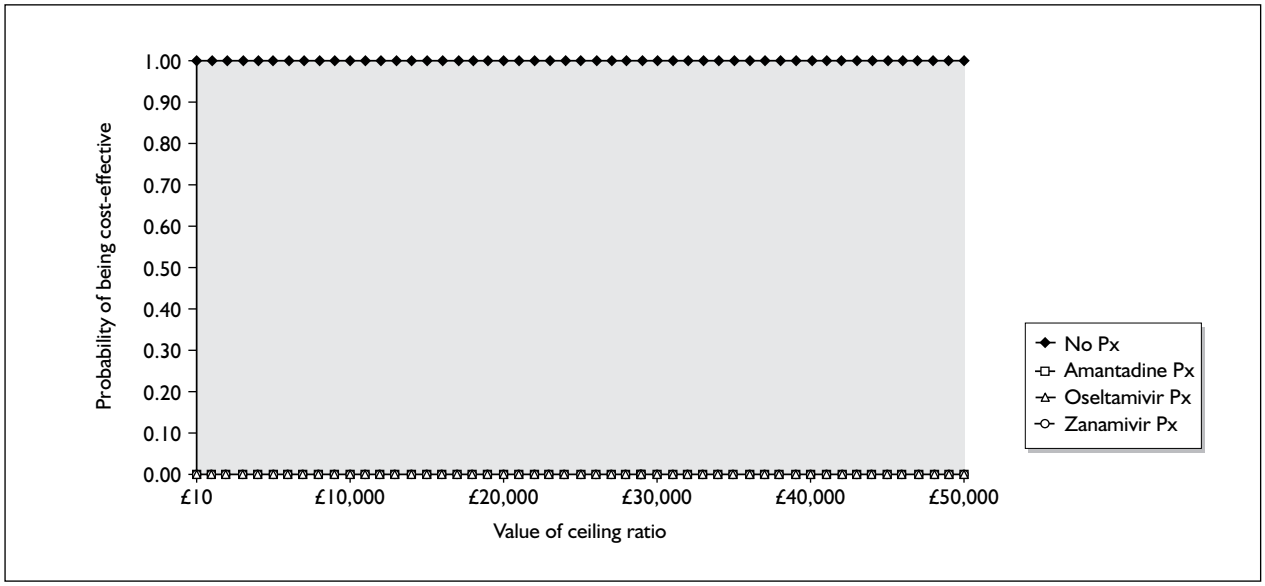

FIGURE 11 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy adults (prior vaccination). Px, prophylaxis.*

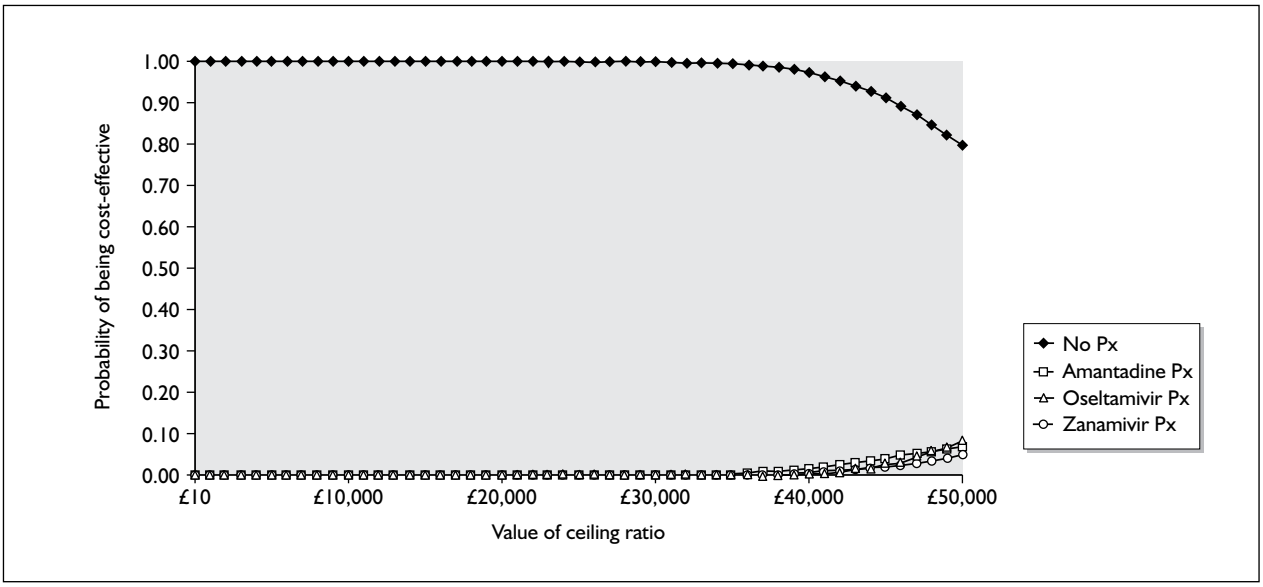

FIGURE 12 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk adults (no vaccination). Px, prophylaxis.*

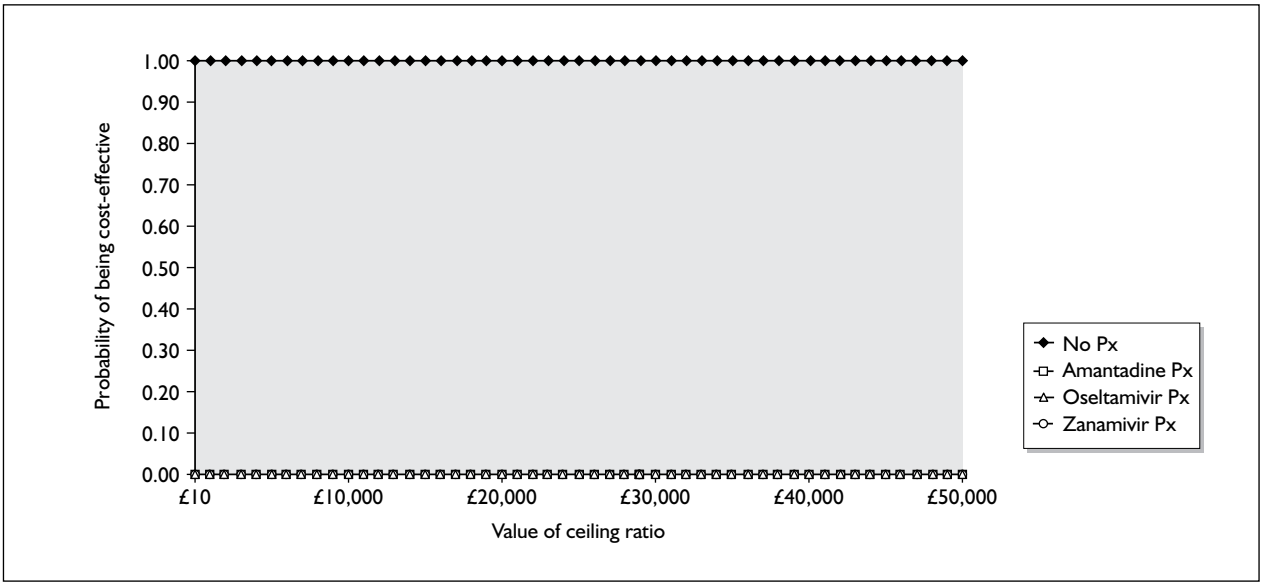

FIGURE 13 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk adults (prior vaccination). Px, prophylaxis.*

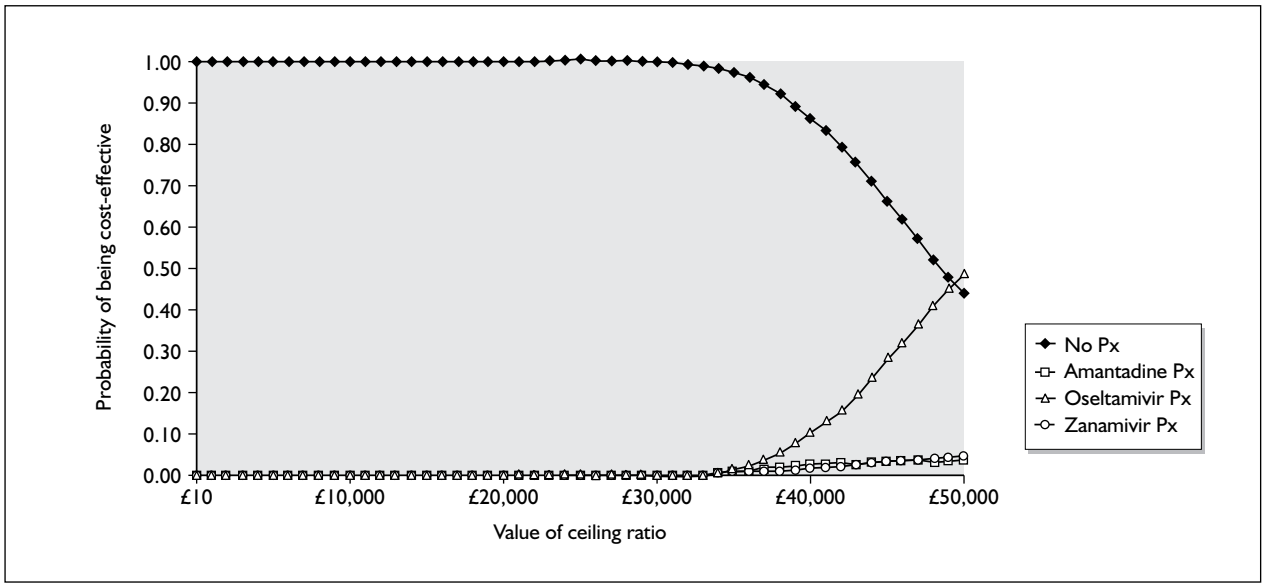

FIGURE 14 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy elderly (no vaccination). Px, prophylaxis.*

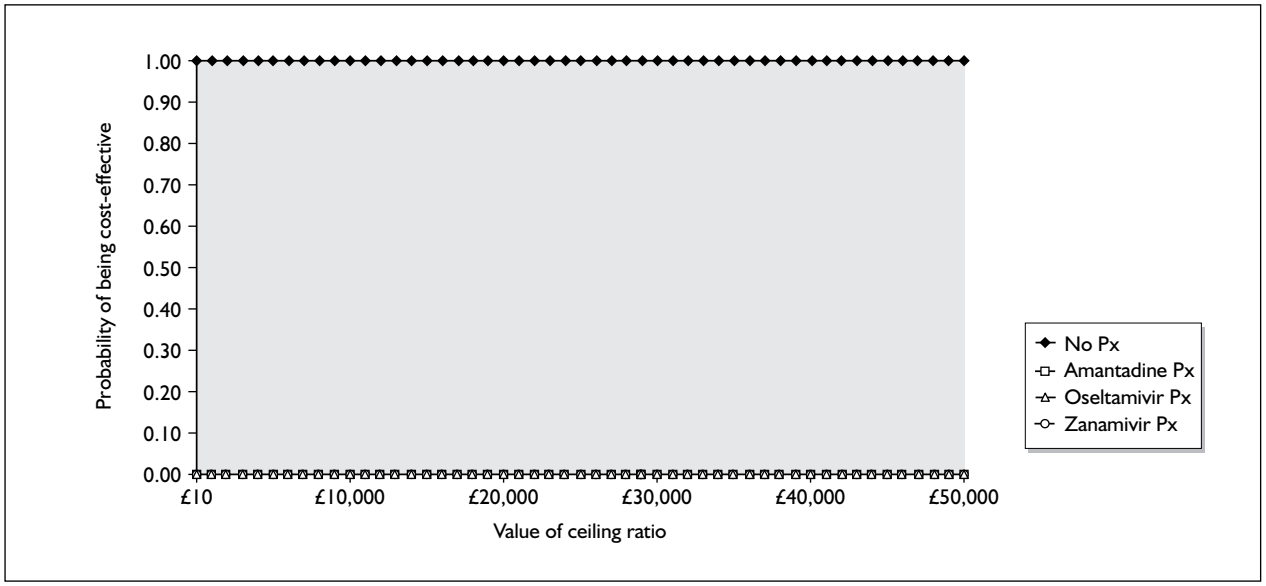

FIGURE 15 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy elderly (prior vaccination). Px, prophylaxis.*

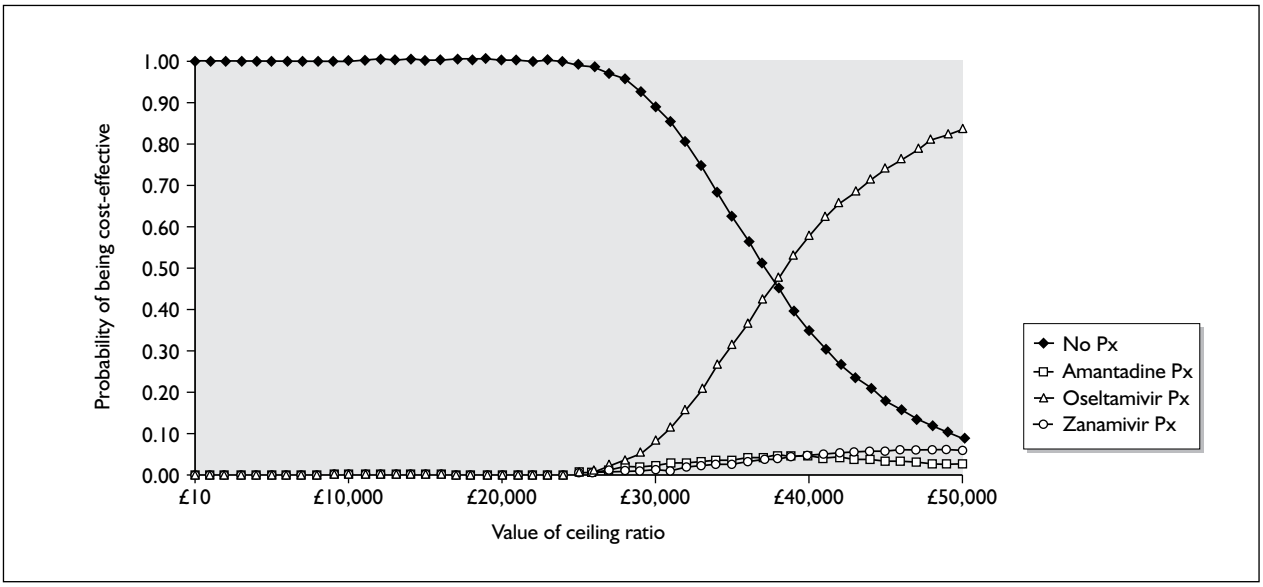

FIGURE 16 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk elderly (no vaccination). Px, prophylaxis.*

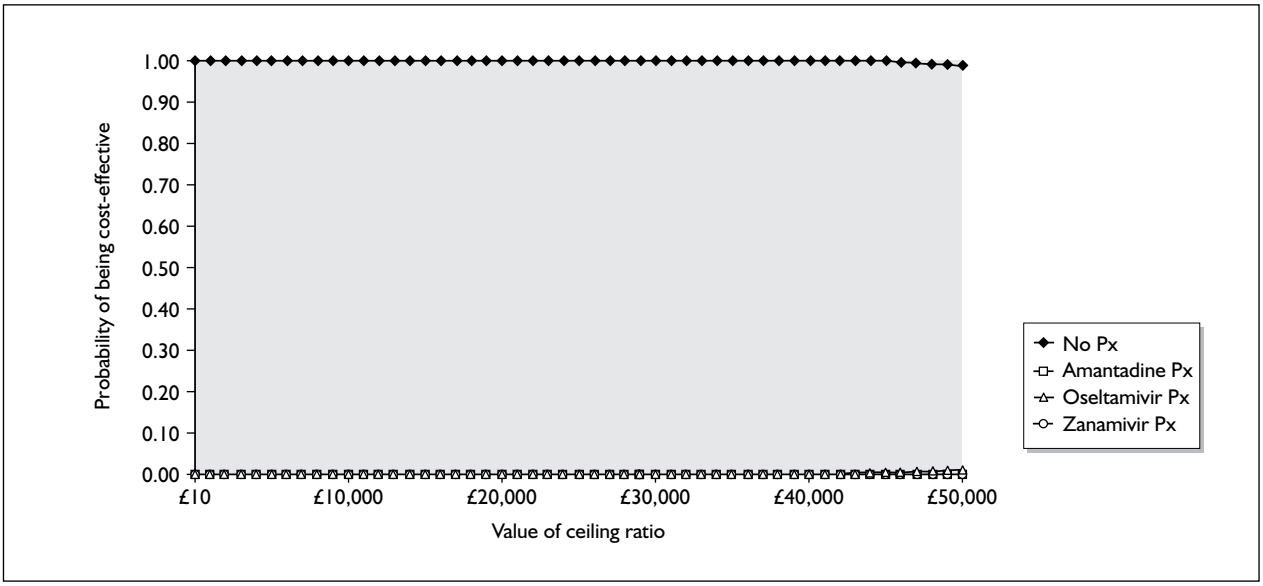

FIGURE 17 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk elderly (prior vaccination). Px, prophylaxis.*

Cost-effectiveness acceptability curves for post-exposure prophylaxis

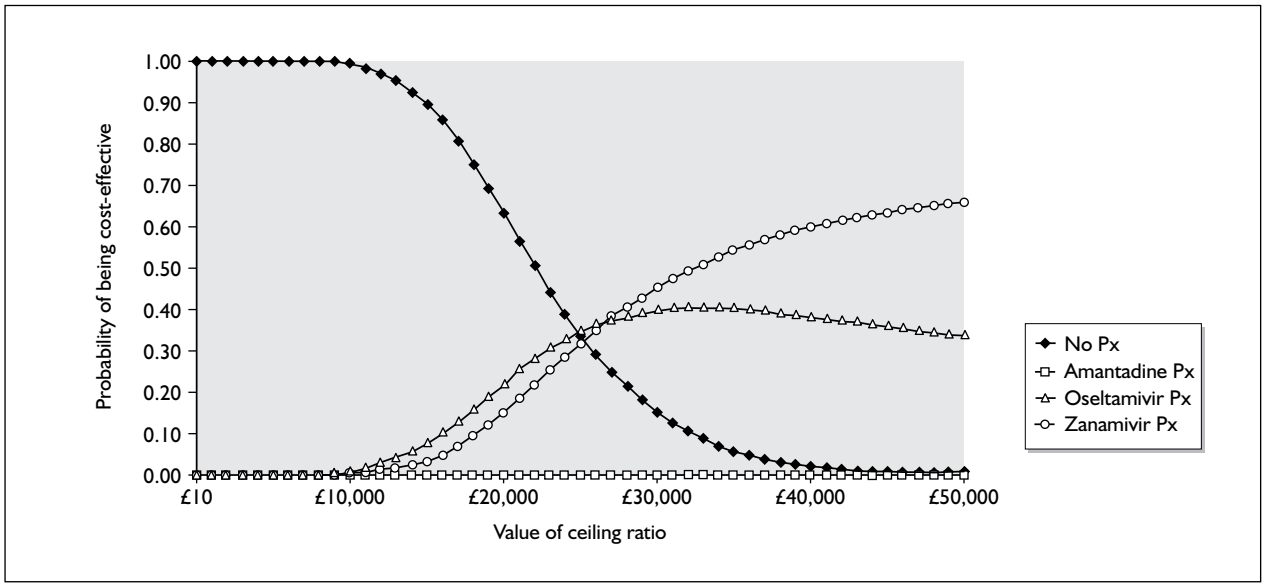

FIGURE 18 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy children (no vaccination). Px, prophylaxis.*

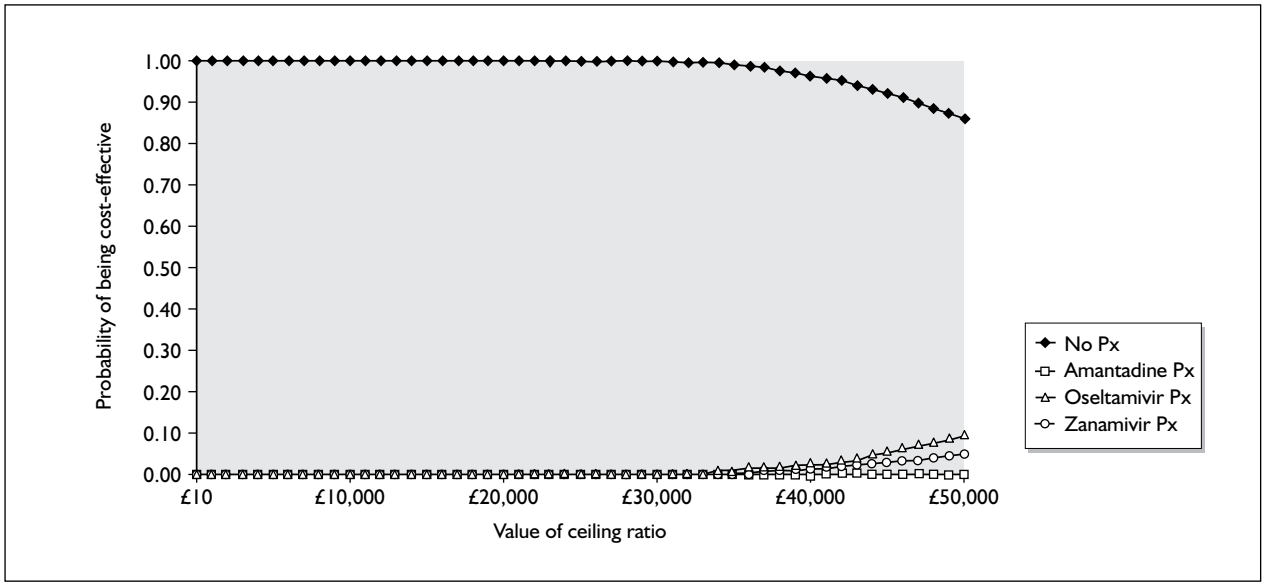

FIGURE 19 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy children (prior vaccination). Px, prophylaxis.*

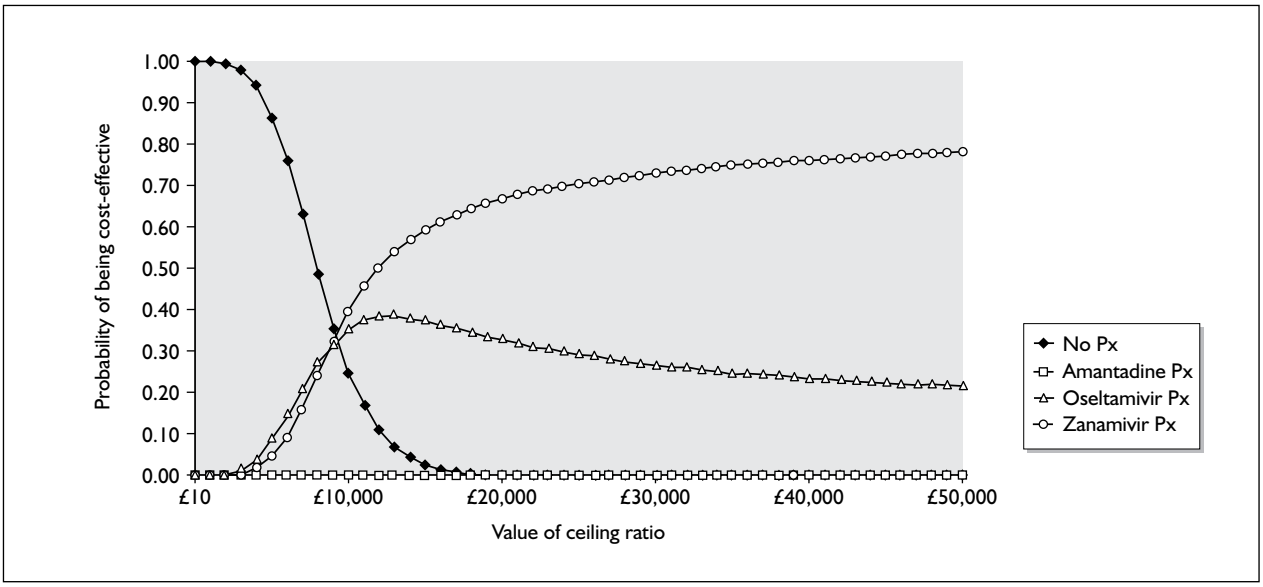

FIGURE 20 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk children (no vaccination). Px, prophylaxis.*

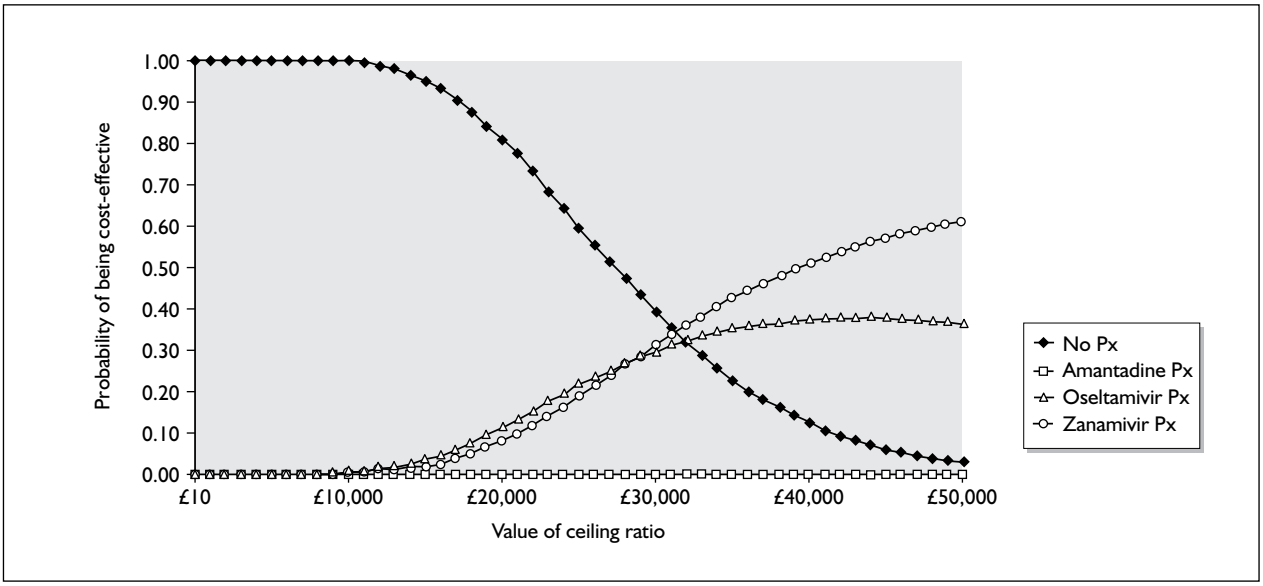

FIGURE 21 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk children (prior vaccination). Px, prophylaxis.*

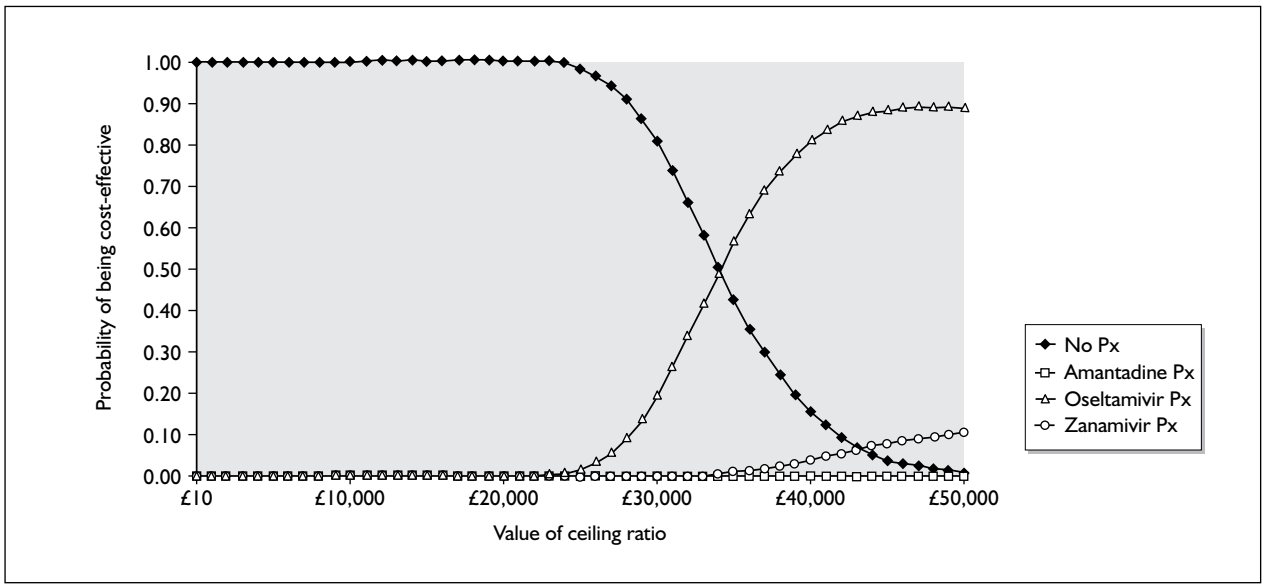

FIGURE 22 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy adults (no vaccination). Px, prophylaxis.*

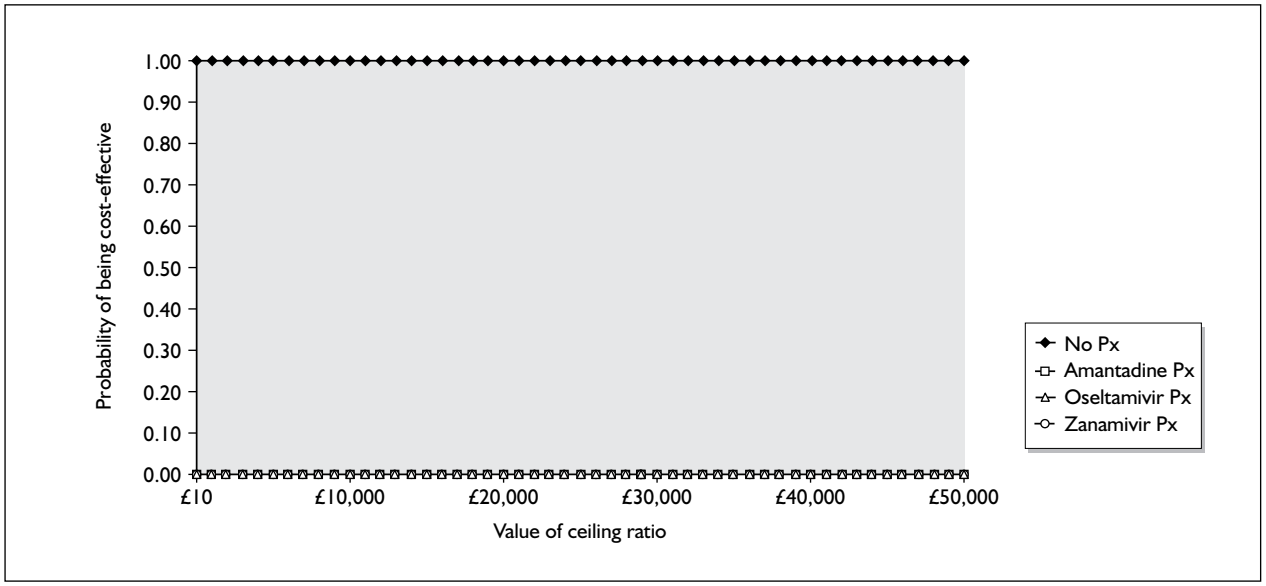

FIGURE 23 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy adults (prior vaccination). Px, prophylaxis.*

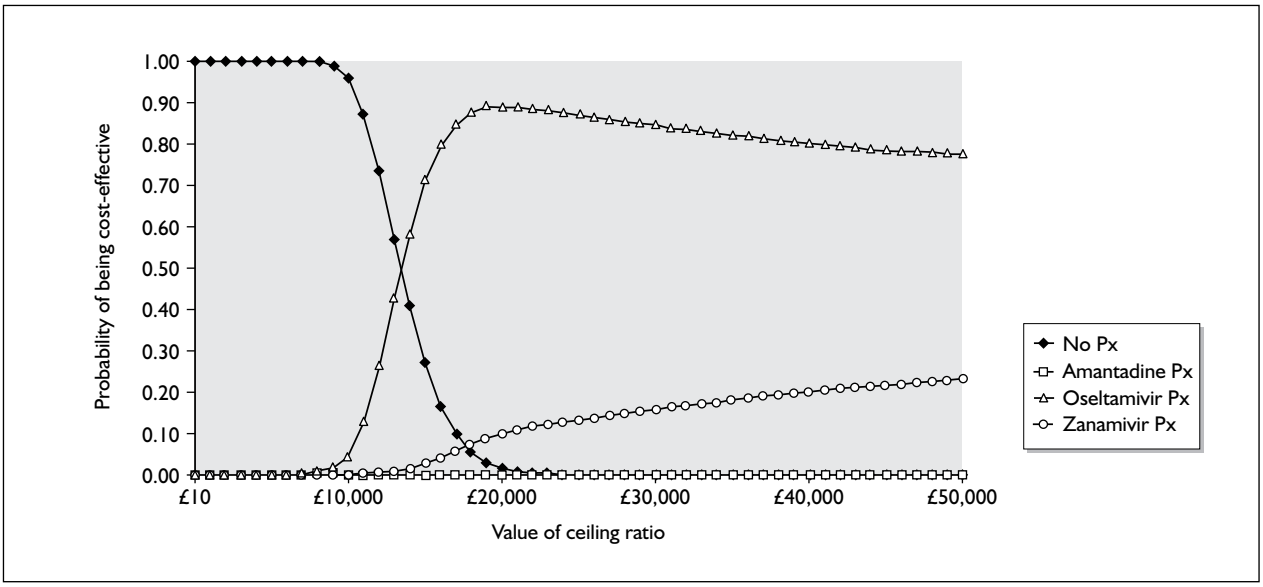

FIGURE 24 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk adults (no vaccination). Px, prophylaxis.*

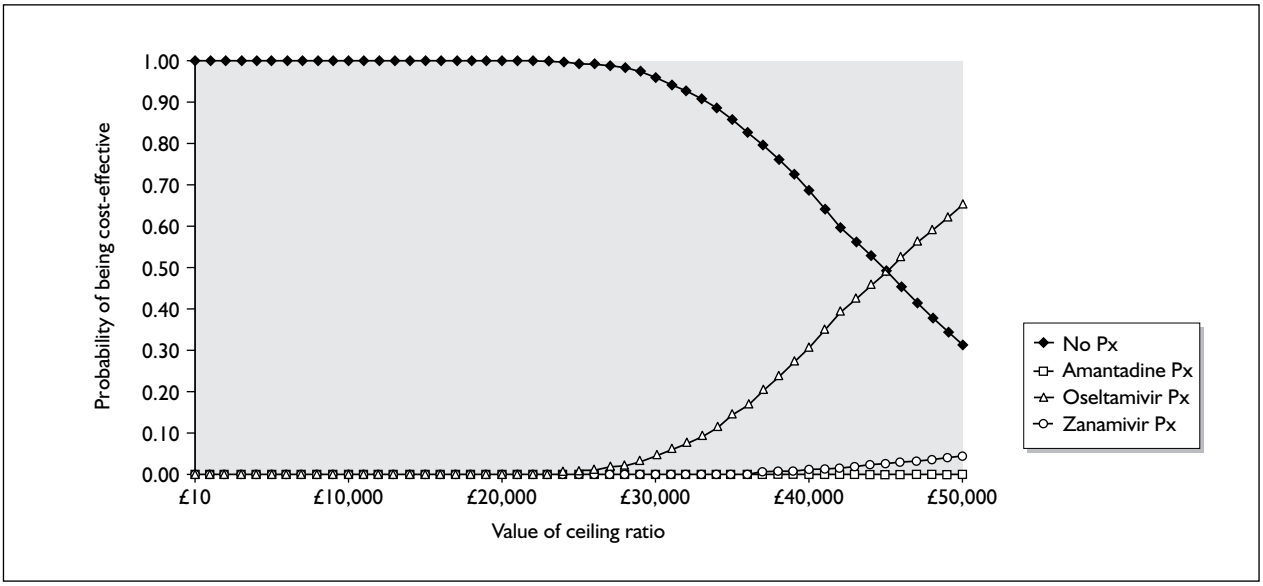

FIGURE 25 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk adults (prior vaccination). Px, prophylaxis.*

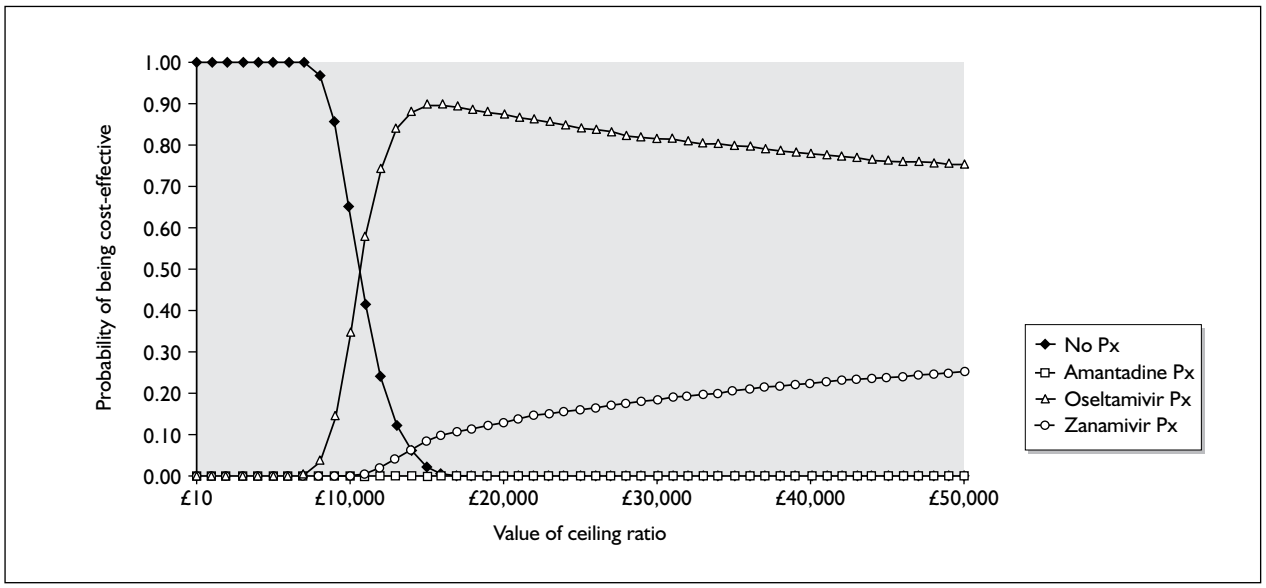

FIGURE 26 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy elderly (no vaccination). Px, prophylaxis.*

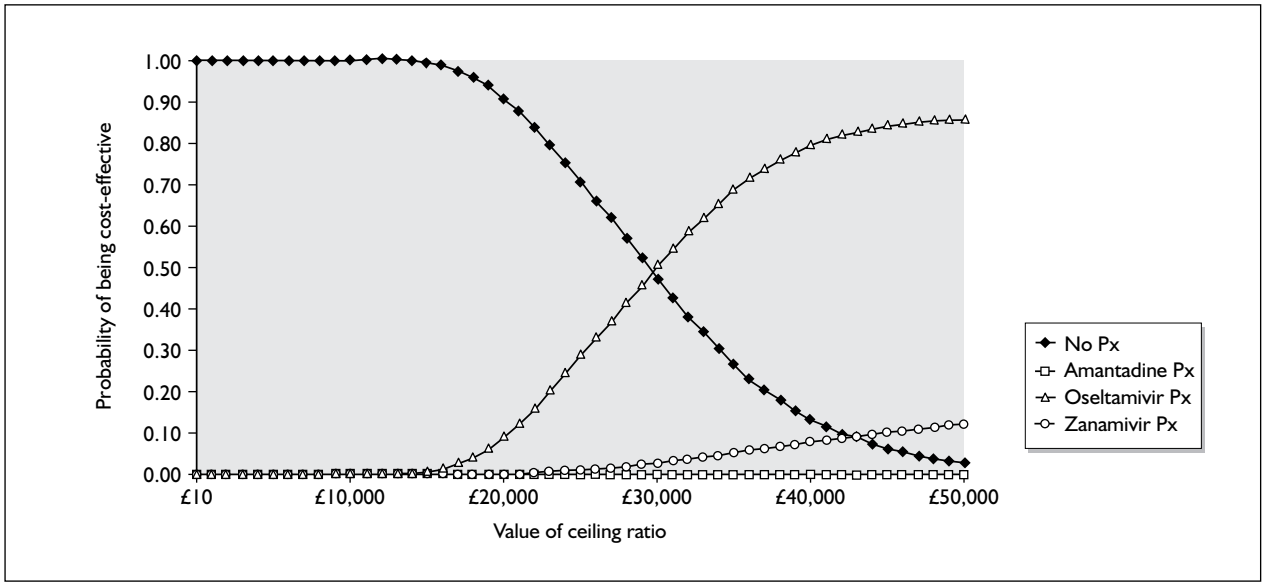

FIGURE 27 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy elderly (prior vaccination). Px, prophylaxis.*

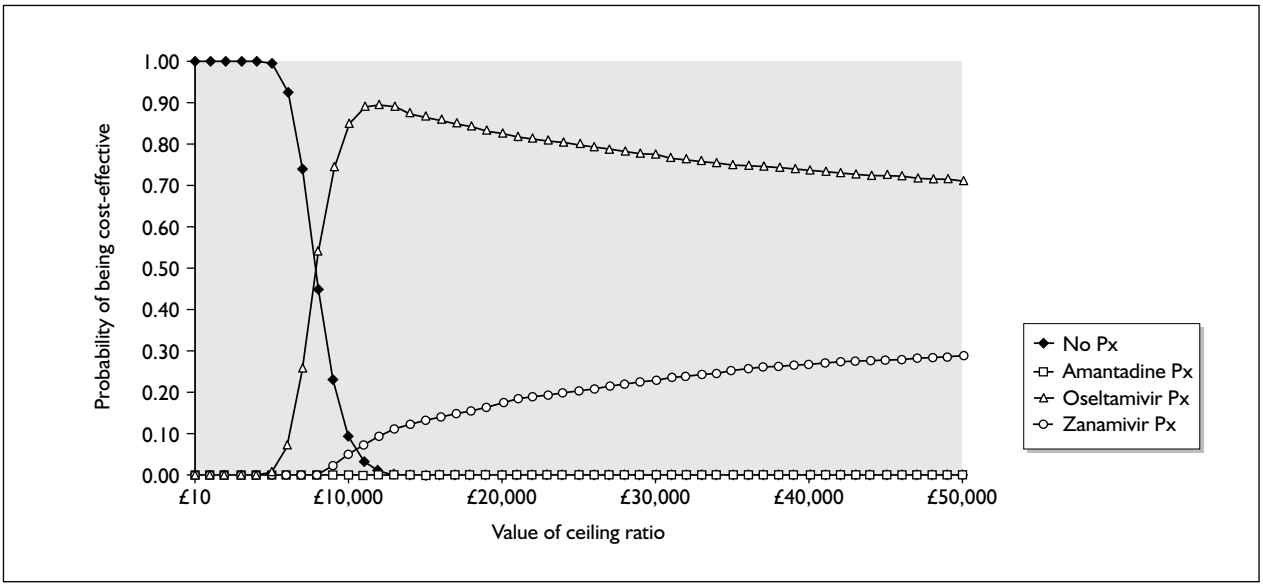

FIGURE 28 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk elderly (no vaccination). Px, prophylaxis.*

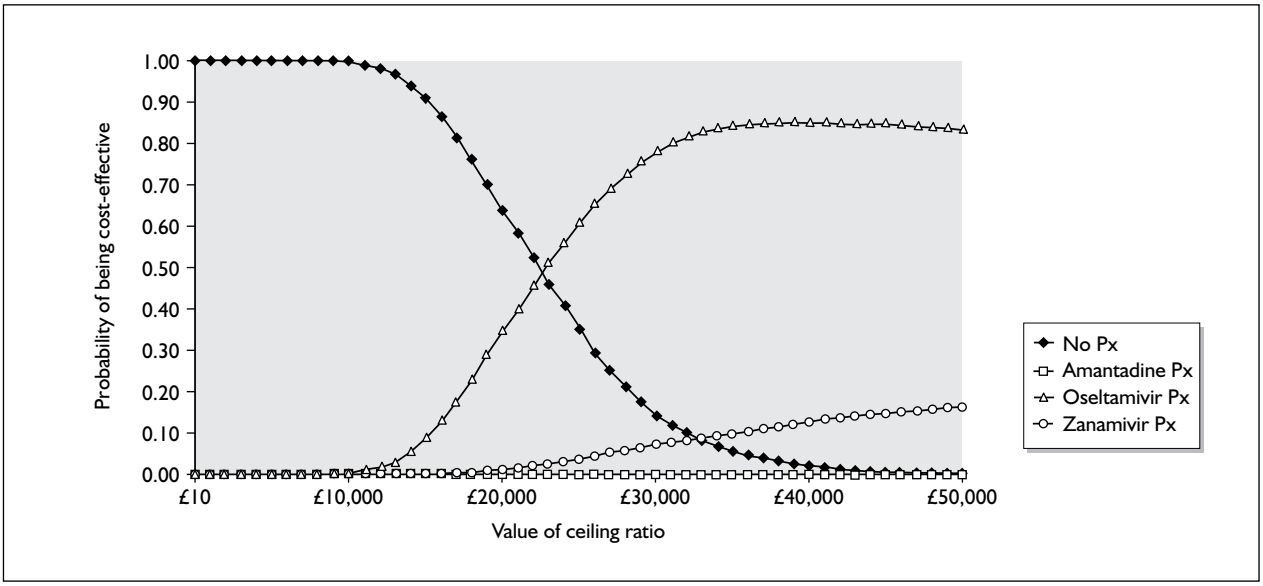

FIGURE 29 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk elderly (prior vaccination). Px, prophylaxis.*

Appendix 9

Cost-effectiveness acceptability curves (incorporating proposed price reduction for zanamivir)

Cost-effectiveness acceptability curves for seasonal prophylaxis

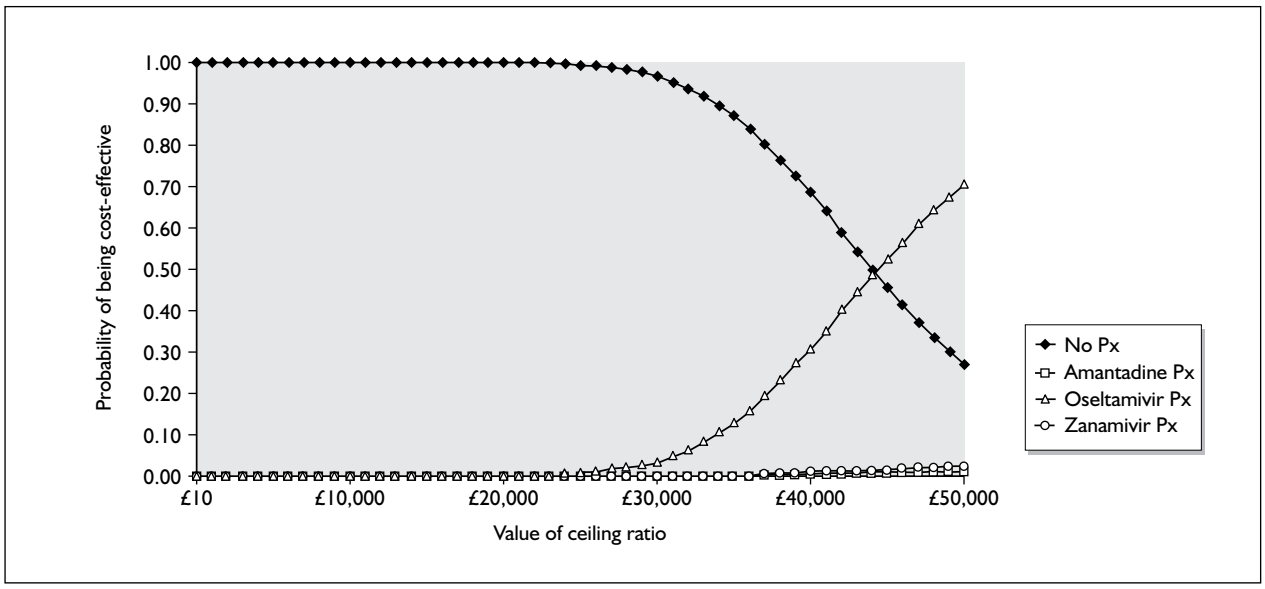

FIGURE 30 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy children (no vaccination). Px, prophylaxis.*

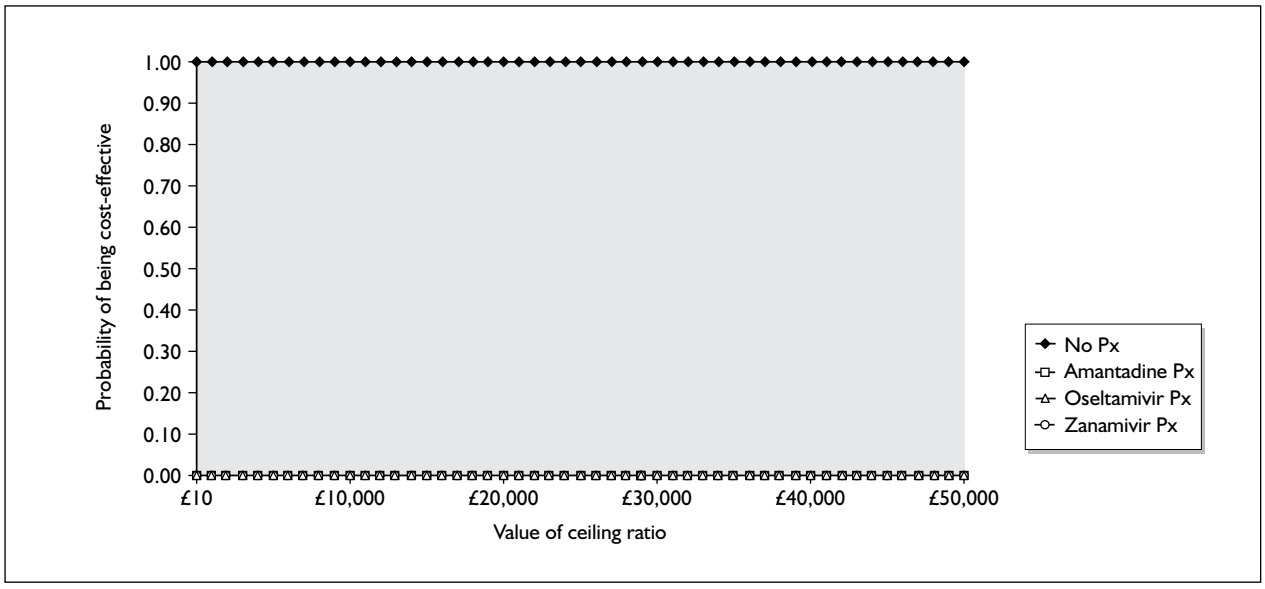

FIGURE 31 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy children (prior vaccination). Px, prophylaxis.*

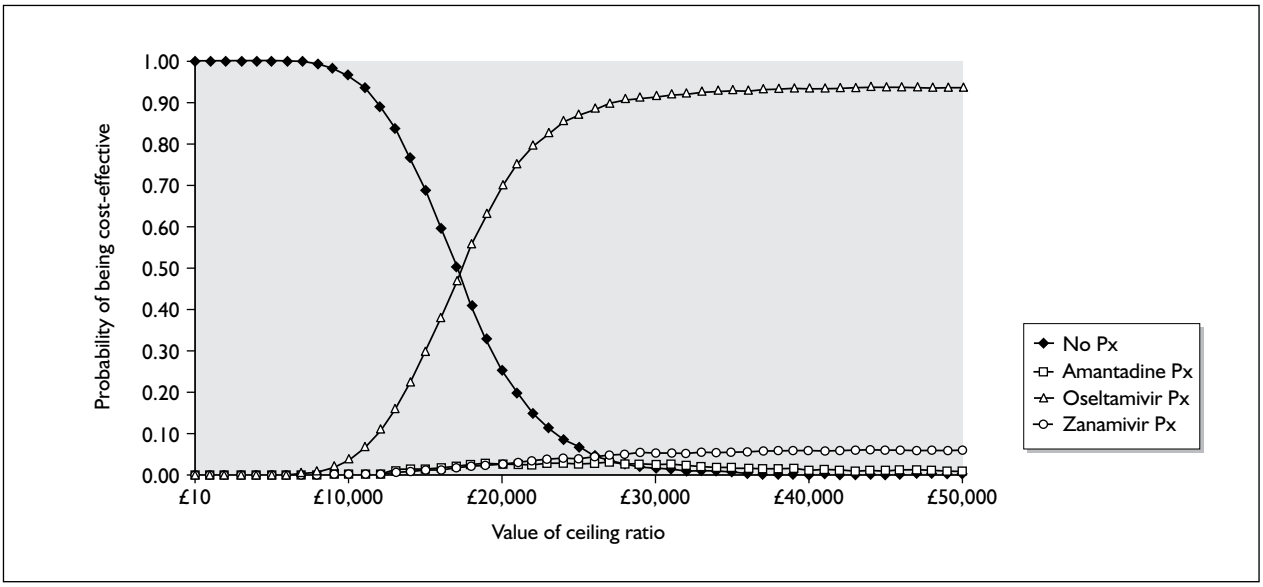

FIGURE 32 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk children (no vaccination). Px, prophylaxis.*

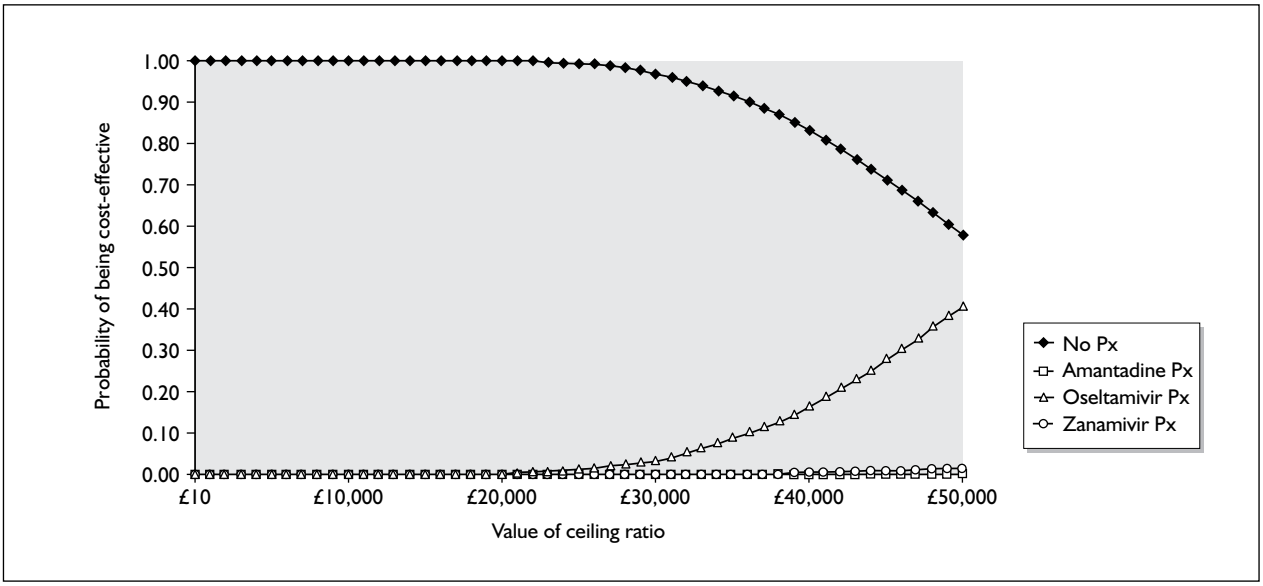

FIGURE 33 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk children (prior vaccination). Px, prophylaxis.*

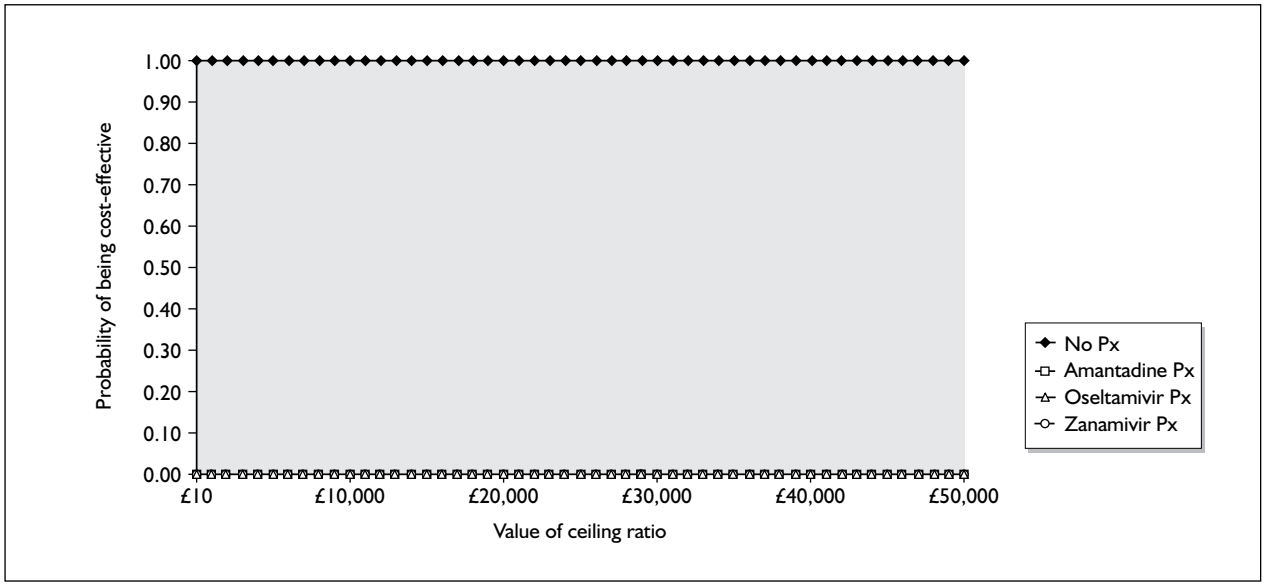

FIGURE 34 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy adults (no vaccination). Px, prophylaxis.*

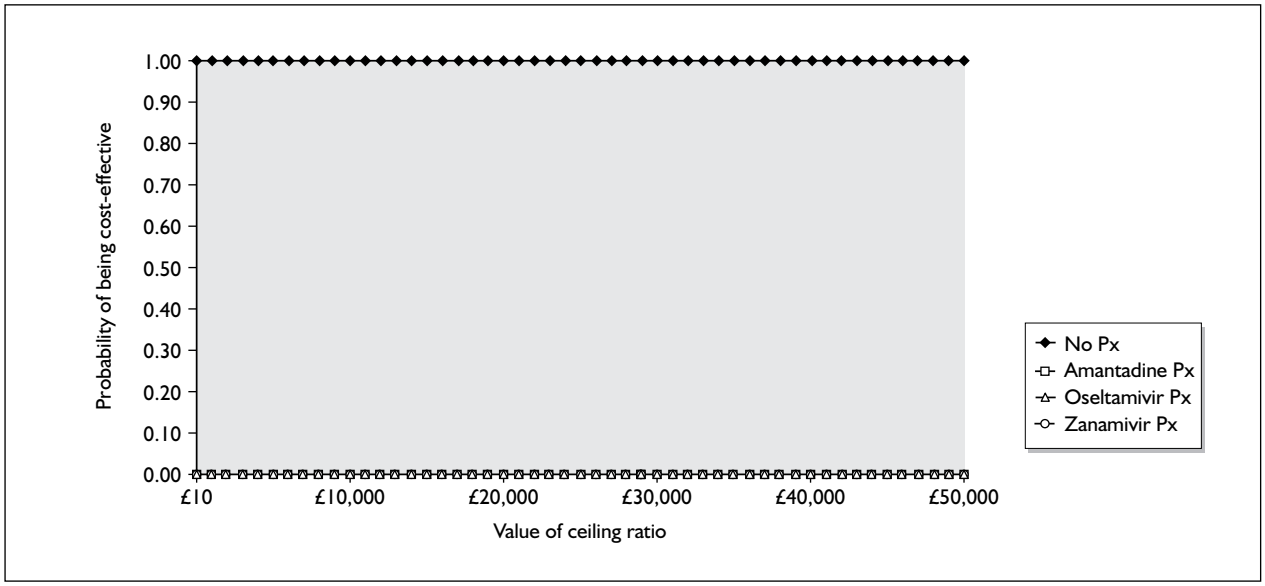

FIGURE 35 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy adults (prior vaccination). Px, prophylaxis.*

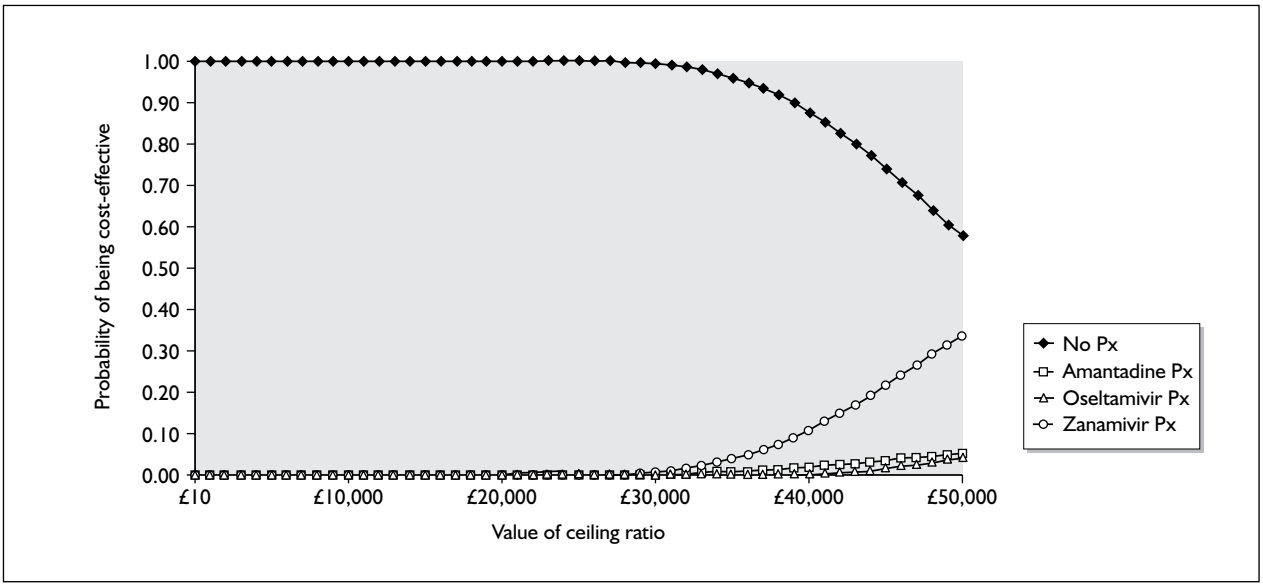

FIGURE 36 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk adults (no vaccination). Px, prophylaxis.*

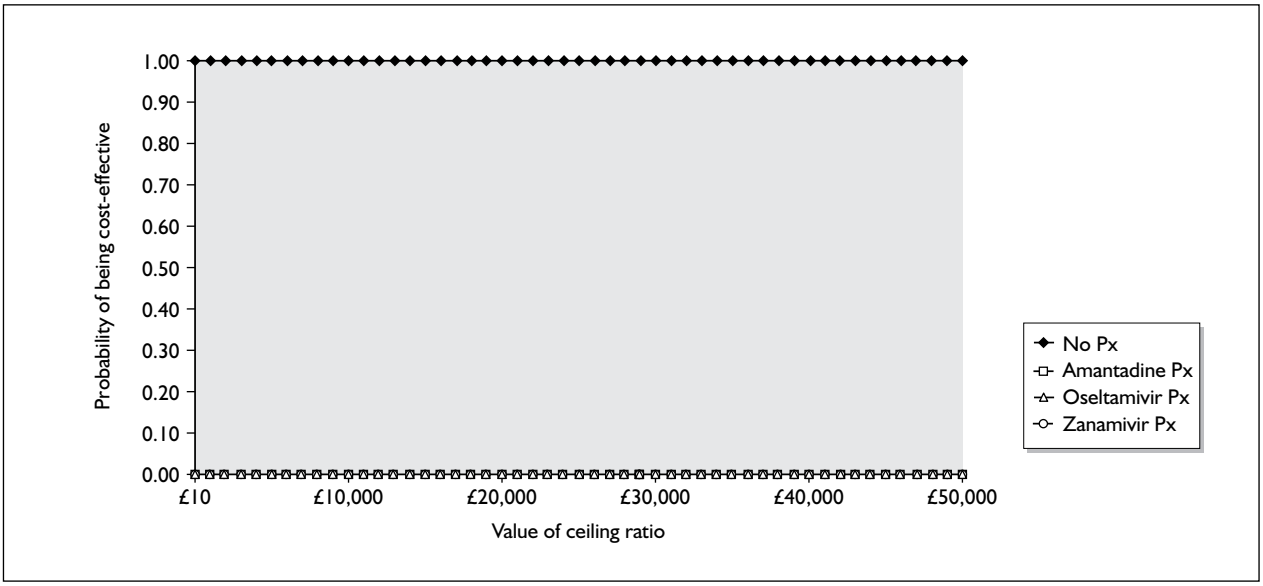

FIGURE 37 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk adults (prior vaccination). Px, prophylaxis.*

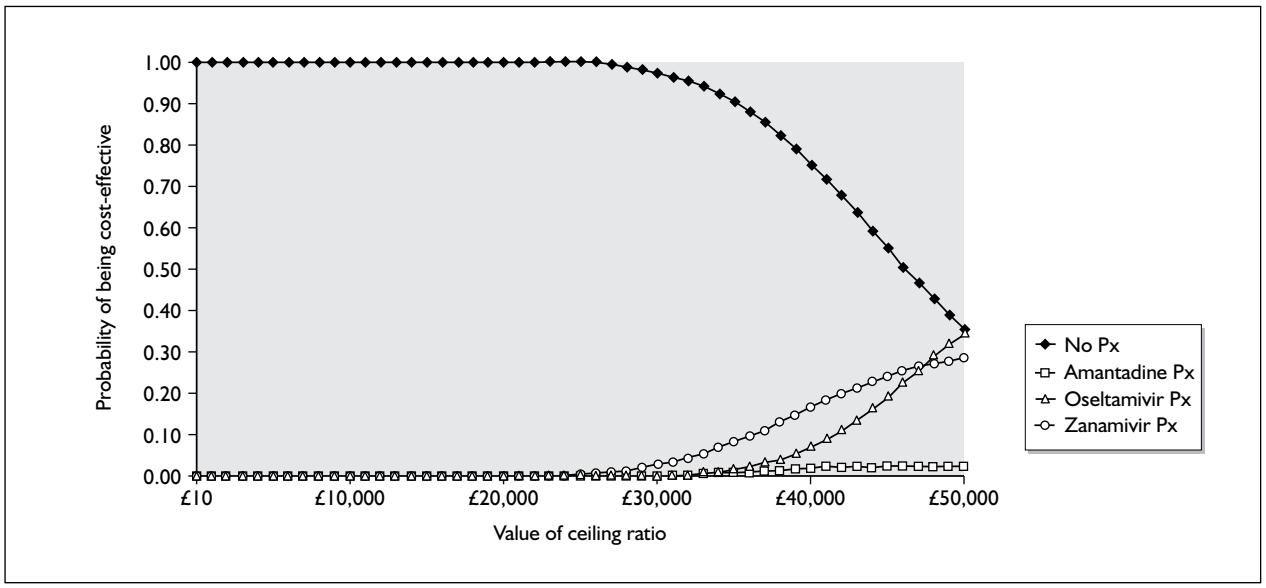

FIGURE 38 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy elderly (no vaccination). Px, prophylaxis.*

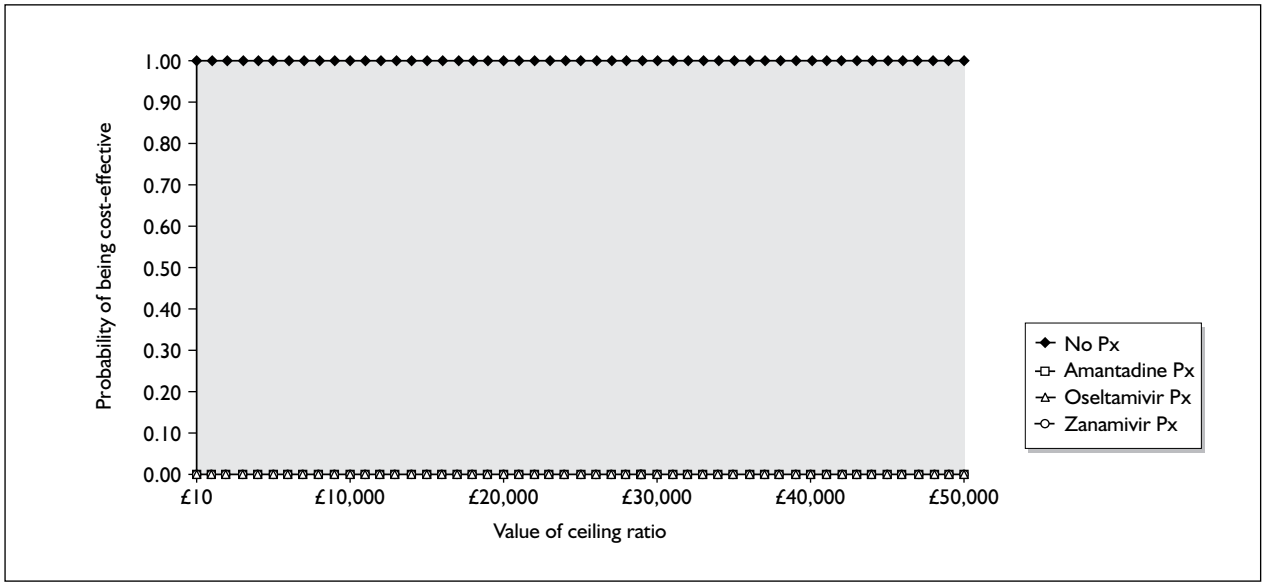

FIGURE 39 *Cost-effectiveness acceptability curves: seasonal prophylaxis, healthy elderly (prior vaccination). Px, prophylaxis.*

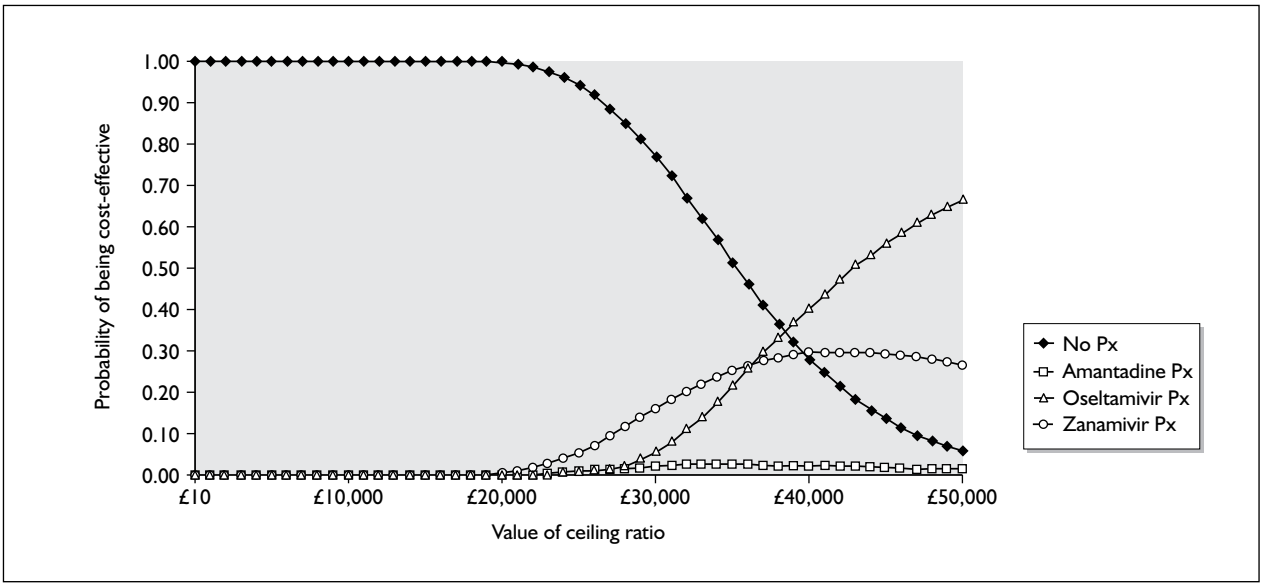

FIGURE 40 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk elderly (no vaccination). Px, prophylaxis.*

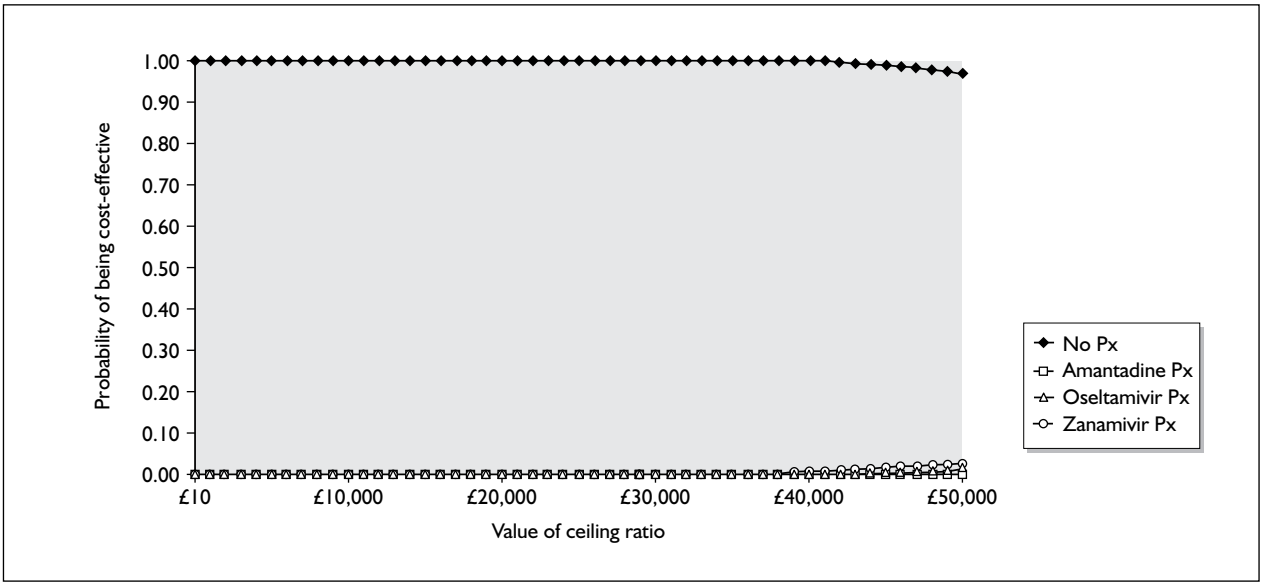

FIGURE 41 *Cost-effectiveness acceptability curves: seasonal prophylaxis, at-risk elderly (prior vaccination). Px, prophylaxis.*

Cost-effectiveness acceptability curves for post-exposure prophylaxis

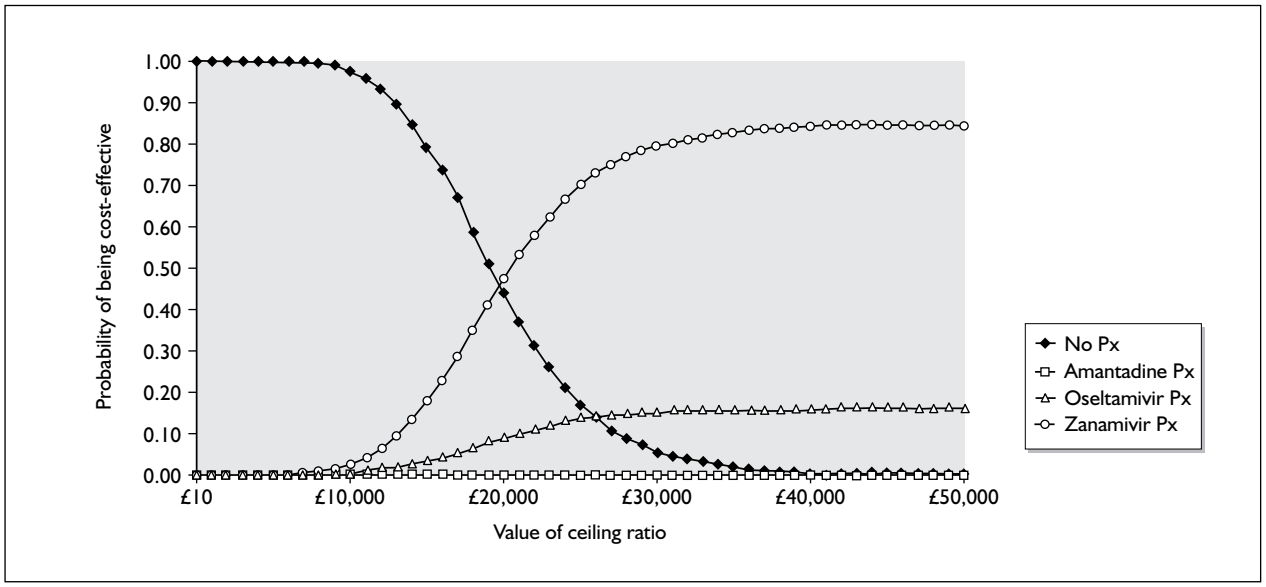

FIGURE 42 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy children (no vaccination). Px, prophylaxis.*

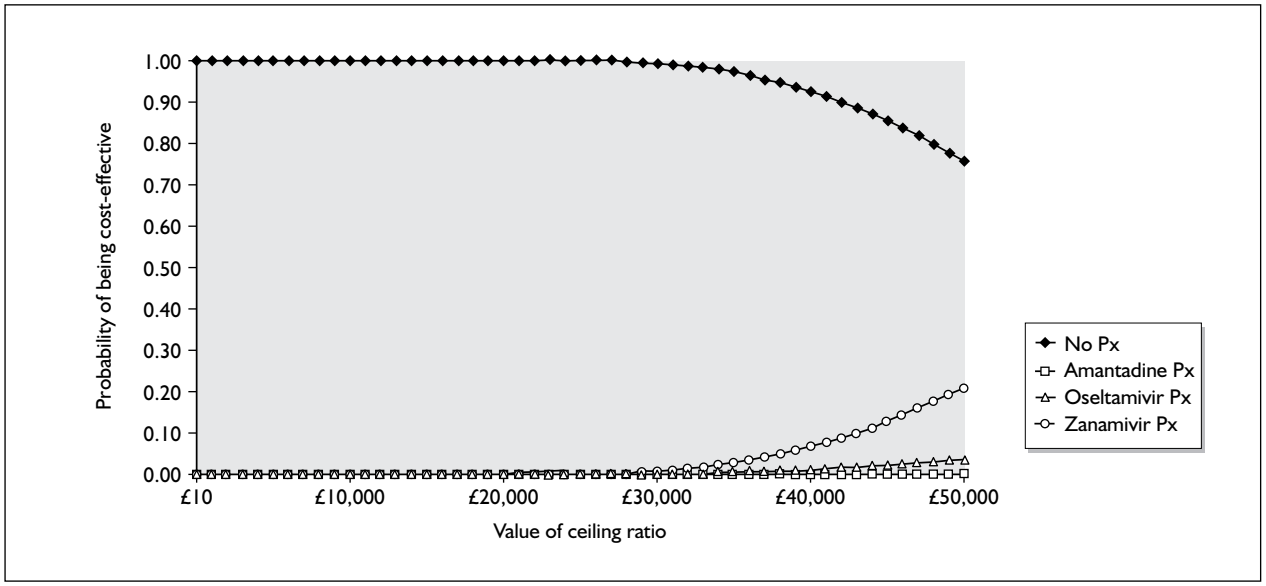

FIGURE 43 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy children (prior vaccination). Px, prophylaxis.*

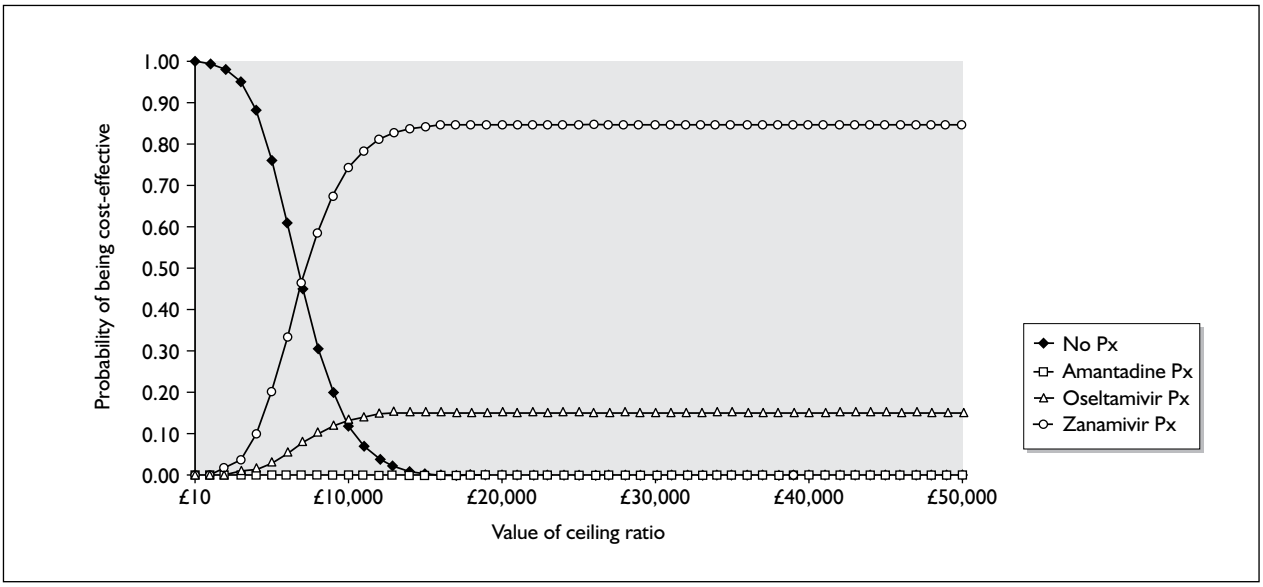

FIGURE 44 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk children (no vaccination). Px, prophylaxis.*

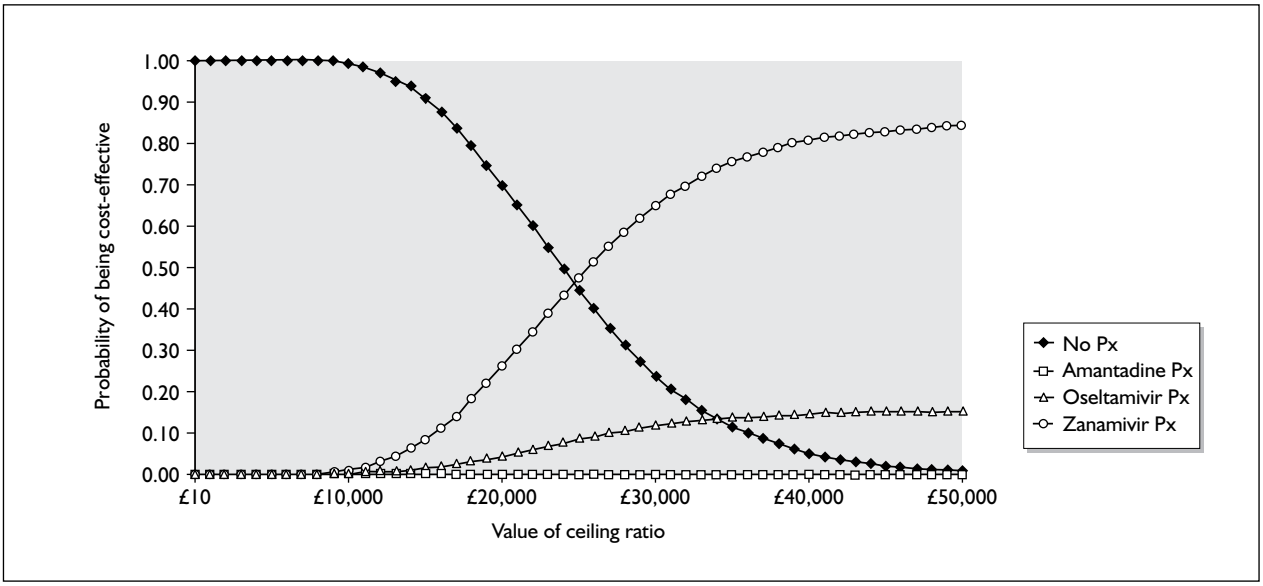

FIGURE 45 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk children (prior vaccination). Px, prophylaxis.*

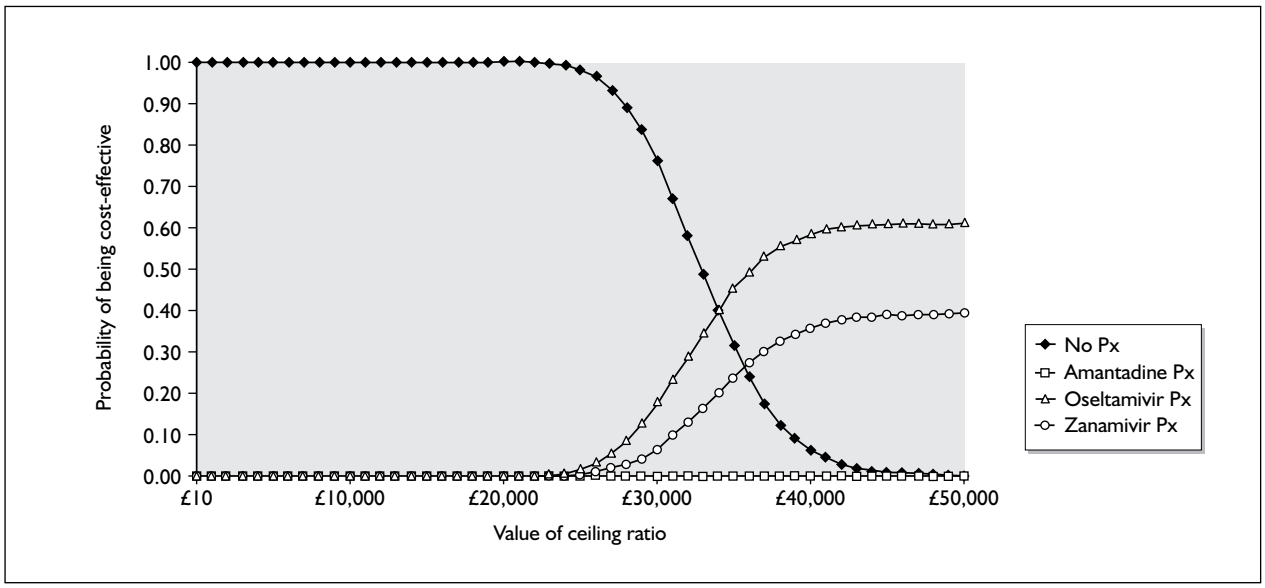

FIGURE 46 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy adults (no vaccination). Px, prophylaxis.*

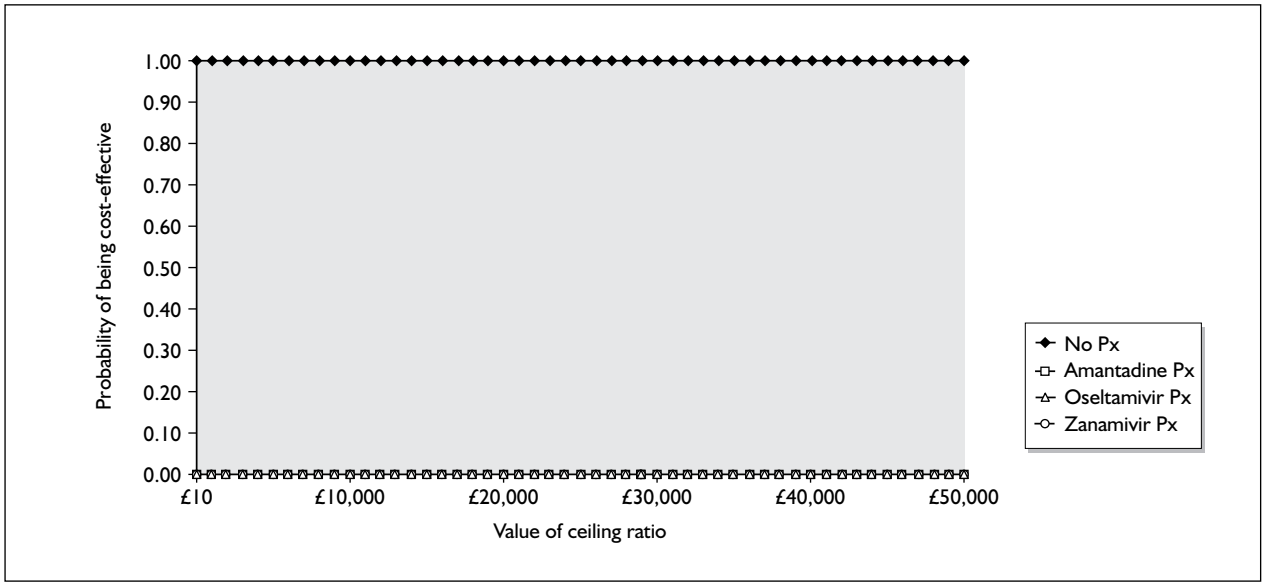

FIGURE 47 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy adults (prior vaccination). Px, prophylaxis.*

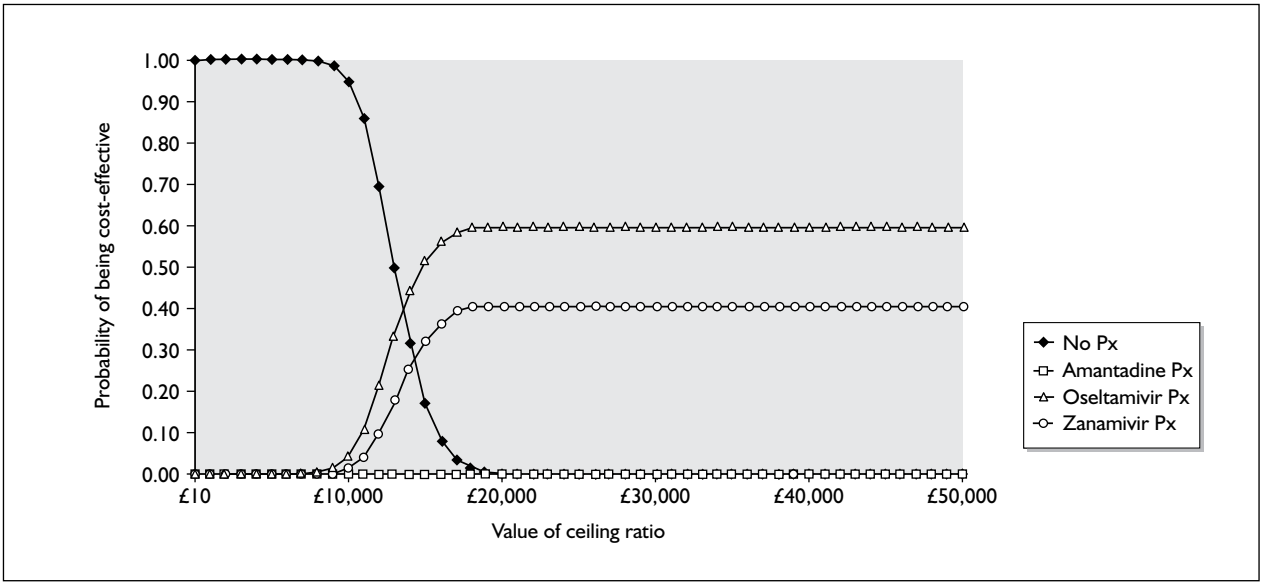

FIGURE 48 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk adults (no vaccination). Px, prophylaxis.*

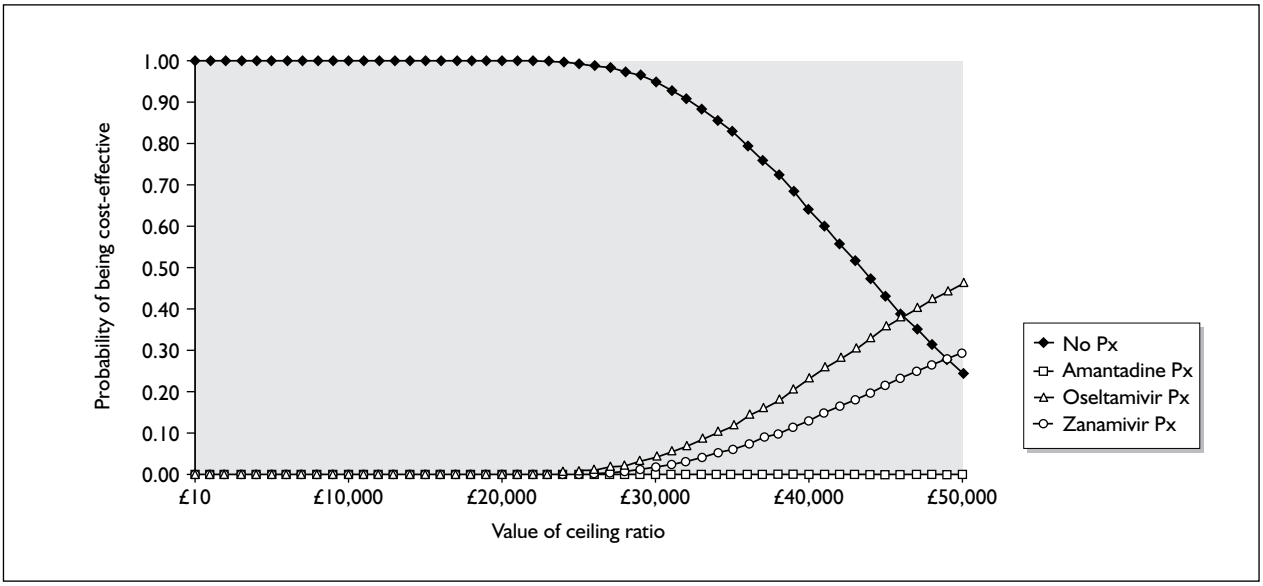

FIGURE 49 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk adults (prior vaccination). Px, prophylaxis.*

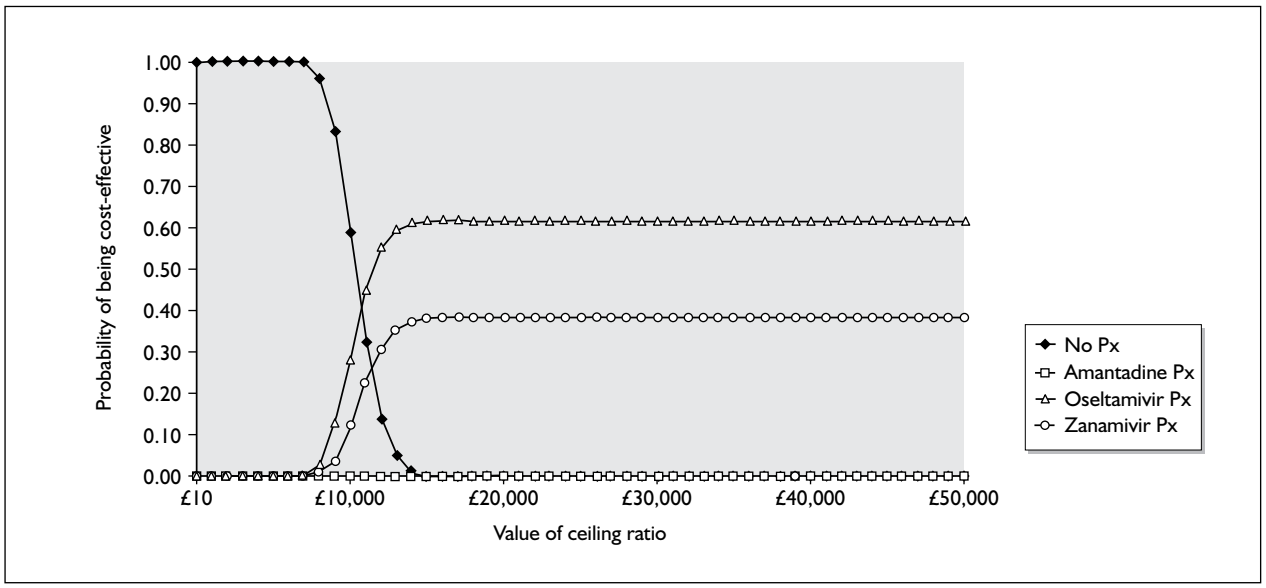

FIGURE 50 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy elderly (no vaccination). Px, prophylaxis.*

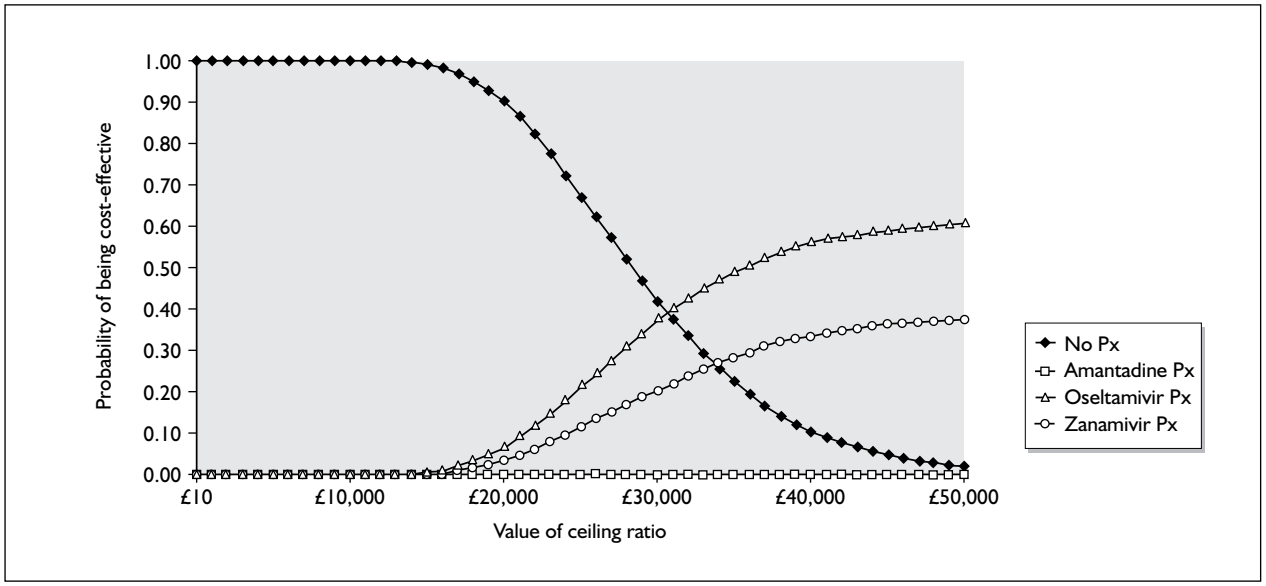

FIGURE 51 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, healthy elderly (prior vaccination). Px, prophylaxis.*

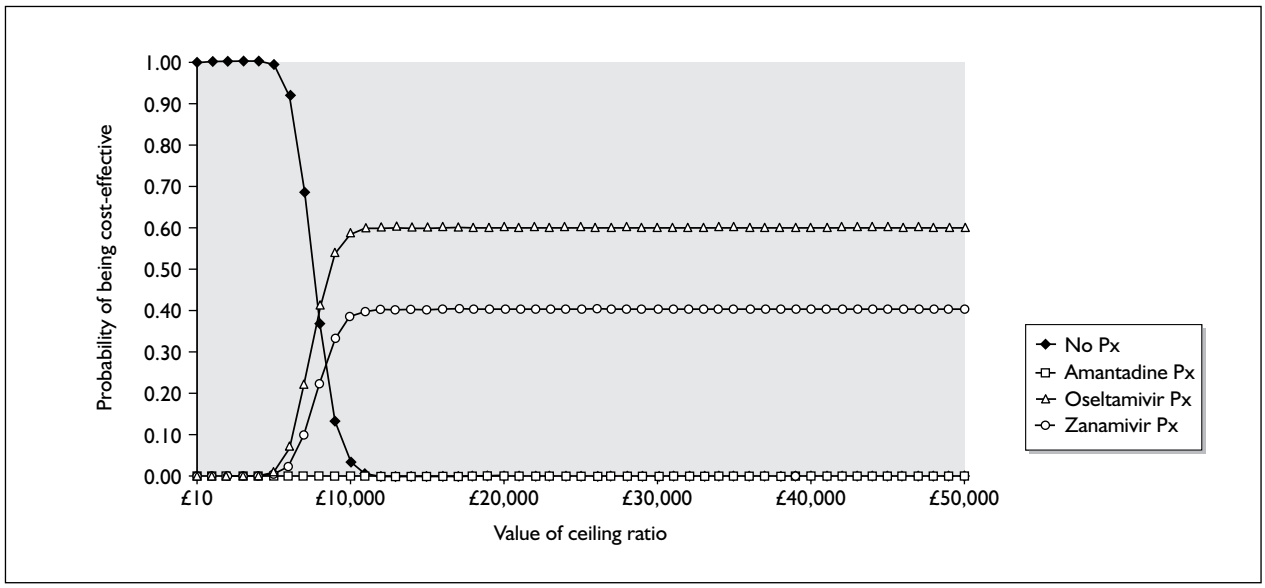

FIGURE 52 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk elderly (no vaccination). Px, prophylaxis.*

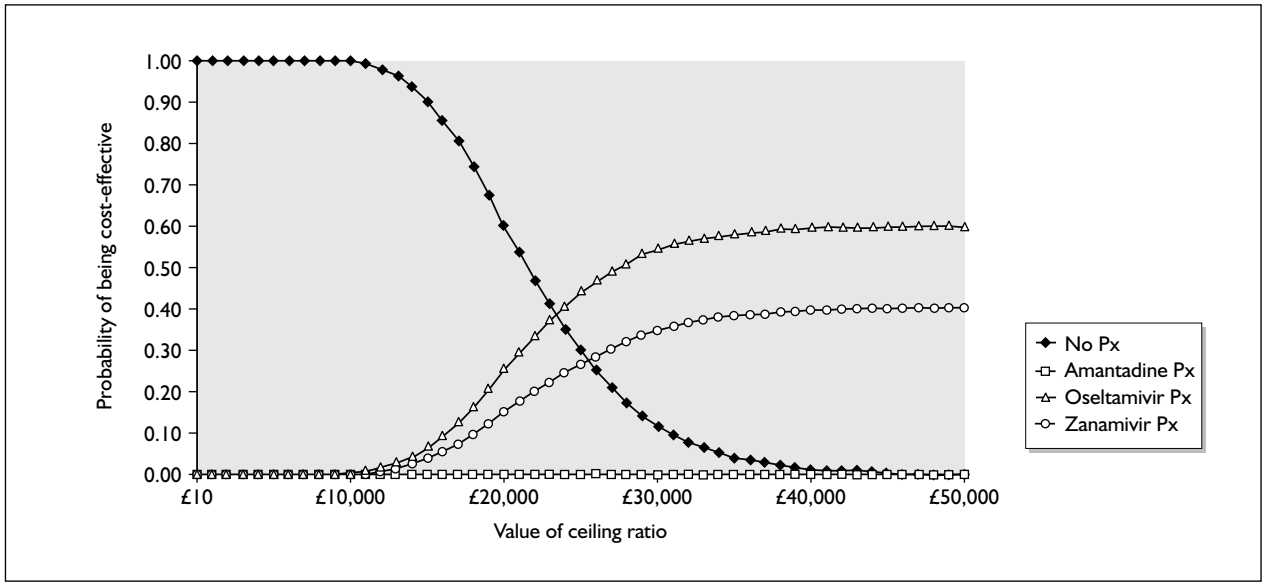

FIGURE 53 *Cost-effectiveness acceptability curves: post-exposure prophylaxis, at-risk elderly (prior vaccination). Px, prophylaxis.*

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Professor Julian Little, Professor of Human Genome Epidemiology, University of Ottawa

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Professor Rajan Madhok, Medical Director and Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Miranda Mugford, Professor of Health Economics and Group Co-ordinator, University of East Anglia

Professor Jim Neilson, Head of School of Reproductive & Developmental Medicine and Professor of Obstetrics and Gynaecology, University of Liverpool

Mrs Julietta Patnick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Director of Clinical Research, Bayer Diagnostics Europe, Stoke Poges

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon Primary Care Trust, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James's University Hospital, Leeds

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Professor Sarah Stewart-Brown, Professor of Public Health, Division of Health in the Community, University of Warwick, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick, Coventry

Mrs Joan Webster, Consumer Member, Southern Derbyshire Community Health Council

Professor Martin Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Children's Health, Lymington

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The NIHR Coordinating Centre for Health Technology Assessment
Alpha House, Enterprise Road
Southampton Science Park
Chilworth
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278