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Systematic review and economic decision modelling for the prevention and treatment of influenza A and B

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Systematic review and economic decision modelling for the prevention and treatment of influenza A and B

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Abstract

Systematic review and economic decision modelling for the prevention and treatment of influenza A and B

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Objectives: To establish the clinical and cost-effectiveness of amantadine, oseltamivir and zanamivir compared to standard care for the treatment and prevention of influenza.
Data sources: Electronic databases. Reference lists of identified articles and key publications. Relevant trials.
Review methods: A systematic review and meta-analysis of the randomised evidence was undertaken to investigate the effectiveness of oseltamivir and zanamivir compared to standard care for treatment and prophylaxis use for influenza A and B. An additional systematic review of the effectiveness of amantadine for treatment and prophylaxis use for influenza A in children and the elderly was also undertaken. Economic decision models were constructed to examine the cost-effectiveness and cost–utility of the alternative strategies for treating and preventing influenza A and/or B. This was informed by the systematic reviews outlined above and additional sources of information where required.
Results: The systematic review of the treatment of influenza found that oseltamivir reduced the median duration of symptoms in the influenza positive group by 1.38 days for the otherwise healthy adult population, 0.5 day for the high-risk population, and 1.5 days for the children population. This compared to 1.26 days, 1.99 days, and 1.3 for the similar groups for inhaled zanamivir. The systematic review of the prevention of influenza found that the relative risk reduction for oseltamivir was between approximately 75 and 90% and approximately 70 and 90% for inhaled zanamivir depending on the strategy adopted and the population under consideration. For the economic model a base case was constructed that focussed primarily on the health benefits generated by shortening the period of influenza illness. This base case found that, compared to standard care, the estimated cost per quality-adjusted life year ranged from £6190 to £31,529 for healthy adults, from £4535 to £22,502 for the 'high-risk' group, from £6117 to £30,825 for children, and from £5057 to £21,781 for the residential care elderly population. The base case model included valuations of the health effects of pneumonia (and otitis media in the children's model) based on observed rates in the trials. However it does not include the cost of hospitalisations as only very limited data was available for the effects of antivirals on hospitalisation rates. As for mortality rates, deaths from influenza were rare in trials of neuraminidase inhibitors (NIs). Therefore, suitable data on mortality were not available from these sources. As avoided hospitalisation costs and avoided mortality are potentially important we also carried out sensitivity analysis that involved extrapolating the observed reductions in pneumonias in the NI trials to hospitalisations and deaths. In all four models the cost-effectiveness of NIs is substantially improved by this extrapolation. For prophylaxis, antiviral drugs were compared with vaccination as preventative strategies. In all cases the cost-effectiveness ratios for vaccination were either low or cost-saving. In the base case the cost-effectiveness of antivirals was relatively unfavourable, there were scenarios relating to the elderly residential care model where antivirals as an additional strategy could be cost-effective.
Conclusions: The cost-effectiveness varies markedly between the intervention strategies and target populations. The estimate of cost effectiveness is also sensitive to variations in certain key parameters of the

model, for example the proportion of all influenza-like illnesses that are influenza. The effectiveness literature that was used to inform the economic decision model spans many decades and hence great caution should be exercised when interpreting the results of indirect intervention comparisons from the model. Further randomised trials making direct comparisons would be valuable to verify the model's findings.

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Glossary and list of abbreviations

Glossary

Incremental cost-effectiveness ratio (ICER) (Drummond and colleagues, 1997)

Option	Total cost	Total outcome	Average cost-effectiveness ratio	ICER
Option 1	C_1	E_1	C_1/E_1	$\frac{C_1 - C_2}{E_1 - E_2}$
Option 2	C_2	E_2	C_2/E_2	

Note that if the ICER is below some ceiling ratio, *Rc*, corresponding to a decision-maker's maximum willingness to pay for health gain, then (subject to uncertainty) that intervention represents good value for money.

Cost-effectiveness acceptability curve (Stinnett and Mullahy, 1998) The cost-effectiveness decision rule:

$$\frac{C_1 - C_2}{E_1 - E_2} < Rc$$

can be rearranged to obtain an expression for net (monetary) benefit:

Net (monetary) benefit $= Rc\ (E_1 - E_2) - (C_1 - C_2) > 0$

A positive net benefit suggests that the intervention represents good value for money. A **cost-effectiveness acceptability curve** plots the proportion of the estimated net-benefit density that is associated with positive values as a function of the ceiling ratio, *Rc* (i.e. the maximum cost per unit of effect that a decision-maker is prepared to pay).

Fixed and random effect meta-analysis (Sutton and colleagues, 2000) Meta-analysis is an established tool for combining quantitative information from a number of different but related studies. A **fixed effect** model assumes that all the studies are estimating the same underlying effect size. Under the conditions of heterogeneity, for the fixed effect model, the confidence interval for the overall treatment effect reflects the random variation **within** each trial, but not potential heterogeneity **between** trials, so the confidence interval is artificially narrow. A **random effects** model includes both sources of variation, the **between** and **within** study variance. That is, it assumes the studies are estimating different (underlying) effect sizes, and takes into account the extra variation implied in making this assumption. The underlying effects are assumed to vary at random.

References

Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford University Press; 1997.

Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness. *Med Decis Making* 1998;**18**:S65–S80.

Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. Chichester: Wiley; 2000.

List of abbreviations

ACIP	Advisory Committee on Immunization Practices
AIDS	acquired immunodeficiency syndrome
ARI	acute respiratory illness
AUC	area under the curve
BAL	bronchoalveolar lavage
CA	cold-adapted
CCA	chick cell agglutination
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CDC	Centers for Disease Centrol and Prevention
CDSC	Communicable Disease Surveillance Centre
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPMP	Committee for Proprietary Medicinal Products
CSF	cerebrospinal fluid
DH	Department of Health
DIC	disseminated intravascular coagulation
DIF	direct immunofluorescence
DVRD	Division of Viral and Rickettsial Diseases
EISS	European Influenza Surveillance Scheme
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
GBS	Guillain–Barré syndrome
GMT	geometric mean time
GPRD	General Practice Research Database
HA	haemagglutinin
HAI	haemagglutination inhibition
HIV	human immunodeficiency virus
HRG	Healthcare Resource Groups
ICC	intra-cluster correlation
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IDA	illness day avoided
ILI	influenza-like illness
ITT	intention-to-treat
LRTC	lower respiratory tract complication
LYG	life year gained
MCA	Medicines Control Agency
MDCK	Madin–Darby canine kidney
MRC	Medical Research Council
MVH	Measurement and Valuation of Health
NA	neuraminidase
NCID	National Center for Infectious Diseases
NI	neuraminidase inhibitors
NP	nucleoprotein
NIAID	National Institute of Allergy and Infectious Diseases
NICE	National Institute for Clinical Excellence
NIRC	National Influenza Reference Centre
OR	odds ratio

ORS	oculo-respiratory syndrome
OTC	over-the-counter
P & I	pneumonia and influenza
PCR	polymerase chain reaction
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PHLS	Public Health Laboratory Service (now Health Protection Agency)
PK	Pharmacokinetics
PPA	Prescription Pricing Authority
PPV	positive predictive value
QALD	quality adjusted life-day
QALY	quality adjusted life-year
QoL	quality of life
RCGP	Royal College of General Practitioners
RCT	randomised controlled trial
RR	relative risk
RSV	respiratory syncytial virus
RTI	respiratory tract infection
SA	sialic acid
SD	standard deviation
SE	standard error
SP	split product
SRD	single radial diffusion
TTO	Time Trade Off
URTI	upper respiratory tract infection
VAS	visual analogue scale
WRS	Weekly Returns Service
WV	whole virion
WTP	willingness-to-pay

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 at the end of the table.

Executive summary

Objective

This study aimed to establish the clinical and cost-effectiveness of amantadine, oseltamivir and zanamivir for the treatment and prevention of influenza. The preventative strategies considered were amantadine, oseltamivir, zanamivir and vaccine, compared with no intervention. Vaccine was considered both on its own and in combination with amantadine, oseltamivir and zanamivir. The treatment strategies addressed were amantadine, oseltamivir and zanamivir compared with standard care. Four patient groups were considered: (i) children (aged ≤ 12 years); (ii) healthy adults (aged 12–65 years); (iii) 'high-risk' (aged ≥ 65 years and/or with concomitant disease); and (iv) elderly residential population.

Background

Influenza is a common condition affecting all age groups. For those individuals at 'high risk' (e.g. aged ≥ 65 years, or with concomitant disease such as chronic respiratory disease, diabetes or significant cardiovascular disease), influenza can cause serious complications and in some cases these complications lead to hospitalisation and even death. Current policy recommends that 'high-risk' individuals (as defined above) be vaccinated against influenza each year. For the 'otherwise healthy' individuals, influenza is usually considered to be a self-limiting illness with most symptoms alleviated within 1 week. Nevertheless, such individuals can still experience influenza complications and can inflict considerable costs on the economy through lost workdays.

Technologies

Amantadine (Lysovir or Symmetrel, Alliance Pharmaceuticals): licensed for prophylaxis use during an outbreak of influenza A, for persons aged ≥ 10 years and, more particularly, for certain groups (e.g. un-immunised, healthcare workers).

Oseltamivir (Tamiflu, Hoffman La Roche Pharmaceuticals): received US Food and Drug Administration approval in November 2000. Submitted to the Committee for Proprietary and Medicinal Products in February 2001 for the treatment of influenza A and B in adults and children and the prevention of influenza A and B in adolescents and adults.

Zanamivir (Relenza, GlaxoSmithKline Pharmaceuticals): licensed for the treatment of influenza A and B, for individuals aged ≥ 12 years, within 48 hours of onset.

Questions addressed by this review

1. To establish whether amantadine, oseltamivir and zanamivir are effective and cost-effective alternatives in the treatment of influenza types A and B (amantadine type A only) relative to the existing method of treatment (i.e. receiving either no treatment at all or antibiotics).
2. To establish whether chemoprophylactic use of oseltamivir and zanamivir are effective and cost-effective alternatives to the existing method of prevention (i.e. no intervention or vaccine).

Methods

A systematic review and meta-analysis of the randomised evidence was undertaken to investigate the effectiveness of oseltamivir and zanamivir for treatment and prophylaxis use for influenza A and B. Where necessary, pharmaceutical companies were contacted for additional information not available from the published literature. An additional systematic review of the effectiveness of amantadine for treatment and prophylaxis use for influenza A in children and the elderly was also undertaken.

Economic decision models were constructed to examine the cost-effectiveness and cost–utility of the alternative strategies for treating and preventing influenza A and/or B. This was informed by the systematic reviews outlined above and additional sources of information where required.

Effectiveness results

Oseltamivir

Treatment

Oseltamivir 75 mg twice daily for 5 days was found to reduce the median duration of symptoms in the influenza positive group by:

- 1.38 days (95% CI 0.80 to 1.96) for the otherwise healthy adult population
- 0.50 days (95% CI –0.96 to 1.88) for the high-risk population
- 1.5 days (95% CI 0.8 to 2.2) for the children population.

Prevention

Oseltamivir 75 mg once daily for 6 weeks was found to provide a relative risk reduction of developing influenza by between approximately 75 and 90% depending on the strategy adopted and the population under consideration.

Zanamivir

Treatment

Inhaled zanamivir 10 mg twice daily for 5 days was found to reduce the median duration of symptoms in the influenza positive group by:

- 1.26 days (95% CI 0.59 to 1.93) for the otherwise healthy adult population
- 1.99 days (95% CI 0.90 to 3.08) for the high-risk population
- 1.3 days (95% CI 0.3 to 2.0) for the children population (high-risk and otherwise healthy combined).

Prevention

Inhaled zanamivir 10 mg once daily for 6 weeks was found to provide a relative risk reduction of developing influenza by between approximately 70 and 90% depending on the strategy adopted and the population under consideration.

Economic evaluation

UK-based estimates of cost-effectiveness were derived using all data available.

Amantadine

Treatment

The incremental costs per quality-adjusted life-year (QALY) gained in the base-case treatment analysis of amantadine were:

- £6190 per QALY for the otherwise healthy adults population
- £4535 per QALY for the high-risk population
- £5057 per QALY for the residential population
- £6117 per QALY for the children's population.

Uncertainty analysis suggests a probability of approximately 60% of a cost per QALY below £30,000 for any of four populations considered.

Prevention

In the base-case prophylaxis analysis, amantadine prophylaxis was dominated by vaccination. For both amantadine and vaccination the incremental cost per QALY gained for the residential population was £28,920 compared with vaccine. For all of the remaining populations the incremental costs per QALY gained were much higher, ranging from £124,854 to £909,210. These values do not include a value for adverse events from taking amantadine; including adverse events would worsen the cost per QALY ratios. Probabilistic analysis suggests a probability of 45% for a cost per QALY below £30,000 for the residential population if the effect of adverse events is excluded. None of the other models had a probability >1% of a cost per QALY below £30,000.

Oseltamivir

Treatment

The incremental costs per QALY gained in the base-case treatment analysis of oseltamivir were:

- £19,015 per QALY for the otherwise healthy adults population
- £22,502 per QALY for the high-risk population
- £21,781 per QALY for the residential population
- £19,461 per QALY for the children population.

Uncertainty analysis suggests a probability between approximately 55% and 60% of a cost per QALY below £30,000 for any of four populations considered.

Prevention

In the base-case prophylaxis analysis, oseltamivir was dominated by vaccine. For both oseltamivir and vaccine the incremental cost per QALY gained for the residential population was £64,841 compared with vaccine. For all of the remaining populations the incremental costs per QALY gained were much higher, ranging from £251,004 to £1,693,168 per QALY. Uncertainty analysis suggests a probability of 3% of an incremental cost per QALY below £30,000 in the residential population. None of the other populations have a probability of >1% of an incremental cost per QALY below £30,000.

Zanamivir

Treatment

The incremental costs per QALY gained in the base-case treatment analysis of zanamivir were:

- £31,529 per QALY for the otherwise healthy adults population
- £17,289 per QALY for the high-risk population
- £16,819 per QALY for the residential population
- £30,825 per QALY for the children population.

Uncertainty analysis suggests a probability between approximately 50% and 68% of a cost per QALY below £30,000 for any of four populations considered.

Prevention

In the base-case prophylaxis analysis, zanamivir was dominated by vaccine. For zanamivir in addition to vaccine the incremental cost per QALY gained for the residential population was £84,682 compared with vaccine. For all of the remaining populations the incremental costs per QALY gained were much higher, ranging from £324,414 to £2,188,039 per QALY. Uncertainty analysis suggests a probability <1% of a cost per QALY below £30,000 for all populations.

Vaccine

Prevention

The incremental cost per QALY gained in the base-case prophylaxis analysis of vaccine were:

- £10,184 per QALY for the otherwise healthy adults population
- £2333 per QALY for the high-risk population
- –£769 (cost saving) per QALY for residential population
- £5024 per QALY for the children population.

Sensitivity analysis

Sensitivity analyses showed the results to be highly sensitive to a number of model parameters.

Treatment model

- Mortality, hospitalisations, QALY values, the probability that influenza-like illness is influenza and the probability that patients receive treatments if presenting after 48 hours.

Prophylaxis model

- Attack rate, deaths, QALY value of a death.

Generally conclusions were not changed by varying model parameters

Analysis of cost-effectiveness

In all cases the cost-effectiveness ratios for vaccination were either low or cost-saving. In the base case the cost-effectiveness of antivirals was relatively unfavourable, there were scenarios relating to the elderly residential care model where antivirals as an additional strategy could be cost-effective.

Conclusions

The cost-effectiveness varies markedly between the intervention strategies and target populations. The effectiveness literature that was used to inform the economic decision model spans many decades and hence great caution should be exercised when interpreting the results of indirect intervention comparisons from the model. Further randomised trials making direct comparisons would be valuable to verify the findings from the model.

This study identified a number of areas where further research would be useful.

- Randomised trials making direct comparisons between the two NI drugs and with amantadine would aid the identification of the most appropriate drug treatment.
- More evidence is needed on the effectiveness of NIs for treatment in 'high-risk' individuals.
- More evidence is needed on the effectiveness of NIs in preventing influenza in elderly residential care settings.
- There is insufficient evidence on the effectiveness of antiviral drugs in decreasing hospitalisations and deaths. Because of the rarity of these events this information is most likely to be obtained from well-designed observational studies.
- There is a need for high quality-of-life data for estimating utilities in cost per QALY studies.
- Further appraisal and development of rapid diagnostic testing to evaluate the use of this technique alongside antiviral drugs.

Chapter 1

Aim of review and context

Overall aim and title

Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.

Objectives of this review

This review aims to identify the optimal prevention and treatment strategies for influenza and, in particular the role, if any, that neuraminidase inhibitors (NIs) have to play. As part of this process, the existing evidence on the use of NIs, in terms of both prophylaxis and treatment, has been systematically reviewed and synthesised. In conducting this particular systematic review, extensive use of contacts with the pharmaceutical industry have been necessary in order to identify, and obtain, all the relevant evidence relating to the use of NIs. In addition to the systematic review on NIs, a Cochrane review on the use of amantadine has also been extended. The preventative strategies considered here will be vaccination, amantadine prophylaxis and NI prophylaxis, and the treatment strategies considered will be amantadine, NIs and standard care.

Evidence on the costs and effectiveness of each of the prevention and treatment strategies is used to construct economic decision models examining the cost-effectiveness of NIs and also of alternative strategies for treating and preventing influenza. The perspective adopted is that of the NHS. An initial base case analysis is undertaken using both a deterministic and a probabilistic model. In order to explore the robustness of the conclusions derived using the base case analysis, a number of one-way sensitivity analyses are also undertaken. Results of the modelling exercise are presented as both cost per illness day avoided and incremental mean cost per quality-adjusted life-year (QALY), and as cost-effectiveness acceptability curves (CEACs). Although the systematic reviews undertaken have enabled a number of inputs of the decision model to be propagated, further *ad hoc* reviews and meta-analyses have also been necessary in order to augment this information.

The population/patient groups considered are (i) children (aged ≤ 12 years); (ii) healthy adults (aged 12–65 years); (iii) 'high-risk' (aged ≥ 65 years and/or with concomitant disease); and (iv) (in the case of prophylaxis) individuals in residential homes.

How this project differs from previous published reviews

Context

As can be seen by the brief summary of currently published systematic reviews and modelling exercises in *Table 1*, the project reported here is the most comprehensive to date, in that it considers both the prevention and treatment of influenza, in three separate populations, children, healthy adults and high-risk individuals, using amantadine, oseltamivir and zanamivir.

A further more detailed critique of all seven previous economic models is given in Chapter 6.

Structure of report

The rest of the report is structured with Chapter 2 giving an introduction into the background, including the epidemiology, of influenza together with details of the interventions under consideration. Chapters 3 and 4 report systematic reviews and, when appropriate, meta-analyses; for the treatment and prevention, respectively, of influenza with NIs. Key results are presented in *Tables 50–54* and 77. Chapter 5 presents the results of a systematic review on the use of amantadine hydrochloride for both treatment and prophylaxis of influenza in children and the elderly. Key results are presented in *Tables 82, 83* and *85*. Chapter 6 describes the development of the economic decision model and presents both a base-case analysis and a variety of sensitivity analyses and together with the results obtained using a probabilistic model. Key results are presented in *Tables 90–93* for treatment and *94–97* for prophylaxis. Finally, Chapter 7 discusses some of the limitations of the report and places the results in a clinical/NHS context.

TABLE I *Summary of published systematic reviews and decision models for amantadine, oseltamivir and zanamivir*

	Amantadine						Oseltamivir						Zanamivir					
	Prevention			Treatment			Prevention			Treatment			Prevention			Treatment		
Authors	**Children**	**Adults**	**High-risk**	**Children**	**Adults**	**High-risk**	**Children**	**Adults**	**High-risk**	**Children**	**Adults**	**High-risk**	**Children**	**Adults**	**High-risk**	**Children**	**Adults**	**At-risk**
Armstrong *et al.*, 2000[1]	–	–	–	–	DM	–	–	–	–	–	DM	–	–	–	–	–	–	–
Burls *et al.*, 2002[2]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	SR+DM	SR+DM
Jefferson *et al.*, 2000[3]	–	–	–	–	–	–	–	SR	–	–	SR	–	–	SR	–	–	SR	–
Jefferson *et al.*, 2000[4a]	–	SR	–	–	SR	–	–	–	–	–	–	–	–	–	–	–	–	–
Mauskopf *et al.*, 2000[5]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	DM
Brady *et al.*, 2001[6]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	DM	DM
Husereau *et al.*, 2001[7]	–	–	–	–	–	–	–	–	–	–	SR+DM	SR+DM	–	–	–	–	–	–
Scuffham and West, 2002[8]	–	–	–	–	–	–	–	–	DM	–	–	DM	–	–	DM	–	–	DM
Buda *et al.*, 2002[9b]	SR	–	SR	SR	–	SR	–	–	–	–	–	–	–	–	–	–	–	–
Harnden *et al.*, 2002[10]	–	–	–	–	–	–	SR	–	–	SR	–	–	SR	–	–	SR	–	–
O'Brien *et al.*, 2003[11]	–	–	–	–	–	–	–	–	–	–	DM	–	–	–	–	–	–	–

SR, systematic review; DM, decision model.
[a] Systematic review did not differentiate between NIs.
[b] Currently Cochrane Collaboration Review Protocols.

Chapter 2

Background of influenza and interventions

Introduction

This chapter provides background information of relevance to the systematic review and economic modelling of the NIs, amantadine and vaccines against influenza. The next section describes the pathogens responsible for influenza, the antigens used in vaccine production and targets for antiviral therapy. The epidemiology of influenza and methods of surveillance are described in the subsequent section. The following section describes the illness and its complications including deaths, and the final section provides an overview of the prevention and treatment of influenza with vaccines and antivirals.

The influenza viruses

Introduction

The influenza viruses belong to the family Orthomyxoviridae, from the Greek *myxa*, meaning mucus, a reference to the special association of the virus with mucosal surfaces. Influenza viruses are unique among respiratory viruses with respect to their segmented genome and great antigenic diversity. There are three types of influenza virus, A, B and C, although only types A and B are considered to cause significant morbidity in humans. The structures of influenza A and B viruses are similar. The haemagglutinin (HA) and neuraminidase (NA) surface glycoproteins and the M2 membrane ion channel of influenza A penetrate the lipid bilayer surface of the virion that envelopes the M1 matrix protein. Influenza viruses possess a segmented genome. Within the shell of M1 protein are eight ribonucleoprotein particles, each consisting of negative-sense single-stranded RNA, nucleoprotein (NP) and polymerase proteins. An important difference between influenza A and B is in the membrane ion channel – in influenza A it is the M2 protein whereas in influenza B it is the NB protein. This difference is of relevance with regard to susceptibility to amantadine.

Influenza A, B and C were originally distinguished serologically into three distinct types on the basis of antigenic differences between their NP and matrix proteins. Influenza A viruses are further divided into subtypes depending upon antigenic differences between their surface glycoproteins – the HA and NA. Fifteen distinct HAs and nine different NAs are now recognised. Influenza type A viruses of all HA and NA antigenic subtypes have been recovered from aquatic birds, whereas only a few antigenic subtypes of influenza A infect other animal species, mostly humans, pigs and horses. These observations indicate that birds are the natural reservoirs of influenza A. Influenza type B is restricted to humans.

Nomenclature

Each strain of influenza is identified on the basis of type (i.e. influenza A, B or C), the original host of origin, the place of virus isolation, the strain number, the year of isolation and, for influenza A viruses, the subtypes of the HA and NA antigens. Although the original host is included for animal strains, it is not included for human strains. Thus,

- Influenza A/Hong Kong/156/97 (H5N1) is a human strain of influenza A virus isolated in Hong Kong, strain number 156, in 1997, with HA type 5 and NA type 1.
- Influenza A/equine/Miami/1/63 (H3N8) is an equine strain of influenza A virus isolated in Miami , strain number 1 in 1963 with HA type 3 and NA type 8.
- B/Hong Kong/330/2001, the influenza B strain included in vaccines for the 2002–03 season, was isolated in Hong Kong, strain number 330, in 2001.

Antigenic shift and drift of the surface HA and NA glycoproteins

Influenza viruses are unique among respiratory viruses in their segmented genome and great antigenic diversity. The antigenic variability of influenza viruses takes two forms – antigenic 'drift' and antigenic 'shift'.

Antigenic drift

Antigenic drift occurs in all influenza types but is more frequent in type A influenza. Antigenic drift arises as a result of gene mutations encoding the HA and NA that are selected in response to immune pressure from host antibodies. Antigenic drift results in a constant evolution of the

TABLE 2 *Results of HA inhibition with postinfection ferret sera for influenza B viruses*

	B/Sichuan/379/99	B/Shandong/7/97	B/Hong Kong/330/01
B/Sichuan/379/99	**640**	<10	<10
B/Shandong/7/97	<10	**320**	1280
B/Hong Kong/330/01	<10	160	**1280**
B/Canada/29/2002	<10	80	1280
B/Hong Kong/666/2001	<10	160	1280

Source: Recommended composition of influenza virus vaccines for use in the 2002–2003 season. *Weekly Epidemiological Record* 2002; No. 8: 62–6

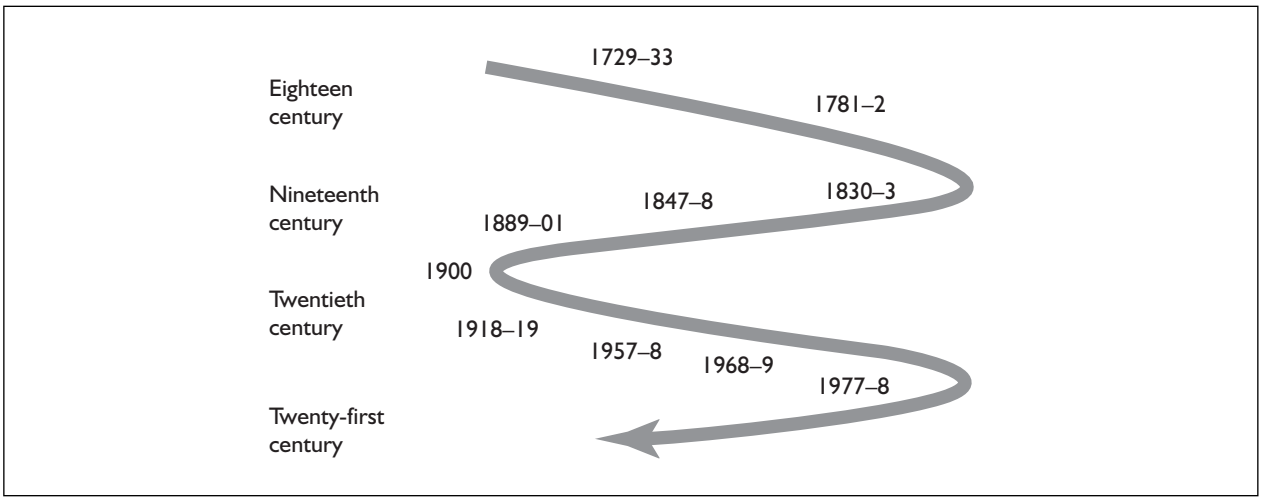

FIGURE 1 *Pandemics of influenza/influenza-like illness since the beginning of the 18th century. Reproduced from Nicholson KG, Webster RG, Hay AJ. Textbook of influenza. Oxford: Blackwell Science, 1998, by permission of Blackwell Publishing.*

antigenic properties of the virus that can be demonstrated by HA inhibition tests with postinfection ferret sera. For example, *Table 2* shows that both B/Sichuan/379/99 and B/Hong Kong/330/01 viruses are antigenically distinct from one another and that B/Sichuan/379/99 differs from earlier isolates.

During the 2001–2 season, influenza B viruses circulated widely, causing outbreaks and sporadic cases in both the northern and southern hemispheres. In HA tests with postinfection ferret sera, many influenza B viruses from the Americas, Asia, Europe and Oceania were antigenically closely related to B/Sichuan/379/99. However, B/Hong Kong/330/01-like viruses have spread in an increasing number of countries. Accordingly, the decision was taken to include an influenza B/Hong Kong/330/01-like virus in the vaccines to be used during the 2002–3 winter in the northern hemisphere. Antigenic shift can result in occasional mismatches between the vaccine and circulating strains that may occur during inter-pandemic periods. New strains of influenza evolve within each type and subtype of influenza at rates depending upon the genetic stability of the virus and immune pressure.

Antigenic shift

Epidemiological studies of influenza in humans indicate that influenza A is responsible for periodic worldwide pandemics (*Figure 1*). Unlike many infectious diseases, influenza has no pathognomonic features, so a precise picture of its impact was not possible until after the isolation of influenza A in 1933, influenza B in 1940 and influenza C in 1947. However, knowledge of its characteristics (tendency to seasonality; short incubation period; rapid dissemination; respiratory and systemic features) provide a picture of pandemics of influenza/influenza-like illness (ILI) since ancient times.

Pandemic (from the Greek *pan* meaning 'all' and *demos* meaning 'people') influenza is considered imminent or exists when there is:

- antigenic 'shift'
- a high proportion of the population lacking immunity to the new virus

- spread of the new virus from person to person causing disease
- rapid spread of the virus beyond the community in which it was first identified.

'Antigenic shift' reflects a major change in the HA and possibly NA antigens and occurs only with influenza A virus. This second type of antigenic change is far less frequent than antigenic drift. Antigenic shift can occur when two different influenza viruses, each from a different host species (e.g. humans and birds), co-infect a single host – possibly a pig (which can be infected by both 'human' and 'avian' subtypes of influenza A) or humans – which serves as a 'mixing vessel'. Because influenza virus possesses a genome with eight separate segments, gene reassortment with 256 possible gene combinations may occur during co-infection, and a new virus may be created that has elements of both parental strains. This process results in strains of unpredictable pathogenicity, but it may lead to the generation of virus that remains virulent for humans **and** possesses 'new' surface antigens from the non-human virus. If a substantial proportion of the human population lacks immunity to these surface antigens, then the new subtype of influenza may spread widely from person to person, causing disease.

Genetic analyses revealed that the A/Asian/57 (H2N2) pandemic virus had acquired genes for the HA, NA and PB1 protein from an avian influenza virus, but the remaining genes were identical with those in the previously circulating H1N1 virus. Similarly, analysis of the influenza A/Hong Kong/68 (H3N2) virus showed that it had newly acquired genes for the HA and PB1 protein from an avian virus and, as before, the remaining genes were identical with those in the previously circulating H2N2 virus. H1N1 virus re-emerged in 1977. Because a substantial proportion of the older population had been infected with the earlier H1N1 virus, the emergence of the influenza A/USSR H1N1 virus in 1977–78 did not cause a pandemic. Genetic analysis revealed that its genetic makeup was identical with a human virus that circulated in the 1950s. It is unclear where this virus emerged from, but the possibility of it emerging from a freezer has not been excluded.

The surface glycoproteins and virus ion channel of influenza A and B viruses

The structures of influenza A, B and C are generally similar when visualised by electron microscopy. Most influenza viruses are spherical particles with an average diameter of 1270 Å. Influenza B preparations reveal less variation in size and shape and most particles appear round. When negatively stained, spikes, representing the surface glycoproteins, the HA and NA, can also be seen on the viral surface. The NA tends to be found in discrete patches, whereas the HA is more evenly distributed. The surface of influenza type A and B contains about 400–500 glycoprotein (HA and NA) spikes per virion, with about 10 times more HA than NA projections, although the NA content per virion may vary between strains. Influenza C particles are of similar shape and size but differ from influenza A and B by having a single surface glycoprotein, the haemagglutinin–esterase fusion protein.

Three proteins are embedded within the lipid membrane of influenza types A and B – the two spike glycoproteins, the HA and NA and a membrane channel protein. The membrane ion channel for influenza type A, known as the M2 protein, is encoded by gene segment 7; for influenza B it is the NB protein and is encoded by segment 6; and for influenza C it is CM2, encoded by RNA segment 6. Differences in the structure of the membrane channels of influenza A, B and C are associated with differences in their susceptibility to the antiviral agents amantadine and rimantadine. Only influenza A is susceptible.

During the early 1940s, investigators noted that a suspension of influenza virus would agglutinate red blood cells. These observations showed that influenza virus possessed an HA and that the specific receptor for the influenza virus was present on the surface of erythrocytes. It provided a method of detecting and titrating the virus and its antibodies.

When the influenza virus and erythrocytes were warmed to 37°C, the erythrocytes dispersed but did not reagglutinate on subsequent exposure to fresh virus. However, fluid from the original mixture of virus and cells would still agglutinate fresh cells. This phenomenon suggested that the virion possesses an enzyme that destroys its own receptor. The substance cleaved from red blood cells was subsequently identified as sialic acid (SA) (*N*-acetylneuraminic acid) and the receptor-destroying enzyme was called the neuraminidase (NA) or sialidase. The HA is now the primary constituent of influenza vaccine and the NA has become a major target for antiviral treatment.

Haemagglutinin

The HA facilitates entry of the virus into cells as the initial step in virus replication. The first important function of the HA is to **attach** the virus

to SA containing receptors on the cell surface; the virus then undergoes endocytosis, exposing the HA to a relatively low pH. This decrease in pH results in an irreversible conformational change in the HA that is essential for **fusion** of the virus envelope with the cell membrane; this represents the second important function of the HA.

The HA represents the major antigenic determinant of influenza types A and B and induces neutralising antibodies. For survival, influenza viruses must evade immune recognition by a process of continual evolution. Human influenza viruses respond readily to immune pressure, with new variant viruses emerging with each round of replication. Mutations resulting in HAs that evade immune recognition define four or five major antigenic sites, known as Sa, Sb, Ca and Cb for H1 subtypes, and A, B, C, D and E for H3 subtypes. These sites form an almost continuous surface across the top of the HA spike. Influenza B virus evidently has a single immunodominant region corresponding to sites Sa and Sb of the H1 subtype of influenza A and sites A and B of the H3 subtype. The ability to form variants that escape immune recognition (i.e. antigenic drift) is considered a further important function of the HA.

The predominant SA involved in the binding of influenza A and B viruses is 5-*N*-acetylneuraminic acid. 'Human' influenza viruses bind preferentially to terminal SAs with an α2,6 linkage to galactose (SAα2,6-gal) on cell surfaces; avian influenza viruses bind preferentially to SAs with α2,3 linkages to galactose. This may explain in part why only a few (H1, H2 and H3) of the 15 HA subtypes of influenza A in nature have stably infected humans during the last 80 years.

Neuraminidase

The NA is the second major antigenic determinant of influenza types A and B. The viral NA has a mushroom-like appearance with a centrally placed stalk and is made from four identical subunits. The head contains both the enzyme activity and antigenic sites of the molecule. The crucial activity of the NA is to catalyse the cleavage of glycosidic linkages to SA. The active site of the NA is a shallow pocket on the top surface of each of the four subunits that is lined by a shell of strictly conserved amino acids that directly interact with the substrate, *N*-acetylneuraminic acid, also known as a-sialic acid or Neu5Ac. The pocket is lined by five arginyl residues (at positions 118, 152, 224, 292 and 371), four glutamyl residues (119, 227, 276 and 277) and one aspartyl residue (151). Surrounding this shell is another shell of mostly conserved or homologous residues. The following functions have been proposed for the enzyme activity of the NA:

- Assisting in the release of progeny virus particles from the surface of infected cells. Without a functional NA, progeny virus forms large aggregates that are immobilised at the cell surface.
- By removing SA from the virus HA, NA prevents virus clumping, so each virion can function as an independent infectious unit.
- Facilitating cleavage of HA (by modifying HA carbohydrate side-chains) – viral NA may thus be implicated in virulence.
- Facilitating dispersion of virus though inhibitory mucopolysaccharides coating the respiratory tract epithelium.

Evidence also suggests that antigenic drift of the NA helps the virus to survive in nature. Single amino acid sequence changes on the top of the NA head, on the rim around the active enzyme site, result in antigenic variants that escape immune recognition. The location of these changes defines four antigenic sites. Antibodies directed against sites 1, 2 and 3 can protect animals against experimental infection, with the greatest protection being afforded by antibodies to site 1.

The M2 virus ion channel

M2 is an integral part of the envelope of influenza A. The function of M2, common to all subtypes of influenza A, is to facilitate the uncoating of the virus during entry of virus into cells so that its ribonucleoprotein can enter nuclei and initiate replication. It does this by acting as an ion channel. Flow of hydrogen ions through M2 into the virion interior triggers the conformational change in the HA required for fusion and promotes a low pH-induced dissociation of the M1 protein from the ribonucleoproteins. This activity can be blocked in influenza A viruses only by amantadine and rimantadine.

Epidemiology

Transmission

Human influenza is spread by virus-laden respiratory secretions. Most infections appear to be transmitted by droplets several micrometres in diameter that are expelled during coughing and sneezing, rather than fine droplet nuclei. Large

particle droplets (>5 μm) and direct or indirect contact represent other possible modes of transmission. The human infectious dose is estimated to be 0.6–3 tissue culture infectious doses ($TCID_{50}$) following small particle aerosol exposure, and about 100 times greater for virus administered by nose-drops. Pathological evidence suggests initial or early involvement of the distal airway, a site accessible only to droplets up to 5 μm in diameter.

The 4–6-hour cycle of replication is followed by virus release for several hours before cell death and progeny virions initiate infection in adjacent cells throughout the upper and lower airways. Within a short period, high titres of virus are found in respiratory secretions. Virus shedding occurs for about 1–2 days before and about 5–7 days after the onset of symptoms and tends to be prolonged in young children and in immunocompromised patients.

The high infectivity of the virus, coupled with the short incubation period (about 2 days), high titres in nasopharyngeal secretions and the period of shedding, account for the rapid dissemination. In 'institutional settings' (e.g. schools, nursing homes, hospital wards, ships and barracks), many individuals will be infected within 1–2 weeks. Influenza is an important cause of nosocomial infection and considerable morbidity and mortality can occur in acute medical wards, neonatal intensive care units and wards for the elderly.

Seasonality

Endemic year-long transmission of influenza is described in the tropics with increased activity during the wet season, but in temperate zones influenza demonstrates marked seasonality. This may be related to behavioural factors influencing exposure, including indoor crowding in bad weather, school activity and possibly the greater survival of virus in aerosols during the winter.

Outbreaks often coincide with increased activity from respiratory syncytial virus (RSV) and occur when other respiratory pathogens, including coronaviruses, rhinoviruses and adenoviruses, are prevalent. In the northern hemisphere inter-pandemic epidemics of varying intensity occur virtually every year almost exclusively during the 'winter' months from October to April and in the southern hemisphere from May to September. Summertime outbreaks are reported occasionally in the northern hemisphere. Endemic year-long transmission is described in the tropics with increased activity during monsoon or wet seasons. Singapore, which functions as a busy interface between both hemispheres, has a major season from April to July and a second season from November to January.

Outbreaks usually appear abruptly, peak within 2–3 weeks and tend to be of short duration (about 5–6 weeks). Nationwide epidemics may last for about 3 months, but 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.

Co-circulation of influenza A and B

Influenza A subtypes H3N2 and H1N1 and influenza B have been co-circulating since 1977. All three types are usually detected each month globally, but one virus usually predominates. The viruses causing outbreaks in the northern hemisphere during any one season tend to be the same, but differences are occasionally observed. Outbreaks with more than one influenza subtype of influenza A or both influenza A and B, or even both subtypes H3N2 and H1N1 and influenza B, may occur in a given country during a single winter (*Figure 2*).

Attack rates

Longitudinal studies carried out within family and practice settings in several locations in the USA have provided valuable information on the annual occurrence of influenza, age-related attack rates, the ratio of subclinical to clinical infections and the difference in severity between H3N2 and H1N1 subtypes of influenza A and B. Additional information on the occurrence of influenza is available from randomised double-blind, placebo-controlled trials of influenza vaccines and antivirals. Many studies worldwide have shown that the highest attack rates occur in children and that school-age children play a central role in the dissemination of influenza in households and the community (see *Figure 3*).

Surveillance

Unlike many infectious diseases, influenza has no pathognomonic clinical features. Its impact is quantified by virological surveillance combined with an assessment of its contribution to illness and death in the community.

The WHO global surveillance system

Because of the antigenic variability of influenza viruses and its consequences, the WHO in 1947 established an international network of laboratories to monitor the emergence and spread

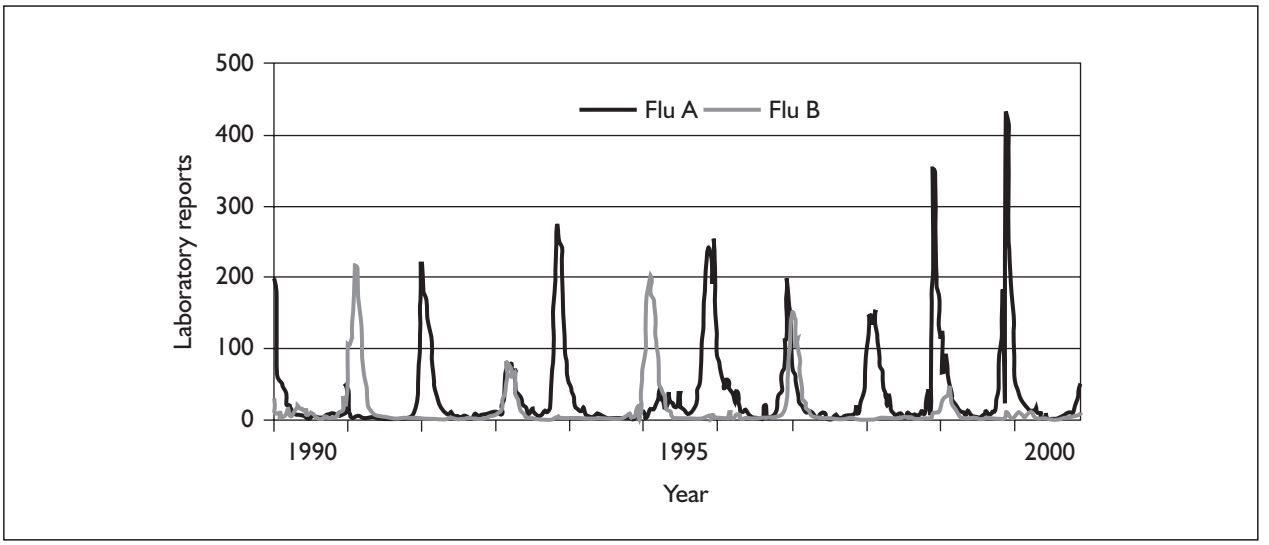

FIGURE 2 *Weekly PHLS reports of influenza A and B showing seasonal occurrence of influenza. Source of raw data:* CDR Weekly, *published by the Public Health Laboratory Service (PHLS).*

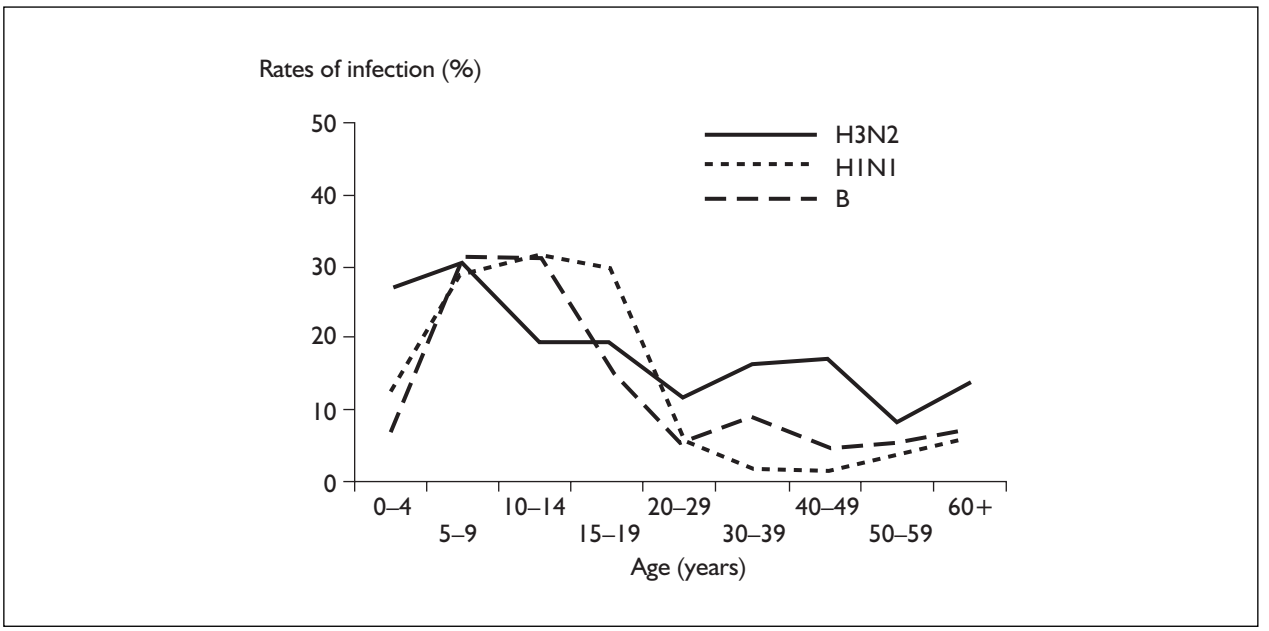

FIGURE 3 *Age-related rates of influenza infection (clinical and subclinical). Influenza A/H3N2, 1977–8 and 1980–1; influenza A/H1N1, 1977–8, 1978–9 and 1980–1; influenza B, 1976–7 and 1979–80.*

of new strains of influenza. This network has expanded considerably since 1947 and includes four International WHO Collaborating Centres located in Atlanta, London, Melbourne and Tokyo, and 110 National Influenza Centres in 83 countries (*Figure 4*).

Together these laboratories form a global influenza surveillance system which gathers epidemiological information and virus isolates for antigenic and molecular characterisation. The principal objectives of the network are:

- early detection of novel subtypes of influenza A with the potential to cause pandemics
- detection of the emergence and spread of influenza viruses that differ antigenically from previously circulating strains, that may signal the need to update the composition of the influenza vaccines to ensure continuing effectiveness.

FIGURE 4 *WHO influenza surveillance network, 1999. (Source: http://www.who.int/en).*

On the basis of this information, recommendations are made concerning the composition of influenza vaccine for use in both the northern and southern hemispheres.

Regional surveillance systems

Regional surveillance systems include the Pacific Basin Respiratory Virus Research Group and within Europe the European Influenza Surveillance Scheme (EISS) and EuroGROG. Their goal is to foster collaboration and exchange of information about influenza between different countries within a geographic region. The EISS presents virological and clinical data concerning influenza in 18 European countries: Belgium, Czech Republic, Denmark, France, Germany, Ireland, Italy, The Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland and the UK. EISS is used by its members as an early warning system for influenza epidemics. A wide variety of partners participate in EISS in each country: sentinel surveillance networks, national reference laboratories and national communicable disease surveillance centres.

EuroGROG is a pan-European system, which was created in the early 1990s to provide a bulletin dedicated to the European continent. EuroGROG is a network for the rapid exchange of epidemiological information between the National Influenza Reference Centres and other data-collecting institutions within Europe. The 30 countries covered by EuroGROG are Austria, Belgium, Belarus, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Great Britain and Yugoslavia. Unlike EISS, EuroGROG is not as strict in the data collection and reporting criteria of its members.

National influenza reference centres and indices of influenza

National influenza reference centres (NIRCs) evaluate the activity of agents causing ILI, provide diagnostic facilities, obtain early virus isolations, identify the isolates and report to one of the four WHO Collaborating Centres. They may also collate information on the level of susceptibility of the local population by serological surveys. The Influenza Section of the Enteric, Respiratory and Neurological Virus Laboratory at the Central Public Health Laboratory Service (PHLS) Laboratory, Colindale, is the WHO NIRC for the UK. One of its functions is to obtain influenza viruses isolated in public health laboratories and PHLS laboratories in the UK. The antigenic and genetic properties of the viruses are analysed in detail and compared with previously circulating influenza viruses. A representative selection of the viruses from Colindale (and other NIRCs) are sent to the

International WHO Collaborating Centres at the Medial Research Council (MRC) National Institute for Medical Research, Mill Hill, London, for comparative analyses.

It is also the function of each NIRC to organise locally surveillance systems to evaluate influenza activity throughout the year, monitoring both morbidity and mortality due to influenza. Surveillance programmes vary from country to country, but many countries have a network of sentinel general practitioners (family doctors) who notify cases of clinical influenza or ILI. Variations in the methods employed to produce consultation rates and in the definitions used to monitor illness mean that comparisons between illness rates reported by different schemes must be interpreted with care. However, comparisons from week to week or from year to year within an individual country are considered safe provided that the population sampled is sufficiently large and representative of the population as a whole. Schemes that incorporate virological surveillance are especially valuable, but even without these, weekly consultation rates for influenzal illness usually correlate extremely well with laboratory reports of influenza and other non-specific indices, including pneumonia and influenza admissions, and all-cause mortality.

The PHLS, Colindale, and the Royal College of General Practitioners (RCGP) collaborate to produce combined virological and clinical surveillance data in England and Wales. All virological and clinical data (see below) are collated by the PHLS Surveillance of Influenza Group, which comprises the Influenza Section of the Enteric, Respiratory and Neurological Virus Laboratory, and the Communicable Disease Surveillance Centre (CDSC).

The Birmingham Research Unit of the RCGP coordinates a scheme providing clinical data from sentinel GPs in approximately 70 'spotter practices' covering a population of about 700,000 people. CDSC Wales receives reports from 34 sentinel practices in Wales covering a population of about 233,000 people. A similar scheme is coordinated in by the Scottish Centre for Infection and Environmental Health. Each scheme uses different case definitions for influenza and consultation rates calculated from data from each scheme cannot be compared directly. Information about ILI among 8000 children in 32 boarding schools is provided by the Medical Officers of Schools Association. The Emergency Bed Service in London reports both the number of emergency admissions to London hospitals and the proportion that require medical refereeing for compulsory admission when beds are not readily available. Weekly data on all-cause mortality in England and Wales and the numbers of deaths due to respiratory diseases including influenza, pneumonia and bronchitis are provided by the Office for National Statistics.

Other sources or indices of clinical influenza activity include paediatricians, the armed forces, boarding schools, absence from school or work, sickness certification, sales of drugs such as aspirin or paracetamol and other remedies for 'colds' and flu, private medical insurance claims, demand for hospital beds for emergency medical admissions, hospital admissions for respiratory illness and mortality statistics.

The clinical picture

Introduction

Influenza has no pathognomonic features so a precise picture of its impact was not possible until the first isolations of influenza A in 1933,[12] influenza B in 1940[13,14] and influenza C in 1947.[15] Further knowledge of the illness came with the discovery of the haemagglutinating properties of the influenza virus in 1941[16] and the development of diagnostic methods based on haemagglutination inhibition.

Replication and shedding

It is considered that infection begins in the tracheobronchial epithelium and then spreads. Lesions have been identified in the tracheobronchial mucosa in bronchoscopic biopsies from young adults with uncomplicated Asian influenza which correspond with, but are not so severe as, those found in the trachea and bronchi of fatal cases. Histological studies of fatal cases, nasal exudates cells and tracheal biopsies indicate that virus replication may occur throughout the entire respiratory tract, the principal site of infection being the ciliated columnar epithelial cells.

In vitro studies suggest that the cycle of replication takes about 4–6 hours. Thereafter virus is released for several hours before cell death and progeny virions initiate infection in adjacent cells, so that within a short period many cells in the respiratory tract are either infected, releasing virus, or dying. The pattern of virus replication in relation to clinical symptoms and immune responses has been studied by several investigators, both during

natural infection and during volunteer challenge studies. Virus can be detected shortly before the onset of illness, usually within 24 hours, rises to a peak of 10^3–10^7 $TCID_{50}$/ml of nasopharyngeal wash, remains elevated for 24–72 hours and falls to low levels by the fifth day.[17] In young children, virus shedding at high titres is generally more prolonged and virus can be recovered up to 6 days before and 21 days after the onset of symptoms.[18,19]

Attempts to demonstrate viraemia have been inconclusive – a few investigators have demonstrated viraemia, even before the onset of symptoms,[20–22] but others have been unsuccessful.[23,24] Nonetheless, several investigators have noted the occasional presence of influenza A and B, viral RNA or viral antigens at extrapulmonary sites including the brain, cerebrospinal fluid, liver, muscle and amniotic and middle-ear fluids.[25–38]

The incubation period of influenza ranges from 1 to 7 days but is commonly 2–3 days. This short period, coupled with the relatively high titres in nasopharyngeal secretions, the fairly lengthy periods of virus shedding (especially in children) and the relatively small amounts necessary to initiate infection in susceptible contacts, explains the explosive nature of influenza outbreaks.

Clinical features

The spectrum of influenza is broad ranging from asymptomatic infection through febrile illness with minimal respiratory illness, respiratory illness with systemic features, multi-system complications affecting the lung, heart, brain, liver, kidneys, and muscle, to death, most commonly due to primary viral or secondary bacterial pneumonia. The clinical outcome can be influenced by a number of potentially confounding features including the age of the patient, prior infection with an antigenically related virus, intrinsic properties of the virus (i.e. whether influenza A H1N1 of H3N2 or influenza B, and possibly adaptation of newly emerged pandemic strains to humans), the presence of chronic medical conditions such as heart or lung disease, renal failure and disorders of immunity, and also pregnancy and smoking. Review of the syndromes due to H1N1, Hsw1N1, H2N2 and H3N2 strains of influenza reveal no important differences; however, comparative studies carried out during the late 1970s and early 1980s suggest that H3N2 infections produce more severe illness than H1N1[39–41] and that influenza B is intermediate in severity between H3N2 and H1N1.[41] In the USA, average seasonal rates of excess pneumonia and influenza (P & I) hospitalisation during 26 influenza seasons (1970–95) were twice as high during A(H3N2) influenza seasons as during A(H1N1)/B seasons.[42] Similarly, during the period 1972–92, most influenza A (H3N2) seasons were associated with high numbers of excess deaths (23,000–45,000 all-cause excess deaths), whereas most A(H1N1) and B seasons were associated with fewer deaths (0–23,000).[43]

Review of previous descriptions of 'influenza' reveal many instances of selection bias, with investigators focusing on febrile patients with a typical 'influenzal' illness during a known outbreak or on seriously ill patients in hospital. Family observational studies conducted throughout an influenza season reveal that many infections are asymptomatic or 'subclinical', indicating that descriptions of a typical influenzal illness are less representative than generally appreciated. Moreover, infections in neonates and infants may present non-specifically with lethargy, poor feeding and apnoea,[44] unexplained fever or pneumonia,[45] croup or bronchiolitis (generally associated with parainfluenza viruses and RSV)[46,47] or otitis media. Myalgia, sweats, sputum production and other lower respiratory tract infections are far less common in children than adults.[41,48] Drowsiness is uncommon in adults, but occurs in about 10% of children 5–14 years of age and 50% of children <4 years of age. At the other end of the age spectrum, fever may be absent in the elderly. Despite these limitations, it is remarkable how little the clinical descriptions of 'influenza' have varied over decades of observation. Although influenza cannot be distinguished readily on clinical grounds from other acute respiratory infections, the use of case definitions coupled with virology to confirm the presence of an outbreak in the vicinity can be used to identify patients with influenza (see Appendix 16).

The symptoms recorded during 10 studies of adults with uncomplicated virologically confirmed influenza A during the period 1937–92 are shown in *Figure 5*. The onset of symptoms is typically abrupt with prominent systemic features including malaise and feverishness, chills, headache, anorexia, myalgia affecting the back and limbs and dizziness. Fever in the range 38–40°C is the most prominent sign of infection. The pyrexia peaks at the height of systemic features and is typically 3 days in duration but may last for 1–5 days. The early systemic features are often accompanied by a non-productive cough, nasal discharge or obstruction and sneezing, sore throat and less frequently by productive cough,

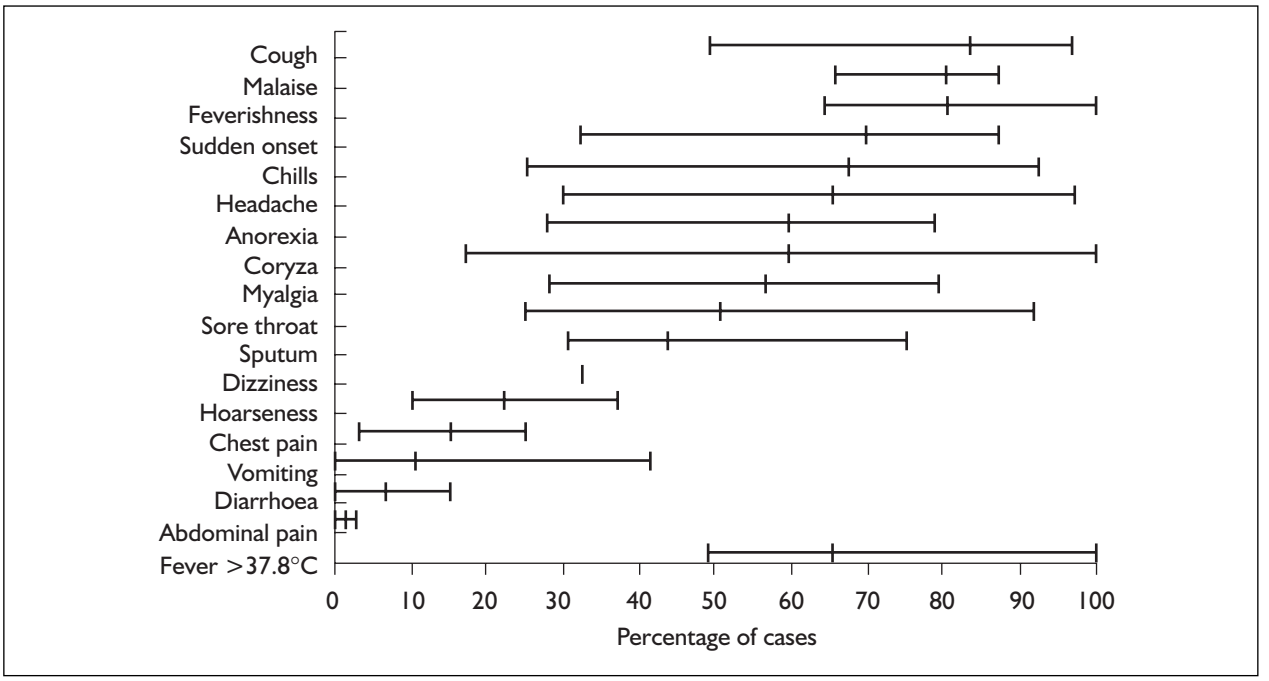

FIGURE 5 *Overall incidence and highest and lowest incidence of symptoms recorded during 10 studies of 520 adults with virologically confirmed uncomplicated influenza A during the period 1937–92. Data from Jordan and colleagues (1958),[48] Burch (1959),[49] Stuart-Harris (1961)[50] Lindsay (1970),[51] Gaydos (1977),[52] Ksiazek (1980),[53] Mathur (1980),[54] Wright (1980),[39] Weingarten (1988)[55] and Wald (1995).[56]*

hoarseness and substernal soreness. Crackles and wheezing are heard in about 10% of cases. These symptoms and signs usually occur for 3–5 days, but cough, lassitude and malaise may persist for 1–2 weeks after the fever has settled.

Respiratory illness caused by influenza is difficult to distinguish from illness caused by other respiratory pathogens on the basis of symptoms alone, especially in children when RSV is co-circulating. Reported sensitivity and specificity of clinical definitions for ILI that include fever and cough have ranged from 63 to 78% and from 55 to 71%, respectively, compared with laboratory diagnosis.[57,58]

Influenza and its complications in children

Infants beyond the age when maternally derived antibodies provide protection and those with congenital abnormalities are at increased risk from the complications of influenza.[18,46,59,60] Otitis media complicates about 20–25% of cases in young sero-negative children[60] and occurred in 67% of infections with influenza A in otitis-prone 1–3-year-old children.[61] Acute bronchitis is the most common lower respiratory tract complication of influenza. However, the reported incidence in primary care is very variable. Brocklebank *et al*.[46] diagnosed bronchitis in nine (12%) of 76 children hospitalised with virologically confirmed influenza A/Hong Kong. Laryngotracheobronchitis (croup) is found in 5–15% children hospitalised with influenza.[33,46,62,63] Influenza A H3N2 and influenza B infections were confirmed in 67% and 36%, respectively, of croup admissions during the peak months of influenza A H3N2 and B infection during 1957–76.[47] X-ray evidence of pneumonia was found in 5.1% of symptomatic children with 'Asian' influenza[64] and five (8%) of 121 young seronegative children developed clinical and X-ray evidence of pneumonia during an interpandemic outbreak of H3N2 influenza.[65]

Influenza virus infections in asthmatic children and adults have consistently precipitated exacerbations. For example, a study by Minor *et al*.,[66] which involved 41 children aged 3–17 years and eight adults with a history of 'infectious' asthma, showed that 55% of all respiratory infections precipitated asthma. Five patients had influenza A infections and four were associated with asthma. Kondo and Abe[67] studied the time course of influenza-induced asthma in 20 asthmatic children at a residential asthma clinic in Japan from 1978 to 1985. Fifteen children had a decrease in forced expiratory volume in 1 second (FEV_1) of >20% from baseline during the acute stage. The mean decrease was maximal at –30.3% on the second day and returned to within a 10% difference on the 7–10th day. Roldaan and Masural[68] observed declines in FEV_1 ranging from

55 to 75% in three children. Gbadero *et al*.,[69] in an urban tropical setting in Nigeria, found influenza type A infection in 16% of 74 children hospitalised with exacerbations. Influenza has been implicated in 4–17% of exacerbations of cystic fibrosis;[70–72] such exacerbations can be severe, resulting in periods of hospitalisation of 2–3 weeks.[73]

Febrile convulsions are especially prominent among hospitalised cases in children <5 years of age, occurring in more than 20% of children with influenza in seven studies.[33,46,62,63,74–76] Abdominal pain is a recognised feature of influenza. Among hospital admissions there can be a predominance of gastrointestinal manifestations – notably abdominal pain, diarrhoea and vomiting, especially in children aged ≤ 6 months – that can mimic appendicitis. During an epidemic of influenza B, 41% of 68 admissions had abdominal pain.[75] Myalgia affecting the legs and back can be a prominent feature that occurs early during the course of the illness. Myositis (and myoglobinuria with and without renal failure) is an infrequent complication generally occurring during the recovery phase. Myositis mostly occurs with influenza B.[77] Typically leg pains and muscle tenderness last 1–5 days and no true muscle weakness is apparent, although children often refuse to walk or do so with an unusual gait. Muscle enzymes are increased in about two-thirds of the cases. Influenza B-associated cases tend to be benign and of short duration.

Reye's syndrome, a multisystem disorder characterised by encephalopathy and fatty liver, occurred during the 1970s with an estimated rate of 31–58 cases per 100,000 influenza B infections[78,79] and from 2.5 to 4.3 cases per 100,000 influenza A infections.[80] There is a strong association between the use of salicylates and Reye's syndrome, and probably because of reduced salicylate usage, recent trends in the USA and UK indicate a decreased incidence of cases. In the British Isles recent active surveillance reveals an annual incidence of about one case per million population aged ≤ 16 years.[81]

During the peak epidemic months of 13 consecutive influenza A epidemics and six influenza B epidemics, influenza accounted for 35.6 and 10.8%, respectively, of all hospitalisations for respiratory illness in children <8 years of age.[47] During December 1989 to February 1990, influenza A and B infection was identified in almost 21.7% of all paediatric admissions in Kawasaki, Japan.[63] The risk of hospital admission for children <5 years of age in Harris County, TX, was estimated to be 690 per 100,000 during the A/Victoria/75 outbreak.[82] Review of three later epidemics (H1N1, H3N2 and influenza B) in Harris County identified hospitalisation rates of at least 500 per 100,000 regardless of the type of influenza virus prevalent at the time.[83] Recent American studies[42,84–87] have demonstrated rates of hospitalisation for cardiopulmonary disease during the influenza season, among children ≤ 4 years of age, ranging from up to 1000/100,000 population for those without high-risk conditions to up to almost 2000/100,000 for those with high-risk conditions (see *Table 3*). The hospitalisation rates were greatest among children ≤ 1 year of age, for those both with and without conditions that put them high risk for influenza complications. These rates are comparable to those for adults ≥ 65 years of age. However, the impact of influenza on paediatric hospitalisation is undoubtedly underestimated since influenza often presents with non-respiratory complications.

A review of 15 fatalities occurring among children hospitalised with influenza reveals that two-thirds had congenital abnormalities, nine of 14 whose age was reported were ≤ 3 years of age, and only three fatalities occurred in previously well children ≥ 4 years of age.[33,45,46,62,74,75,88] The overall mortality rate among children hospitalised with proven influenza in the above reports and those described by Sugaya *et al*.[63] was 3.8% (15 of 392).

Respiratory complications of influenza in adults

The complications of influenza in adults are predominantly respiratory. In normal individuals with uncomplicated influenza, pulmonary function tests have revealed frequent airway hyper-reactivity, peripheral airway dysfunction and abnormalities in gas exchange that can persist for some weeks after clinical recovery.[89–91] Interestingly, no changes in bronchial reactivity to inhaled methacholine occurred in healthy subjects with and without allergic rhinitis who were inoculated intranasally with influenza A/Kawasaki (H1N1) virus. This suggests that influenza routinely replicates in the lower airways during natural infection.

Acute bronchitis

Acute bronchitis is the most common lower respiratory tract complication of influenza occurring in about 20% of cases.[92] These investigators found that the risk of bronchitis complicating influenza was higher in elderly patients and in those with chronic medical

TABLE 3 *Data from Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP) February 2001: estimated rates of influenza-associated hospitalisation by age group and risk group from selected studies*[a]

Study years	Population	Age group (years)	Hospitalisations/ 100,000 persons at high risk	Hospitalisations/ 100,000 persons not at high risk
1973–93[b,c]	Tennessee	0–11 months	1900	496–1038[d]
1973–93[c,e]	Medicaid	1–2	800	186
		3–4	320	86
		5–14	92	41
1992–7[f,g]	Two health	0–23 months		144–187
	maintenance	2–4		0–25
	organisations	5–17		8–12
1968–9[h,i]	Health	15–44	56–110	23–25
1970–1	maintenance	45–64	392–635	13–23
1972–3	organisation	≥ 65	399–518	–
1969–95[i,j]	National	<65	–	20–42[k,l]
	hospital	≥ 65	–	125–228[l]
	discharge data			

A link to the title report can be accessed at the website for the Influenza Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, CDC, at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5004a1.htm.

[a] Rates were estimated in years and populations with low vaccination rates. Hospitalisation rates would be expected to decrease as vaccination rates increased. Vaccination can be expected to reduce influenza-related hospitalisations by 30–70% among elderly persons and likely by even higher percentages among younger age groups when vaccine and circulating influenza virus strains are antigenically similar.

[b] *Source*: Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. Effect of influenza on hospitalisations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000;**342**:255–31.

[c] Outcomes were for acute cardiac or pulmonary conditions.

[d] The low estimate is for infants aged 6–11 months, and the high estimate is for infants aged 0–5 months.

[e] *Source*: Neuzil KM, Wright PF, Mitchel EF, Griffin MR. Burden of influenza illness in children with asthma and other chronic medical conditions. *J Pediatr* 2000;**137**:856–64.

[f] *Source*: Izurieta HS, Thompson WW, Kramarz P. *et al*. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000;**342**:232–9.

[g] Outcomes were for acute pulmonary conditions. Influenza attributable hospitalisation rates for children at high risk were not included in this study.

[h] *Source*: Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. *AM J Epidemiol* 1980;**112**:798–811.

[i] Outcomes were limited to hospitalisations in which either pneumonia or influenza was listed as the first condition on discharge records (Simonsen) or included anywhere in the list of discharge diagnoses (Barker).

[j] *Source*: Simonsen, L, Fukuda, K, Schnoberger LB, Cox NJ. Impact of influenza epidemics on hospitalizations. *J Infect Dis* 2000;**181**:831–7.

[k] Persons at high risk and not at high risk are combined.

[l] The low estimate is the average during influenza A(H1N1) or influenza B-predominant seasons and the high estimate is the average during influenza A (H3N2)-predominant seasons.

conditions. The reported incidence of pneumonia complicating influenza is very variable. During the A/Asian H2N2 pandemic in 1957 the incidence of influenza-related pneumonia diagnosed clinically in general practice was ~2%.[93–98] However, other studies in primary care that included radiology revealed that >5% of cases of 'Asian' influenza developed pneumonia.[64,99] Thus the pneumonia rate of 2.9% reported during the H3N2 epidemic of 1989–90 in Wales is probably an underestimate. More reliable are studies that incorporate both virology and radiology. In such studies, pneumonia was identified in 5–38% of patients with influenza A.[52–54] Pneumonia was reported in 9.6% of 219 troops with influenza B[100] and pneumonia requiring hospitalisation occurred in 5 (~4%) of 129 symptomatic residents of a nursing home during an outbreak. In contrast, Foy *et al*.[101] described no cases of pneumonia among 37 with influenza B.

Pneumonia

Two main types of pneumonia are recognised – a primary viral pneumonia and a secondary bacterial

pneumonia. The latter occurs either with viral pneumonia or as a 'late' complication. There have been a few reports of pulmonary fibrosis, obliterative bronchiolitis and reduction in gas transfer as long-term complications in those who survive primary influenzal pneumonia.[102–106] During the 1957 pandemic, around 25% of fatal pneumonias were viral and the lungs of most patients with secondary bacterial pneumonia were co-infected with influenza virus. Patients with pneumonia often deteriorate rapidly. During the 1957 pandemic, 18% of 477 deaths reported by the PHLS died before hospitalisation and two-thirds died within 48 hours of admission.[107] Rapid deterioration was also seen during the 1989–90 epidemic in Leicestershire, England. Overall, 78 of 156 pneumonia and influenza admissions died during the admission; more than one-third succumbed within 2 days of admission and less than one-third survived for longer than 8 days. The median interval between onset of illness and death was 6 days. Mortality from pneumonia is higher in patients with chronic lung disease than in the previously fit, as shown, for example, by Angeloni and Scott:[108] 6/13 (46%) versus 3/28 (11%).

Almost three-quarters of patients with fatal or life-threatening influenzal pneumonia have a secondary bacterial infection. *Staphylococcus aureus*, either as sole pathogen or together with other microorganisms, was identified in most cases during the 1957 pandemic and was also identified in more than one-quarter of cases during the 1968–69 pandemic. Other causes include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Branhamella catarrhalis* and Gram-negative organisms. Several factors, including age, pre-existing disease and the nature of the invading microbe can affect the outcome of secondary bacterial pneumonia. Robertson *et al*.[109] observed that mortality from staphylococcal pneumonia (around 47%) during the 1957 pandemic was almost three times as high as from non-staphylococcal pneumonias (16%). The mortality from staphylococcal pneumonia was similar at all ages and similar in those with and without underlying high-risk conditions. In contrast, in the non-staphylococcal group, mortality was concentrated in those with chronic medical conditions and in those aged ≥ 55 years.[110] Up to 50% of those with staphylococcal pneumonia and 35% of those with other forms of pneumonia during pandemics have no underlying medical conditions. This states the case for much wider use of influenza vaccine when a new pandemic strain emerges.

The rapid deterioration of patients with secondary pneumonia provide little opportunity for successful intervention. In 1937, Scadding observed a mortality of 37% among 19 patients with secondary bacterial pneumonia. Similar mortality rates occurred during the pandemics of 1957 and 1968,[51] suggesting that mortality from secondary bacterial pneumonia has been affected little by the introduction of antibiotics.

Exacerbations of asthma

Influenza virus infections have consistently precipitated attacks of wheezing in both adults and children. Severe epidemics of influenza result in a small but significant excess mortality attributed to asthma. During the 1920s and 1930s, asthma deaths increased in England and Wales by 15–44% during the most severe epidemics.[111] Similarly, asthma deaths increased by 19–46% in the USA during influenza A outbreaks in 1957, 1958, 1960 and 1963, but not during milder epidemics.[112]

Exacerbations of chronic obstructive airways disease

Up to 28% of exacerbations of chronic obstructive airways disease are associated with influenza A or B.[113–117] An association between influenza and deaths from chronic bronchitis was recognised during the pandemic in 1889 and was highlighted by Stocks,[111] who showed that deaths from chronic bronchitis increased by up to 52% in England and Wales during epidemics from 1921 to 1933. Chronic obstructive pulmonary disease (COPD) is a major risk factor for hospitalisation of elderly people with influenza. In Rochester between November and April during 1989–92, 90 (43%) of 210 influenza-infected people who were admitted for acute cardiopulmonary conditions had underlying chronic obstructive airways disease.[118]

Other pulmonary complications

These include lung abscess, emphysema and invasive pulmonary aspergillosis. Pulmonary aspergillosis has been reported on at least eight occasions as a complication of influenza A in immunocompetent subjects.[110] It is considered to be facilitated by the lymphocytopenia and loss of ciliary function in the trachea and bronchioles that accompany influenza, and by broad-spectrum antibiotics, corticosteroids and diabetes. Only one of the eight cases survived. Surgical emphysema was described in 15 of 200 'pneumonic' cases of influenza during the 1918–19 pandemic.[119]

Complications affecting other body systems

The cardiovascular system

That influenza affects the cardiovascular system was suggested by the near doubling of deaths from

heart disease in Paris and the 2.5-fold increase in mortality from 'diseases of the organs of circulation' in Dublin during the pandemic of 1889–90.[120] Hypotension, relative bradycardia, heart failure, pericarditis, pericardial effusions, pericardial, subpericardial, epicardial and subendocardial haemorrhages, cardiac dilatation and friability of the heart muscle were all described as complications of influenza during the 1918–19 pandemic, but it was not until the advent of diagnostic tests in the 1930s that the role of the influenza virus was established.

Various electrocardiographic abnormalities, including various T wave abnormalities, ST segment elevation, sinus bradycardia or tachycardia, nodal rhythm, atrial fibrillation, ventricular extrasystoles and ventricular fibrillation, have been found in up to 81% patients with influenza in hospital[121–123] and in 43% of cases in the community[124] – mostly in people without cardiac symptoms. They may be transient, lasting no longer than 24 hours, but occasionally persist for months or years.[124,125] The underlying abnormalities (fragmentation of myocardial fibrils, interstitial haemaorrhage and oedema and lymphocytic infiltration[124,126,127]) may cause fatal arrhythmia or restrictive cardiomyopathy long after recovery from influenza.[128,129] The electrocardiographic findings, together with multidirectional echocardiography and elevated levels of the cardio-specific MB-CK isoenzyme, indicate that myocarditis is common in influenza, but is mostly asymptomatic.[123] Pericarditis has been described infrequently as a complication.[130–132] Historical reviews point out (a) the lack of correlation between the severity of influenza and myopericarditis, (b) the infrequency of cardiac complications during the acute respiratory phase and (c) that recovery is generally prompt.

That influenza involvement of the cardiovascular system may be important was recently established by demonstrations of vaccine effectiveness in preventing episodes of congestive cardiac failure,[133] recurrent myocardial infarction,[134] and primary cardiac arrest.[135] The US nationwide Medicare Influenza Vaccine Demonstration Project provided Falsey *et al*.[118] in Rochester, NY, USA, with the opportunity to collect nasopharyngeal specimens from patients ≥ 65 years of age who were hospitalised with acute cardiopulmonary conditions or ILI. Acute cardiopulmonary conditions included pneumonia, exacerbation of COPD, bronchitis, asthma, congestive heart failure, cardiac arrhythmia or influenza. Between November and April 1989–92, 221 of 2091 individuals (11%) who were tested were positive for influenza, indicating that a substantial number of acute medical admissions during the winter are influenza-related. Most had discharge diagnoses of pneumonia (54%) or COPD (11%), but almost one in six had a discharge diagnosis of congestive cardiac failure. Thus an appreciable number of influenza admissions in the elderly are 'hidden' as heart failure.

Diabetic complications

People with late-onset diabetes are 1.7 times more likely to die from pneumonia and influenza than the general population and one in 33 dies from these conditions overall.[136] The risk of death in a US health maintenance organisation was examined by Barker[137] during epidemics in 1968–9 and 1972–3. The pneumonia and influenza death rate among people with underlying cardiovascular disease was estimated at 104 per 100,000 during influenza A epidemics, but increased more than fourfold to 481 per 100,000 (i.e. one in 208) in those with both cardiovascular disease and diabetes. Diabetic deaths increased by 25% during the first wave of the 'Asian' influenza pandemic in The Netherlands in 1957 in comparison with the pre-epidemic years of 1954–6.[138] Similarly in the USA, deaths from diabetes increased by 5–12% during six of seven epidemics during 1957–66.[112] In England, increases in diabetic deaths of 5–15% were seen during 1921–32 during periods with the highest influenza death rates.[111] More recently, endocrine deaths (mostly diabetic) increased by about 1350 (i.e. by 30%) in England and Wales during the 1989–90 influenza epidemic in comparison with similar periods in 1985–6.[139] The combination of pneumonia and diabetes appears especially serious; in one study, six of nine diabetics with influenzal pneumonia died.[140] Studies of the effectiveness of influenza vaccine in preventing hospital admissions in people with diabetes can provide further insight into the burden of influenza – in Leicester, influenza vaccination was associated with an estimated 79% [95% confidence interval (CI) 19 to 95%] reduction during epidemics in 1989–90 and 1993.[141] Of 37 admissions, 32 (86%) were admitted for reasons of diabetic control rather than acute respiratory conditions. Thus even during an era of improved diabetic control, influenza is still responsible for appreciable morbidity among people with diabetes.

Central nervous system (CNS) complications

Although dementia, seizure disorders, cerebrovascular disease, difficulty with

oropharyngeal secretions and 'neuromuscular disease' have all been identified as risk factors for the development of nosocomial pneumonia and pneumococcal infection, the evidence that chronic CNS disorders increase the risk from influenza is not strong. Persons with Parkinson's disease are three to four times more likely to die from pneumonia and influenza than the general population, presumably because of their relative immobility towards the end of life.[142] During the 1989–90 epidemic of influenza A, chronic neurological disease emerged as a risk factor [odds ratio (OR) 1.65] for influenzal death[143] but not for hospitalisation for P & I.

Review of a representative selection of the literature on influenza suggests that neurological complications, excluding febrile convulsions in children, are not uncommon.[110] Patients with neurological complications associated with H1N1 and H3N2 subtypes of influenza A and influenza B fall into three groups: (i) those with convulsions, mostly young children during the febrile stage – convulsions are not accompanied by pareses, stupor or coma – this is the most common CNS complication, affecting approximately one-fifth of young children hospitalised with influenza; (b) stupor, coma or paresis, with or without convulsions, with a normal cerebrospinal fluid (CSF) – occasional patients have encephalitis, immune-mediated parainfectious encephalomyelitis or Guillain–Barré syndrome (GBS); (iii) stupor, coma or paresis, with or without convulsions or cerebellar features, with an increase in the number of cells in the CSF and/or an increase in CSF protein – most have an influenzal encephalitis, immune-mediated parainfectious encephalomyelitis or GBS. Patients in the second group are younger than the third (median 10 *versus* 36 years) and have higher mortality (6/24 *versus* 0/20). The median interval between onset of influenzal symptoms and stupor, coma or paresis is 5 days (range 0–21 days). The available data do not suggest a special neurotropic effect of a particular type or subtype of virus. The pyrexia, hypoxia and pH abnormalities that accompany influenza may be responsible for a toxic encephalopathy in some cases, whereas others are caused by viral encephalitis, an immune-mediated parainfectious encephalomyelitis or Reye's syndrome. Most patients recover fully, often shortly after the onset of influenza. However, the 1995 influenza epidemic in Japan was exceptionally neurovirulent and lethal. In Nagasaki, 12 cases of influenza encephalopathy were reported with 50% fatality. Twenty-six infants and children with acute encephalitis and encephalopathy were also reported during two seasons in Hokkaido, the northernmost island of Japan. Thirteen died and five had residual neurological sequelae. Influenza virus genome was detected by polymerase chain reaction in nine of 10 CSF samples. Attempts to recover influenza virus from the brain *post mortem*[144,145] or the CSF *ante mortem*[146] are usually unsuccessful, but occasional specimens are positive.[144,147,148]

Other neurological complications

Peripheral neuropathy

The literature on influenza at the beginning of the twentieth century refers to various neurological complications including peripheral neuropathy, but its relation to influenza is questioned by the lack of diagnostic virology at the time. A recent case report describes a multifocal mononeuropathy associated with influenza B.[149]

Bacterial meningitis

The increase in meningococcal infection after the 1989–90 influenza outbreak led British investigators to study the relationship between the two infections by a case–control study. Patients with meningococcal disease were almost four times more likely than controls to have been infected recently with influenza A.[150] The association was also studied in France. Although links were demonstrated, the proportion of cases of meningococcal disease that are causally linked to influenza is considered to be small.[151]

Cerebrovascular disease

The older literature suggest that there may be an increase in deaths from cerebral haemorrhage and atherosclerosis, but this has not been confirmed by studies of excess mortality conducted during the past 40 years. A possible causal link between influenza and subarachnoid haemorrhage was suggested in 1978 by the finding of a fourfold greater incidence of antibody to influenza A virus from patients with subarachnoid haemorrhage than a 'neurology' control group and age- and sex-matched patients.[152]

Encephalitis lethargica

It has been reasoned that the global pandemic of encephalitis lethargica followed by postencephalitic Parkinson's disease was causally associated with the influenza pandemic of 1918.[153] However, a causal link remains unproven.[154,155]

Psychoses

Acute psychoses, some with auditory and visual hallucinations, which develop 2–10 days after onset of influenza may represent a manifestation

of encephalitis or immune mediated parainfectious encephalitis. Electroencephalograms of three patients with influenza-associated psychosis were diffusely abnormal and improved slowly over a period of weeks.[156] Recovery is generally rapid.[157]

Subtle changes in brain function

Volunteers infected with influenza B at the MRC Common Cold Unit had significant impairments of reaction times and a visual search task involving five possible target letters was also significantly impaired.[158] Similar tasks were assessed during natural influenza B infection.[159] Comparison of baseline and symptomatic periods revealed a 38% increase in the variable fore-period simple reaction time when symptomatic. Individuals with influenza were 13% slower in performing the repeated numbers detection task than when recruited and they were less accurate than controls in a categoric search task. The effects were comparable to deteriorations seen with alcohol consumption or working at night.

Maternal complications during pregnancy

Pregnant women appear to be at increased risk of severe pulmonary complications of influenza, hospitalisation and death during the second and third trimesters, but the absolute risk appears to be small, particularly during inter-pandemic years. During the Asian influenza pandemic in England and Wales, 12 of 103 fatal influenza cases in females aged 15–44 years were pregnant – about double the expected proportion for this age group.[107] Similarly, among Dutch women 20–39 years of age, the mortality of pregnant women was twice that of non-pregnant women,[138] and in the USA the number of pneumonia and influenza admissions among pregnant women was up to four times higher than expected.[49,160] An insight into the absolute risk to pregnant women during a severe inter-pandemic epidemic was provided by mortality statistics in Great Britain during the 1989–90 epidemic.[139] There was a fourfold increase in deaths among pregnant women during the epidemic in comparison with non-epidemic years. Overall, about 90 excess deaths occurred during pregnancy out of an estimated 25,185 total excess deaths. Although few (2/19, 11%) pregnant women who are hospitalised for complications of influenza have underlying chronic medical conditions,[110] influenza complicating mitral valve disease in pregnancy appears especially serious since it is associated with an overall mortality of almost 45%, and higher (60%) when labour occurs during influenza.

Risks to the foetus

Few attempts have been made to demonstrate transplacental passage of influenza virus. Although several investigators failed to identify the presence of influenza antigen in foetuses from four mothers with fatal influenza,[161,162] influenza virus has been recovered from the amnion.[163,164] Influenza antigens have also been demonstrated in the brain of an infant with complex malformations of the central nervous system at post-mortem.[165] There are reports of an increase in various congenital abnormalities following influenzal illness during pregnancy,[166–171] but there is no consistent association between specific defects and illness, and the virus has not been conclusively implicated.

In contrast, influenza is associated with increases in early and late foetal deaths,[167,172] mortality from premature births,[111] early neonatal mortality[173] and perinatal deaths.[139] Perinatal deaths increased 1.6-fold in the UK during the 1989–90 epidemic, by 255 from ~465 to ~720, compared with a similar period in 1985–6. Crudely analysed, the data suggest that for around every 3000 births in a 12-month period, there was one influenza-associated perinatal death during the 1989–90 epidemic. Irving *et al*.[174] identified intercurrent influenza virus infections in 182/1659 (11.0%) pregnant women (of 3975 women) who were delivered at two Nottingham hospitals between May 1993 and July 1994. They found no significant differences in pregnancy outcome measures between cases and controls, or evidence for transplacental transmission of influenza virus. Although there were significantly more complications of pregnancy in the cases versus the controls, no single type of complication achieved statistical significance.

Several studies indicate a possible association between maternal influenza and illness in the offspring in later life. Studies in the USA and the UK indicate a possible relationship between maternal influenza and childhood leukaemia.[175–178] The relationship, if real, is not a constant finding[177,179] and the effect is considered to be very small. It has been shown that individuals who later develop schizophrenia are more likely to have been born in the late winter and spring than at other times of the year. Against a background of data suggesting that structural abnormalities found in the brains of many schizophrenic patients occurred *in utero*, Mednick *et al*.[180] claimed that a Finnish birth cohort, which had been in the second trimester of pregnancy at

the time of the 1957 pandemic, had an increased hospital admission rate for schizophrenia. Since then, many studies carried out in North America, Japan and several European countries provided conflicting results.[110] The positive findings have implicated exposure during the second trimester and an effect in females but not males. Even if there is real association between prenatal exposure to influenza and development of schizophrenia, the relationship is not necessarily causal, since influenza may lead to drug therapy for symptom relief and obstetric complications (that have also been reported in association with the later development of schizophrenia). The available data do not indicate maternal influenza to be an indication for termination of pregnancy.

Other complications

Toxic shock syndrome

Toxic shock syndrome, more commonly associated with staphylococcal infection secondary to the use of tampons, is an unusual complication of influenza with secondary staphylococcal infection. By 1993, a total of 15 cases had been described, 12 as a complication of influenza B; the overall mortality was 40%.[110] Cases without a rash, that might otherwise meet a definition of probable toxic shock syndrome, have also been described in association with influenza B.[181]

Gastrointestinal

During the Asian influenza pandemic in 1957, petechiae were found at post-mortem in the fundus of the stomach in 10 of 24 cases; gastric erosions, mucosal haemorrhages and coffee-ground material were observed.[182] More recently, seven of 19 young children who were hospitalised for virologically confirmed influenza A/H1N1 developed haematemesis and two died.[88] Attempts to identify the antigen or culture it from post-mortem specimens failed. During the influenza pandemic of 1918–19, Cole[183] and Abrahams *et al.*[119] reported over 40 cases of painless parotitis as a complication. The swellings were either unilateral or bilateral, the ducts were normal and in the majority of cases there was no associated orchitis or suppuration. More recently, parotitis was reported in 12 patients during the 1975–76 influenza epidemic in Massachusetts.[184]

Renal

Myoglonbinuric renal failure, Goodpasture's syndrome[185] and renal failure triggered by disseminated intravascular coagulation[105,186–189] have all been documented in patients with influenza. During outbreaks, influenza A is probably the leading cause of acute myoglobinuric renal failure. The literature also contains reports indicating that influenza virus infection may trigger acute renal allograft rejection.[190,191] Judging by the absence of renal complications in series of patients with proven influenza and the dearth of renal abnormalities in influenza, it is evident that influenza rarely affects the kidneys.

Myositis

Acute myositis occurs mostly in children infected with influenza B. Occasional adults infected with influenza develop myositis,[192] which tends to be more diffuse than in children. A cluster of four cases described in the Japanese literature in association with H3N2 infection raises the possibility that certain strains of influenza have a greater potential to cause this complication.[193]

Haematological

Bleeding disorder(s) in influenza may be due in part to disseminated intravascular coagulation (DIC) which has been associated with both influenza A and B.[105,186–188] Patients with DIC complicating influenza have presented with haematuria, haemoptysis, malaena, vaginal bleeding, purpura, haematemesis, renal failure and jaundice. Virus-associated haemophagocytic syndrome occurs mostly in association with cytomegalovirus and Epstein–Barr virus, but has also been linked with influenza.[194,195] Aplastic anaemia has also been linked with influenza A.[196]

Cutaneous

Cutaneous events are evidently rare in patients with influenza. Stevens–Johnson syndrome, herpes labialis and erythroderma have been reported in association with influenza.[197]

Influenza in the immunocompromised

Not only are transplant recipients and persons with malignancy more susceptible to influenza,[198] they are also at high risk of developing serious pulmonary complications of influenza and dying. Data from 12 reports on influenza in adults and children who have received transplants or have haematological malignancy were recently analysed.[110] Pneumonia occurred in 65% (56/86) of adults and 36% (9/25) of children with influenza, and 20% of both adults (21/104) and children (5/25) died from the infection. Most fatal pneumonias complicating influenza in the immunocompromised are viral rather than secondary bacterial in aetiology,[199,200] thereby underscoring the need for an effective antiviral agent. Graft rejection, possibly arising from the temporary suspension of immunosuppression, is

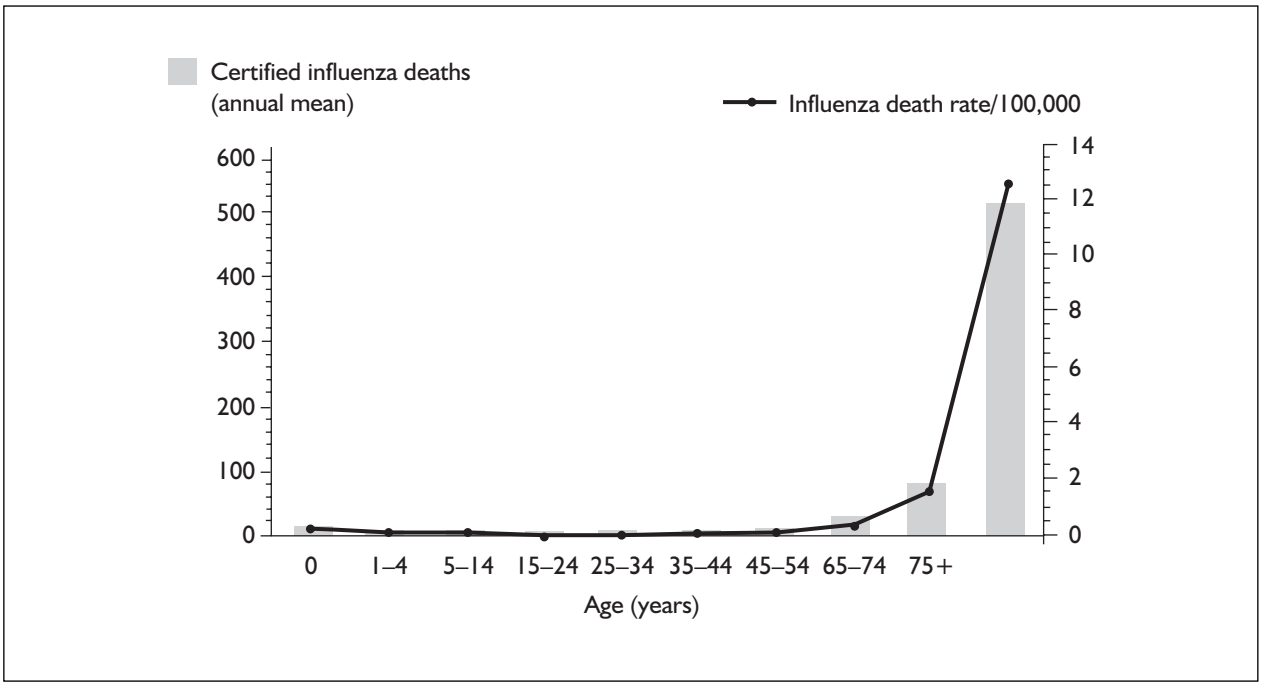

FIGURE 6 *Certified influenza deaths, in England and Wales, 1987–95: annual mean deaths and mean annual death rate/100,000.*

potentially a complication of influenza in transplant recipients.

There is conflicting evidence pointing to an increase in morbidity and mortality from influenza among HIV-infected individuals. Analysis of bronchoalveolar lavage (BAL) fluid from 895 patients, most of whom had immunosuppression due to AIDS, transplantation, malignancy or immunosuppressive therapy revealed that influenza virus was recovered infrequently – only on 11 occasions, but not from any of the 757 BAL fluids from patients with AIDS.[201] Miller *et al*.[202] examined BAL fluid from 44 HIV-positive patients who underwent 47 diagnostic bronchoscopies for lower respiratory disease; influenza virus was recovered from none. Safrin *et al*.[203] reported influenza infection in six HIV-infected patients – one developed pneumonia, but the overall course of illness in this cohort suggested that it was not worsened in comparison with immunocompetent subjects. However, another report demonstrates that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons.[204] In cities with a high incidence of HIV infection, an increase in pneumonia deaths among persons aged 25–44 years during the peak influenza months provides indirect evidence supporting an increase in severity of influenza in adults with HIV.[205] A retrospective cohort study of young and middle-aged women enrolled in Tennessee's Medicaid program found that the attributable risk for cardiopulmonary hospitalisations among women with HIV infection was higher during influenza seasons than during the peri-influenza periods. The risk for hospitalisation was higher for HIV-infected women than for women with other high-risk conditions, including chronic heart and lung diseases.[206] Lin and Nichol[207] used national multiple cause of death data to calculate the number of P & I deaths each month for adolescents and adults with AIDS. Comparisons were made during influenza seasons with adults and adolescents in the general US population and also with the pre-influenza period. The risk for P & I excess deaths was 9.4–14.7/10,000 persons with AIDS compared with rates of 0.09–0.10/10,000 among all persons aged 25–54 years and 6.4–7.0/10,000 among persons aged ≥ 65 years. Thus the available data indicate that persons with AIDS have significant excess P & I mortality during influenza seasons that is at least equivalent to the P & I mortality in the general elderly US population.

Influenzal deaths

Influenza epidemics are often accompanied by excess mortality (i.e. the difference between the observed number of deaths and expected number in the absence of influenza). About 90% of these deaths are among people aged ≥ 65 years[139,208–211] (*Figure 6*). The burden of influenza on mortality is difficult to assess, however, because many deaths related to influenza are often attributed to other causes. In England and Wales, an estimated

6200–29,600 people died during each of the epidemics between 1975–76 and 1989–90;[212] this is about ten times the actual number of death certifications for influenza, indicating that influenza is responsible for many hidden deaths.

Using another method Curwen *et al*.[213] examined 1989–90 mortality data for England and Wales. They showed that certified influenza deaths represented <10% of the excess mortality. In the USA, excess deaths occurred during 17 of 20 influenza epidemics during the period 1972–3 through 1992–93.[43] These epidemics were associated with an average of 21,300 excess deaths from all causes, with greater numbers occurring during influenza A H3N2 seasons than during influenza B or A (H1N1) seasons. Analyses of influenza epidemics occurring from 1972–3 to 1994–5 revealed excess deaths during 19 of 23 seasons. During these 19 seasons, estimated rates of influenza-associated deaths ranged from approximately 30 to >150 deaths/100,000 persons aged >65 years (Influenza Branch, DVRD, NCID, CDC, unpublished data, 1998; cited by the Advisory Committee on Immunization Practices, 2001, at http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm). Despite increasing levels of influenza vaccination in the USA, pneumonia and influenza deaths might be increasing in part because the number of elderly persons is increasing (National Center for Health Statistics. Health, USA, 1998). The cumulative mortality during recent inter-pandemic years is many times greater than the deaths associated with the two most recent pandemics.

Although data for England and Wales (see *Figure 6*) and the USA[214] indicate increasing influenzal mortality with increasing age (from the age of 5 years upwards), it has been questionable whether age is an independent risk factor for influenza mortality because most deaths (about 84% during the 1989–90 epidemic in England[143]) occur in people with one or more underlying medical conditions. Barker and Mullooly[137] examined the risks of death from pneumonia and influenza among 230,000 people in a health maintenance organisation during epidemics in 1968–9 and 1972–3. The mortality was nine per 100,000 for the over-65s without high-risk conditions, but was 20-fold greater in the over-65s with one high-risk condition and 30-fold greater in those with two or more.

As with deaths, studies in both England and Wales,[215] and the USA[216,217] indicate that 70–90% of people aged ≥ 65 years who are hospitalised with P & I have chronic medical conditions. Another study[218] showed that the risk of P & I admission in unvaccinated elderly people during influenza seasons was more than twice as great in those with 'intermediate' risk (baseline diagnosis of diabetes, renal disease, rheumatological disease or dementia and or stroke) as in the low-risk group (9.8/1000 versus 4.4/1000), and more than five times as great in those with a 'high-risk' (heart or lung disease) condition (23.5/1000 versus 4.4/1000). Thus, although the risk of influenzal mortality and hospitalisation increases with age, the presence of certain underlying chronic medical conditions represents the principal risk.

Influenza in residential care

In comparison with elderly people living in the community, residents of nursing homes are at particular risk of serious influenza-related complications. They are older and have a higher rate of chronic ill-health. Living in close proximity facilitates transmission and these patients may respond less readily to vaccination. There have been numerous reports of influenza with high attack rates in homes for the elderly, and mortality rates of >4% are common.[219–221]

Nguyen-Van-Tam and Nicholson[222] examined certified influenza deaths in Leicestershire during the 1989–90 epidemic. The estimated mortality for the fit elderly was about 7 per 100,000. Among non-residential people the rate for certified influenza deaths was 11.6 and 23.1 per 100,000 for those with lung and heart disease, respectively. The major impact of influenza was in residential care facilities where the rates were 343, 499 and 2703 per 100,000 for people with one, two, and three or more medical conditions, respectively. In further studies conducted in (i) people with influenza as a certified cause of death in five health regions in England and (ii) patients admitted to Leicestershire hospitals with P & I-related conditions,[143,215] these investigators found that more than half of those who died lived in residential care (OR 2.08, 95% CI 1.48 to 2.9), as did over 15% of the P & I admissions in Leicester (OR 2.96, 95% CI 1.35 to 6.53). Since only about 5% of the elderly population in England live in residential care, it is evident that this group are at the greatest risk of serious morbidity and mortality. Homes that experience influenza outbreaks tend to be larger (>100 beds) and less well vaccinated (<80% of residents immunised) than other establishments.[223,224]

Employees may represent one of the most important routes of influenza virus entry into

nursing homes. During 1993–4, a comparatively mild epidemic season in Scotland, serological evidence of influenza infection was found in 23% of 970 healthcare workers at four acute hospitals in Glasgow.[225] More than half (59%) of these could not recall having influenza or taking sick (52%) leave for a respiratory infection. Moreover, two other studies have shown that >70% of healthcare workers with laboratory evidence of influenza or influenza-like illness have continued to work.[226,227] It is therefore not surprising that healthcare workers have been implicated as the source of influenza infections in nursing home influenza outbreaks,[228,229] or that vaccination of staff benefits residents.[230]

Prevention and treatment of influenza

Introduction

Most acute respiratory illness is viral in origin. Since specific treatment is unavailable for most respiratory viral illness, patients are educated to stay at home, obtain symptomatic relief with antipyretics, analgesics, antitussives and decongestants, and to seek medical advice and antimicrobial therapy only when complications arise. Antivirals against influenza have been available since 1966 but, outside the USA and the former Soviet Union, the use of amantadine and rimantadine has been limited, largely because of side-effects, lack of perceived benefits and propensity for induction of drug-resistant viral strains. NIs, a 'new' class of antivirals for influenza, have shown considerable promise in clinical trials and are available in some countries. On 21 November 2000, guidance on the use of the antiviral agent zanamivir (Relenza) in the treatment of influenza was issued by the National Institute for Clinical Excellence (NICE). The NICE recommendations regarding the use of zanamivir are as follows:

- The NHS should not use zanamivir to treat influenza in people who are otherwise healthy.
- When influenza is circulating in the community, zanamivir may be used to treat high-risk adults who are able to begin their treatment within 48 hours of the start of their symptoms.

Symptomatic relief

The Department of Health's website advises that treatment of flu is symptomatic and those affected should stay at home, rest and drink plenty of fluids (http://www.doh.gov.uk/flu.htm). Similarly, the National Institute of Allergy and Infectious Diseases (NIAID) in the USA comments that many people treat their influenza infections by simply resting in bed, drinking plenty of fluids and taking over-the-counter (OTC) medications such as aspirin or acetaminophen. However, children and adolescents are advised not take aspirin because of the danger of Reye's syndrome and NIAID (www.niaid.nih.gov/factsheets/flu.htm) advises against routine use of antibiotics. Cough suppressants may enable rest, but they interfere with clearance of secretions during the early symptomatic stage, when ciliary function is impaired, and are probably best avoided.

Antimicrobials

It can be difficult and challenging for primary care physicians to distinguish influenza from other viral respiratory infections and even early bacterial conditions that require treatment with antibiotics. With the increasing incidence of antimicrobial resistance, the use of antibiotics in community-acquired upper respiratory tract infections (URTIs) is a concern, because about half of clinical antimicrobial usage is for infections at this site and most of these infections are viral.

Increasing concern about the misuse of antibiotics coupled with the availability of new antiviral drugs and the extensive promotional activity and media coverage accompanying their release has raised fears about the potential misdiagnosis of influenza and misuse of influenza antivirals. This concern was first voiced in January 2000 by the US Food and Drug Administration (FDA), which issued a cautionary note to physicians when prescribing antivirals for influenza after being informed of patients with serious bacterial infections who initially had influenza-like symptoms and whose bacterial infections progressed during treatment with antiviral drugs alone (www.fda.gov/cder/drug/advisory/influenza.htm; accessed March 2002). Subsequently, Lim and colleagues[231] described a 61-year-old diabetic man who presented with a 1-day history of ILI when influenza A was known to be circulating in the community. One day after being diagnosed with influenza and prescribed zanamivir, he presented with pedal ulceration with osteomyelitis, lobar pneumonia and Group B streptococcal septicaemia. The FDA reminded physicians that antiviral products such as those approved for influenza have no activity against bacterial infections and patients should be treated with appropriate antibacterial therapy whenever bacterial infection is suspected.

The following data provide little support for the routine use of antibiotics in most common respiratory complications of influenza.

Tracheitis and tracheobronchitis are the most common lower respiratory complications of influenza. A recent Cochrane review of antibiotic treatment found that antibiotics have a modest beneficial effect (such as a reduction in the duration of cough of 0.6 days) in patients who are diagnosed with acute bronchitis.[232] However, the magnitude of this benefit is similar to that of the detriment from potential adverse effects

Chronic obstructive airways disease is frequently exacerbated by influenza. A recent meta-analysis of antibiotics in treating exacerbations of COPD suggest a small but statistically significant improvement.[233] The authors concluded that the antibiotic-associated improvement may be clinically significant, especially in patients with low baseline flow rates. Subsequently, the British Thoracic Society (1997) recommended antibiotic therapy when two of the following features are present: worsening dyspnoea, increased sputum volume and increased sputum purulence.

Antibiotics are often prescribed to patients who are admitted to hospital with acute asthma. Their exacerbation is often precipitated by a viral URTI, but in many instances antibiotics are prescribed in spite of questionable efficacy.[234] A recent Cochrane review[234] identified only two trials from 128 potential studies for inclusion in the review. Patients receiving antibiotics appeared to improve at the same rate as patients not receiving antibiotics and subpopulation analyses were not possible. The authors concluded that antibiotics do not appear to provide any added benefit over standard therapy, either in children or adults hospitalised for acute asthma.

Acute otitis media is preceded in many instances by a respiratory viral infection and otitis media is a common finding in young children with influenza. A recent Cochrane review of antibiotics for otitis media in children found that they have a modest beneficial effect [a 28% relative reduction (95% CI 15 to 38%) in pain at 2–7 days; since approximately 80% of patients settle spontaneously in this time, this means an absolute reduction of 5% or that about 17 children must be treated with antibiotics to prevent one child having some pain after 2 days].[235] There was no benefit on hearing problems or recurrence and the marginal benefit from antibiotics has to be weighed against the possible adverse reactions and costs.

Primary viral pneumonia and secondary bacterial pneumonia are recognised lower respiratory complications of influenza and some patients have a rapidly fulminating course. Unnecessary hospital admission is to be discouraged since it can result in nosocomial transmission to patients with chronic medical conditions, placing them at high risk for serious morbidity and mortality. Although some patients can be treated in the community, others with one or more of cyanosis, respiratory rate of >30/min, confusion, diastolic blood pressure <60 mmHg and atrial fibrillation require hospitalisation.

Antivirals

The adamantanes (amantadine and rimantadine) and the NIs (zanamivir and oseltamivir) are potentially useful for 'seasonal' prophylaxis, post-exposure prophylaxis in households, outbreak control in residential care and therapy of influenzal illness.

Amantadine

The parent compound, 1-aminoadamantane hydrochloride, is a C_{10} tricyclic primary amine with a cage-like structure that was discovered in the 1960s to inhibit replication of strains of influenza A. Amantadine was originally licensed for prophylaxis against influenza A (H2N2) infection in 1966, but has had limited clinical application owing to concerns about adverse effects, its limited spectrum of activity and rapid development of resistance. Rimantadine is available in several countries, but is unavailable in the UK.

Antiviral activity of amantadine

Amantadine (and rimantadine) inhibits human H1N1, H2N2 and H3N2 subtypes of influenza A. Avian and equine subtypes of influenza A are also sensitive and it is anticipated that future variants, including pandemic strains, will be susceptible. Low concentrations of amantadine (<5 μmol/l, <0.75 μg/ml) exert a strain-specific inhibitory effect. Neither agent inhibits influenza B. The antiviral activity of amantadine (and rimantadine) occurs through inhibition of the M2 membrane protein ion channel activity. This results in inhibition of the acidification of the virus interior which is required to promote fusion of the viral envelope with the endosome and for dissociation of the M1 matrix protein from the ribonucleoprotein complex (uncoating). As a result, viral replication is blocked at an early stage of the cycle. A second inhibitory effect is seen late in the replication cycle of some avian strains that have an HA that is cleaved intracellularly.

Resistance

Resistance of influenza A strains to both amantadine and rimantadine *in vitro* was first

described in the initial reports of the antiviral activity of these drugs in 1965.[236,237] Resistance was obtained after as few as one passage in tissue culture[236] and is so readily achieved *in vitro*, in animals and humans, that it is probable that all naturally occurring type A viruses are mixtures of sensitive and resistant strains, with sensitive strains predominating. Drug-resistant strains of virus have cross-resistance between amantadine and rimantadine and there are no data to suggest that either agent is more likely to select for resistance than the other.

The primary determinant of drug susceptibility is the M2 matrix protein. RNA sequencing of these amantadine- and rimantadine-resistant viruses has demonstrated that the genetic basis of resistance is a single nucleotide change in the M2 protein, resulting in an amino acid substitution at position 26, 27, 30, 31 or 34 in the membrane-spanning region of M2.[238] Resistant strains have been identified among population-based isolates since the late 1970s.[239] The available data indicate that approximately one in 65 influenza A isolates obtained globally exhibits amantadine resistance with no evidence of a recent increase.[239–246] Elliot and Zambon,[245] at the Central Public Health Laboratory, Colindale, screened a total of 2309 isolates from 1968 to 1999, representing approximately 17% of all influenza viruses isolated in the UK. Confirmatory testing by plaque reduction assay indicated that the overall frequency of phenotypic amantadine resistance for both H1N1 and H3N2 was 2.3%. The M2 genes of resistant viruses were sequenced to determine their drug genotype. Mutations were identified in approximately 43% of phenotypically resistant viruses. Hence the overall incidence of combined phenotypic and genotypic resistance in the general population in the UK is estimated at ~1% (0.43×2.3), that is, approximately 1% of circulating influenza viruses currently exhibit amantadine resistance in the UK.

Although amantadine-resistant influenza A is recovered infrequently during population-based screening, drug-resistant virus appears in more than one-quarter of patients when either amantadine or rimantadine is used therapeutically in children,[247–249] adults[248] or the elderly (Betts, cited by Hayden *et al*.[248]) and the immunocompromised.[250] Studies of the use of amantadine for post-exposure prophylaxis in the family setting revealed prophylactic efficacy in one study[251] but negligible effects in another.[252] In the first study, the investigators gave the drug to contacts only, whereas both the index case and contacts were treated in the second study. Post-exposure prophylaxis with rimantadine was also ineffective when given in households to contacts and index cases,[253] but was effective when given to contacts only.[254] Hayden and colleagues[253] identified drug-resistant viruses in eight index cases and five contacts treated with rimantadine. They concluded that when index cases and contacts are treated concurrently, rapid selection and apparent transmission of drug-resistant virus can occur with little or no benefit to contacts.

Drug-resistant virus has been isolated in nursing homes where it has been given for treatment and prophylaxis.[244,255–260] Overall, 87 of 273 (31.9%) specimens collected from cases in these reports were resistant. These data may be biased since attempts to isolate virus is perhaps more likely in homes where cases continue despite drug use. Conceivably, the likelihood of resistance occurring in residential care is greater than in healthy adults because of the decline in immune function that is associated with ageing.

Resistant virus has been detected within 24–48 hours of initiation of treatment in adults and the elderly,[248,250,257] It is often detectable by the third day of treatment.[248] These reports illustrate the rapidity with which resistant virus can replace sensitive virus during treatment. Patients receiving chemoprophylaxis who develop influenza associated with the recovery of amantadine-resistant virus have a typical influenza illness[240,253,255,257,258] that is associated with bed confinement, restricted activity, pneumonia and death.[256,261] Despite development of resistance, there is some evidence of a net therapeutic benefit to immunocompetent individuals.[248] There is no evidence that resistant virus causes more morbidity than sensitive isolates, but rimantadine recipients shedding resistant virus possibly recover more slowly than those shedding sensitive virus.[247] Significantly more children have been observed to shed influenza virus after cessation of rimantadine than acetaminophen-treated controls.[247] Immunodeficient individuals may shed amantadine-resistant viruses for prolonged periods and with different drug resistance mutations present at different times.[262] Moreover, in immunocompromised patients, influenza-associated mortality is similar among patients with and without documented antiviral resistance,[250] suggesting that viruses resistant to amantadine retain their pathogenicity. Amantadine-resistant viruses are evidently genetically stable as they can be transmitted through six successive generations of exposed chickens and are transmissible in humans.

Pharmacokinetics

Amantadine is absorbed well with an oral bioavailability of 62–93% in the young and 53–100% in the elderly.[263] There are several potentially important differences between the pharmacokinetic profiles and elimination pathways of amantadine and rimantadine. Comparative single-dose pharmacokinetic studies in young (≤ 35 years) and elderly (≥ 60 years) adults reveal peak plasma concentrations approximately 2.5 times greater after amantadine than rimantadine.[264] Although the plasma levels of toxic and non-toxic subjects overlap considerably, plasma drug concentrations of both drugs correlate with symptoms, and it has been suggested that the difference in plasma concentrations after equivalent doses may explain the relative increase in adverse reactions after amantadine.[265]

The volume of distribution of rimantadine is 2.5–3 times greater than that of amantadine.[264] The two drugs are distributed differently in different body compartments. The ratios of nasal mucus to plasma concentrations of rimantadine are significantly higher at 4 and 8 hours than after amantadine and, despite lower plasma concentrations of rimantadine at equivalent oral doses, the concentrations of amantadine and rimantadine in upper respiratory secretions are comparable.[264,266]

Amantadine is excreted renally,[267,268] whereas rimantadine is extensively metabolised by the liver (approximately 65%), and is also metabolised and excreted as unchanged drug by the kidney.[264] The plasma half-life of amantadine is prolonged considerably in patients with impaired renal function, 11.8 hours versus 18.5 hours to 33.8 days (mean 140 hours),[269] and the half-life of amantadine in elderly men after multiple doses is almost double that in the young.[268] Less than 5% of a dose is removed by haemodialysis and average half-lives of 8.3 and 13 days have been recorded in patients on chronic haemodialysis.[269,270] Care must therefore be taken to ensure that amantadine does not accumulate to toxic levels. The amantadine dose needs to be reduced in proportion to the degree of renal dysfunction when creatinine clearance falls below 80 ml/minute.[271]

Adverse effects

Reports of side-effects from amantadine and rimantadine have been generated largely from studies of healthy young volunteers. In placebo-controlled studies there is a modest excess of mild CNS side-effects and gastrointestinal symptoms over placebo and the adverse reactions to both amantadine and rimantadine are qualitatively similar.[272–277] In one study involving 450 volunteers aged 18–45 years who received either rimantadine, amantadine or placebo prophylactically for 6 weeks, withdrawal rates were twice as high in amantadine recipients (22%) than in either rimantadine (10%) or placebo recipients (11%), primarily owing to CNS adverse reactions during therapy (13% versus 6% and 4%, respectively).[278]

'Minor' neurological symptoms include insomnia, light-headedness, difficulty in concentration, nervousness, dizziness and headache. Other adverse effects include anorexia, nausea, vomiting, dry mouth, constipation, abdominal pain and urinary retention. Convulsions have been reported at therapeutic doses of both amantadine and rimantadine and appear to be related to drug levels. Side-effects to amantadine and rimantadine arise mostly within several hours of drug ingestion during the first 3–4 days of treatment and are reversible when the drug is discontinued or the dosage is reduced.

The incidence of side-effects to amantadine in the elderly has been less well documented. A reduced dose of amantadine (<100 mg daily) in elderly people and those with renal dysfunction is recommended. Despite these measures, a high incidence of unacceptable adverse reactions has been demonstrated in nursing home residents taking amantadine prophylactically. Adverse effects to amantadine prophylaxis of 79 elderly residents of a retirement home were reported by Stange and colleagues.[279] These investigators identified attributable adverse effects before, during and after a 10-day period of drug administration by retrospective analysis of nursing home records. Residents (mean age 88 years) were offered amantadine prophylaxis 100 mg daily, and the dose was adjusted for creatinine clearance. The most common adverse events in comparison with baseline were (i) hallucinations, anxiety and weakness, (each occurring with an incidence of 13%), (ii) falls, ataxia, dizziness and increased confusion (each 11%), (iii) psychosis and insomnia (9%); (iv) fatigue (8%), (v) depression (6%), and (vi) irritability (5%). Seizures, inability to concentrate, forgetfulness, drowsiness, slurred speech, rash, headache, nervousness and new or worsening heart failure were each noted in less than 5% of individuals. Overall, 41% of the residents had one or more attributable adverse events. Risk factors for 'severe' adverse effects included residence in the assisted-living section of

the facility, the number of pre-existing medical conditions, the serum creatinine level and congestive heart failure.

In another home, Degelau and colleagues[280] studied adverse events in residents (mean age 87 years) who were given a 2-week course of amantadine, 100 mg daily. Amantadine was discontinued owing to possible toxicity in 14.5% of recipients. Overall, 12 of 53 (22%) individuals experienced adverse events including weakness, fatigue or nausea, and seven fell. The dose (mg/kg/day) was significantly higher in those with adverse events attributed to amantadine and tended to be more frequent in those weighing <50 kg. The drug concentration 24–26 hours after the last dose showed considerable variation (128–5810 ng/ml, median 591 ng/ml) and were unexpectedly high, indicating that further dose reductions would be necessary.

Arden and colleagues[281] gave amantadine 100 mg daily, as either therapy (n = 14) or prophylaxis (n = 41), to 55 residents (median age 74 years) in a nursing home All were monitored daily for 11 clinical manifestations previously associated with amantadine toxicity. Serum amantadine concentrations were collected from 47 residents 24–28 hours after cessation of therapy. During the 28-day period of amantadine administration, 26 (47%) residents developed one or more clinical manifestations compatible with side-effects. The most common were fatigue (33%), anorexia (22%), agitation (18%), depression (18%), insomnia, (15%) and nervousness (11%). Adverse events were considered to be mild and transient and only rarely interfered with the residents' routine activities/level of functioning. Medication was withdrawn in four cases (4/55, 7.3%) – in one subject because of dramatic personality changes with hostile and irrational behaviour; a second person with an active seizure disorder had a convulsion; and two others had falls. Residents with the higher drug levels were more likely to demonstrate adverse events. This group of residents was substantially younger than in the previous report, and the older patients described by Degelau and colleagues[280] seem more comparable to the average UK nursing home population.

In another study, Peters and colleagues[282] initiated institution-wide prophylaxis with amantadine 100 mg daily to 49 residents and dosage reductions to a further 10 residents during an outbreak of A/Sichuan (H3N2) virus. Adverse reactions were identified in 17 of 59 residents. In 11 the occurrence of side-effects led to a reduction in dosage or discontinuation of drug. The drug was discontinued at the request of seven of 59 residents, for gastrointestinal disturbances in four patients, nervousness in two, and insomnia in one. The above reports and others[283–287] indicate that discontinuation of amantadine prophylaxis occurs in ~12.5% of residents because of perceived adverse reactions.

The neuraminidase inhibitors

The influenza NA is required for a number of functions, including the release of progeny virions from the surface of infected cells. NAs cleave the linkage between terminal α-ketosidically linked SA residues and the carbohydrate moieties of cellular and viral glycoconjugates to yield *N*-acetylneuraminic acid (Neu5ac, SA). By cleaving SA from glycoproteins, NA breaks the bond between infected cells and newly synthesised viruses. Because SAs are also found in respiratory mucus, cleavage of these bonds may also facilitate virus dispersal through secretions, thereby helping the virus penetrate respiratory epithelial cells. Additionally, the enzymatic activity of NA provides the virus with the means to prevent virus clumping. The rationale for developing NIs is the thought that because sialidases release infectious virions from the cell surface, an inhibitor of this process may provide the host's immune system with sufficient time to mount an appropriate response before widespread dissemination of infectious particles.

Virion NA is a mushroom-shaped tetramer. A stalk that is embedded in the viral envelope anchors the globular head containing the enzyme-active site (and antigenic site of the molecule) to the virion surface. The NA polypeptide is approximately 470 amino acids in length.[288] The protease cleavage site is near residue 80. Sequence studies show that within the globular head regions, any two NA subtypes are of the order of 45% identical, and that any two influenza A and B strains are ~30% identical.[288] Sequence variation within subtypes may be as low as a few per cent. The catalytic site of the enzyme is a strain-invariant pocket into which SA binds.

The concept of NIs first evolved in 1942 when Hirst first alluded to the probable existence of an enzyme on the surface of the influenza virus.[289] The first NIs to be developed were analogues of the substrate sialic acid. The prototype inhibitor, 2-deoxy-2,3-dehydro-*N*-acetylneuraminic acid (Neu5Ac2en, also known as DANA), was first described in 1969.[290] Although a potent inhibitor

of influenza A and B *in vitro*, Neu5Ac2en was not developed as an antiviral owing to its non-specific inhibition of NAs, lack of efficacy in animal models of infection and lack of the requisite pharmacokinetic properties to have any appreciable effect *in vitro*, because of rapid clearance of the inhibitor.[290] By 1976, Palese and Compans[291] had shown that inhibition of NA *in vitro* with a DANA analogue prevented viral replication and caused aggregation of influenza virions.

In 1983, Colman described the crystal structure of the influenza NA.[288] This laid the foundations for the computer-aided design of several rationally designed 'second-generation' sialidase-based of influenza virus replication.[292–294] One analogue, 4-guanidino-Neu5Ac2en (zanamivir), was found to be a potent and **specific** (i.e. a second-generation NA inhibitor) inhibitor of a wide range of influenza virus types A and B in enzymatic and cell culture assays, and demonstrated efficacy in animal and human challenge models of infection.[295] However, owing to poor oral bioavailability, zanamivir must be delivered directly to the respiratory tract via inhalation therapy.

Further modification of the analogue Neu5Ac2en has led to the development of a range of NIs with potency comparable to zanamivir. An ethyl ester pro-drug (GS 4104) (oseltamivir) of one of these (GS 4071), a carbocyclic transition-state analogue of SA cleavage, was found to be **orally active** (i.e. a third-generation inhibitor) in animal[296] and human challenge models of infection.[297]

Antiviral activity

Zanamivir

Zanamivir has potent selective antiviral activity against a range of influenza A and B viruses in cell culture, including members of all nine NA subtypes of influenza A (IC_{50} range 0.005–16 μM); it also inhibits both amantadine-sensitive and resistant-strains of influenza A.[290,294,298,299] Zanamivir also has potent inhibitory activity against influenza in animal models[298,300,301] and experimental and natural human influenza.[295,302–305] Zanamivir inhibits influenza A and B in the mouse and ferret models of infection when given by intranasal and aerosol routes, both before and shortly after infection.[300,301] Zanamivir is 100–1000 times more potent than ribavirin and amantadine in ferrets experimentally infected with human strains of influenza A and B.[301] It is inactive in the mouse model of infection when given intraperitoneally, and it is only partially effective in chickens infected with highly pathogenic avian viruses by the intratracheal route,[306] presumably because the virus spreads away from the respiratory tract in this species.

Oseltamivir

The activity of GS 4071 [the active moiety of the ethyl ester prodrug, oseltamivir (GS 4104)] is comparable to zanamivir against influenza A and B NA and virus growth *in vitro*.[299,307] Oral GS 4104 is also active against influenza A and B viruses in the mouse and ferret models of infection[308–311] and experimental and natural human influenza.[297,312–314]

Resistance

Methods for determining resistance to NIs

Various methods have been used for susceptibility monitoring of influenza viruses. Susceptibility of amantadine and rimantadine has monitored predominantly by yield reduction assays because plaque formation in cell culture by clinical isolates of influenza is very variable and the methodology is not ideal for large-scale monitoring. However, because of the close functional relationship between the viral HA (responsible for virus attachment to cells) and the NA, it has become apparent that cell-based assays are generally unsuitable for monitoring susceptibility. Thus, with 'weak' HA receptor binding, the NA function in cell-based assays may be bypassed.[315] Mutations selected in the HA, although not apparently contributing to resistance *in vivo*, may result in cell culture-based resistance, and conversely may mask NA resistance in cell culture by modifying receptor binding activity.[315] Moreover, in plaque-reduction assays in MDCK cells in which virus may spread directly from cell to cell (as opposed to the situation *in vivo* where virus is released from the cells' apical surface), the NIs typically reduce plaque size rather than plaque number, making quantitative assessments difficult.[316] Yield-based assays also give variable results, and false-negative resistance may occur with mutations that involve both the HA and NA.[317]

Because the NA functions extracellularly, an *in vitro* assay of neuraminidase enzyme activity is considered to be more representative than *in vitro* cell-based assays. Two assays of enzymatic activity are use to monitor susceptibility; the most widely used employing 2′-(4-NA-Star)-α-D-*N*-acetylneuraminic acid (MUN). Susceptibility assays are supplemented by sequencing of the NA to confirm phenotypic resistance and of the receptor binding region of the HA to define resistance mechanisms better.

Resistance mechanisms

Influenza viruses with reduced sensitivity to the NIs have been isolated following tissue culture passage of virus in the presence of drug and also from humans. To date, two different mechanisms of resistance, involving mutations in both the viral HA and NA, have been identified, and a third mechanism leading to reduced virus susceptibility has recently been described.[318]

Limiting dilution passage of influenza virus in the presence of NIs has led to the isolation of a series of viruses whose sensitivity is reduced by up to 1000-fold.[319] The majority of resistant viruses have a mutation in the HA,[319–326] which generally precedes the acquisition of mutations in the NA. A number of mutations have been reported with most being close to the sialic acid binding site, although a mutation at a more distal location (glycine 75) has also been described.[324] These observations suggest that the mechanism for resistance is due to a decrease in the affinity of the HA to the cellular receptor, which facilitates elution of virus from infected cells without the need for viral NA. Some *in vitro* selected mutants demonstrate drug dependence in cell culture; this evidently arises from increased receptor binding during absorption of the virus when NA activity is inhibited. Several variants have been shown to share cross-resistance with other NIs.

Mutations have also been detected in the NA gene that result in amino acid changes at positions 119, 152, 274 and 292 in the active site of the enzyme. These result in glutamate 119 being substituted by glycine, asparagine or arginine, arginines 152 and 292 changing to lysine, and histidine 274 changing to tyrosine.[317,320–322,326–329] The 119 mutants have been isolated from both influenza A[320,321,324,326] and B.[321,330] These NA mutations either have an adverse effect on NA activity or stability.[331] Although resistant variants with NA mutations replicate efficiently in cell culture, most show reduced infectivity and virulence in animal models.[326,327,329] Hence the relevance of these mutations to the treatment and prophylaxis of humans remains uncertain.

Nedyalkova and colleagues[318] recently generated drug-resistant variants of influenza A viruses that lacked characteristic markers of resistance, such as substitutions in the NA active centre or in the HA. Drug resistance was associated with the accumulation of defective (Delta) RNA segments encoding NA (segment 6). This phenomenon could be explained by reduced dependence of the virus on its NA activity. It has been suggested that a reduced dependence on the NA enzyme is the underlying factor responsible for the accumulation of defective NA genes and that during cell passage, the virus acquires compensatory changes in other genes that allow it to spread despite NA inhibition. Analysis of the last isolates recovered from 11 volunteers, experimentally infected with influenza virus and treated with an NI, revealed that, although they maintained full susceptibility to the drug in the NA inhibition assay (50% inhibitory concentration, 0.35–0.5 nM), the presence of DeltaRNA segments was observed in one of these isolates. These observations suggest that detection of DeltaRNA segments should be considered an additional assay for monitoring of NA inhibitor resistance (see below).

Clinical studies of susceptibility

The extent to which this phenomenon (the development of resistance) occurs during treatment or prophylaxis remains unclear, as does the effect, if any, on the virulence of the mutants. The first report of the emergence of resistance during treatment with an NI (zanamivir) involved a bone marrow transplant recipient who developed influenza B pneumonia.[317] Virus isolated on day 8 had an HA mutation at threonine 198 but by day 12 it had developed an NA mutation at arginine 152. Insufficient data are available to assess adequately the risk of emergence of zanamivir resistance in clinical use. In five subjects with index infections who received zanamivir, the sensitivity of the isolate obtained on day 1 was similar to that of the isolate obtained on day 5.[332] In another report,[333] 41 paired isolates, collected before and during Phase II efficacy studies, demonstrated no shifts in susceptibility to zanamivir when assessed by NA assays. No amino acid changes that were associated with reduced susceptibility to zanamivir were identified.

An NA mutant involving position 119 has been recovered in an oseltamivir treatment study,[334] and mutants involving position 292 have been recovered from patients treated with oseltamivir.[331] Two of 54 volunteers experimentally infected with influenza A/Texas/36/91 (H1N1) virus and treated with oseltamivir had last-day isolates bearing a His274Tyr substitution in the NA.[328] In clinical studies of post-exposure and seasonal prophylaxis, determination of resistance was limited by the low overall incidence rate of influenza infection and the efficacy of oseltamivir (source: www.rocheusa.com/products/tamiflu/pi_only.htm; accessed April 2002). In clinical studies in the treatment of naturally acquired infection with influenza virus, 1.3% (4/301) of post-treatment

isolates in adult patients and adolescents, and 8.6% (9/105) in paediatric patients aged 1–12 years showed emergence of influenza variants with decreased NA susceptibility to oseltamivir carboxylate (source: Hoffman La Roche website). Genotypic analysis of these variants showed a specific mutation in the active site of NA compared with pretreatment isolates. The contribution of resistance due to alterations in the viral HA has not been fully evaluated.

Pharmacokinetics

Zanamivir

The oral bioavailability of zanamivir is low (2%, range 1–5%)[335] and the drug is therefore administered topically to airways using a specially designed breath-activated device for inhaling powder known as a Diskhaler™. Drug is delivered using a Relenza Rotadisk and drug is dispersed into the airstream created when the subject inhales through the mouthpiece. Zanamivir powder is mixed with a lactose powder carrier (20 mg of lactose per 5 mg of zanamivir).

The amount of zanamivir delivered to the respiratory tract depends on patient factors such as inspiratory flow. In a study of five adult and five adolescent patients with obstructive airways disease, the inspiratory flow rates ranged from 66 to 140 l/minute (Glaxo SmithKline, product information). However, in a study of 16 children, inspiratory flow rates were more variable – four did not achieve measurable rates, and inspiratory rates in the remaining 12 children ranged from 30.5 to 122.4 l/minute. Only one of four children <8 years of age had a measurable flow rate (Glaxo SmithKline, product information). The pharmacokinetics of zanamivir have been evaluated in 16 children, aged 6–12 years, with respiratory illness who were given a single 10-mg dose by inhalation. Five had either undetectable or low serum zanamivir concentrations that were not detected after 1.5 hours; these low levels were related to lack of measurable inspiratory flow rates (Glaxo SmithKline, product information). The pharmacokinetics have not been studied in elderly patients.

The deposition and clearance of zanamivir in the respiratory tract have been assessed by gamma scintigraphic images of the chest and oropharynx. The deposition pattern of radiolabelled zanamivir varied among individuals, showing a preferential central disposition in some volunteers and a more uniform distribution pattern in others. The principal distribution site was the oropharynx (mean 77.6%), and whole lung deposition averaged 13.2% with a range of 7.6–20.7% in the 11 subjects with 'fast' peak inhalation flow rates (>49 l/minute).[336] One subject with a 'slow' inhalation rate deposited only 4.5% of the dose in the lungs. Deposition studies have not been reported in elderly patients or those with influenza.

In healthy adults, systemic exposure is low (10–20% bioavailability) after inhalation of powder; after oral administration the bioavailability is 2%.[337] The maximum observed serum concentrations (C_{max}) values of zanamivir were about 97 μg/l after single 10-mg doses and were found within 1–2 hours of dosing. Zanamivir is not metabolised and is rapidly excreted unchanged in the urine (renal clearance approximately 5.7 l/hour) with a serum elimination half-life of approximately 2 hours.[335] Unabsorbed drug is eliminated in the faeces. The pharmacokinetic results of a renal impairment study indicate that there are significant decreases in renal clearance (by more than sixfold in subjects with severely impaired renal function) and increases in half-life (by sixfold) in comparison with normal subjects. However, a reduction in therapeutic dosage is not anticipated as a result of the pharmacokinetic data. The pharmacokinetics of zanamivir have not been studied in patients with impaired hepatic function.

Oseltamivir

Oseltamivir ethyl ester is the oral prodrug of the active drug, oseltamivir carboxylate. Oseltamivir is enzymatically converted – predominantly by hepatic esterases – to active drug after absorption. Whereas the oral bioavailability of the active compound is low in animals (5%), the bioavailability of oseltamivir carboxylate is approximately 80% after oral administration of the oseltamivir prodrug.[338]

The active metabolite is detectable in plasma within 30 minutes. Maximum observed serum concentrations (C_{max}) values of oseltamivir carboxylate reach about 250μg/l after single 100-mg doses at 3–4 hours after dosing.[339] Plasma concentrations are sustained, remaining at ~35% of the peak level 12 hours after administration. Children 1–12 years of age eliminate the active metabolite faster than both adolescents (13–18 years) and adults, resulting in lower exposure to the active drug. In children, oseltamivir 2 mg/kg twice daily resulted in drug exposures within the range associated with efficacy in adults administered approximately 1 mg/kg twice daily.

The bioavailability of oseltamivir is affected minimally by food, and systemic exposure to the prodrug is low, approximately 4% of that of oseltamivir carboxylate, based on area under the curve (AUC) measurements.[338] The carboxylate distributes well to middle ear and sinus secretions in uninfected persons[340] and to bronchoalveolar lavage fluid in ferrets.[338] Oseltamivir is extensively converted to its active metabolite by hepatic esterases and no other metabolites have been identified in humans. Plasma levels of oseltamivir carboxylate decline slowly with an elimination half-life of 6–10 hours.[339]

Steady-state plasma concentrations are achieved within 3 days of twice-daily administration, and at a dosage of 75 mg twice-daily, the steady-state plasma trough concentrations of active metabolite remain above the minimum inhibitory concentration for all influenza strains tested.[339] Oseltamivir carboxylate and its prodrug are primarily eliminated by the kidney through a combination of glomerular filtration and renal tubular excretion. Exposure to the active metabolite at the steady state is approximately 25% higher in elderly than young individuals; no dosage adjustment is necessary.[341] However, in patients with renal impairment, metabolite clearance decreases linearly with creatinine clearance and dosage reduction to 75 mg once daily is recommended for patients with creatinine clearance <30 ml/minute (1.8 l/hour).[339] The pharmacokinetics of oseltamivir have not been studied in patients with impaired hepatic function.

Drug interactions

Neither zanamivir nor oseltamivir has recognised drug interactions. In humans, protein binding of zanamivir is about 10–14%;[342] it is 3% for oseltamivir carboxylate and 42% for the prodrug, which is considered insufficient for significant displacement-based drug interactions (source: www.rocheusa.com/products/tamiflu/pi_only.htm). Zanamivir does not affect the expression of rat hepatic cytochrome P-450 isoenzymes or have a significant effect on the *in vitro* metabolism of any cytochrome P-450 probe substrates in human liver microsomes.[342] *In vitro* activity of zanamivir when used in combination with amantadine, rimantadine or ribavirin is generally additive to synergistic, but its antiviral activity is unaffected by drugs that are used during influenza infection including analgesics/antipyretics, antihistamines, decongestants and the antibiotic amoxicillin–clavulanic acid.[342]

Neither oseltamivir nor its carboxylate interacts with cytochrome P450 mixed-function oxidases or glucuronosyltransferases.[339] Concomitant administration of paracetamol and oseltamivir did not affect the pharmacokinetic profile of oseltamivir carboxylate compared with that of historical controls receiving oseltamivir only.[339] *In vivo* studies have evaluated the renal drug–drug interaction potential of oseltamivir. Crossover studies were conducted in healthy subjects in which oral oseltamivir was administered alone and co-administered with probenecid, cimetidine or amoxicillin.[343] Probenecid completely blocked the renal secretion of oseltamivir carboxylate, increasing systemic exposure (AUC) by 2.5-fold, but no interaction was observed with cimetidine or amoxicillin.

Adverse events

Zanamivir

In published randomised, double-blind, placebo-controlled studies of prophylaxis, the frequency and types of adverse events, most of which are mild or moderate, were no different in zanamivir and placebo recipients.[332,344,345] Compliance at taking zanamivir is high (97%) among healthy adults.[344] The lactose excipient is used in asthma medications, and the dose (80 mg per dose) is believed insufficient to cause symptoms in lactase-deficient subjects.[346]

Most participants of the clinical trials of zanamivir have been healthy adults or subjects with stable chronic underlying medical conditions of mild to moderate severity.[347] Safety has not been assessed in trials with patients with severe, unstable conditions, with hospitalised patients (who are generally admitted too late after onset of illness to obtain benefit from influenza antivirals) or with the frail elderly. Hence pharmacovigilance is essential to monitor safety and drug interactions in these populations. Pooled data relating to over 6000 subjects who participated in the clinical development programme indicate that zanamivir is well tolerated.[347] The most commonly reported adverse events were consistent with the signs and symptoms of ILI and were similar in the zanamivir and placebo groups. Most adverse events were mild and did not result in patient withdrawal from the studies. In addition, 490 healthy volunteers received zanamivir in clinical pharmacology studies. Treatment was well tolerated and the incidence of adverse events was similar in zanamivir and placebo recipients. In addition, no clinically significant clinical chemistry and haematological laboratory abnormalities were detected in studies involving more than 3500 patients. Serious adverse events have occurred with comparable frequency in both zanamivir and placebo recipients.[347]

The principal safety concern with inhaled zanamvir is possible exacerbations of reactive airways disease. In a Phase I study of persons with mild or moderate asthma who did not have ILI, bronchospasm was reported in one of 13 patients following administration of zanamivir.[348] In addition, there was an increased incidence of a >20% decline in FEV_1 or peak expiratory flow rates after treatment of ILI with zanamivir than placebo.[348] Recently, Williamson and Pegram[349] reported the occurrence of respiratory distress and hypoxia in a 65-year-old man with COPD who received zanamivir for empirical treatment of influenza. The US FDA (2000) has received several reports of deterioration of respiratory function following inhalation of zanamivir in patients with underlying asthma or COPD; some cases did not have previous asthma or COPD (http://www.fda.gov/cder/news/relenza/default.htm), and some patients with serious adverse event during treatment have died (product information).

Cass and colleagues (2000)[350] studied 11 subjects with mild/moderate asthma who received zanamivir 10 mg twice daily for 14 days in a double-blind, randomised, placebo-controlled, two-way crossover study. Treatment was well tolerated with no clinically significant adverse events attributable to zanamivir. There were no changes in spirometry or methacholine-induced airway responsiveness when assessed before treatment, after treatment on day 1 and after the last dose of drug. Another study[351] enrolled 525 patients with asthma or COPD aged ≥ 12 years and with ILI. Patients were randomised to inhaled zanamivir 10 mg or matching placebo twice daily for 5 days. Zanamivir did not adversely affect pulmonary function, as determined by group comparisons of FEV_1 and peak expiratory flow. Zanamivir was well tolerated, with a safety profile similar to placebo. Compliance with treatment was high, with 94% patients successfully completing at least 4 days of treatment.

Influenza itself may cause exacerbations of asthma or COPD, but because a reduction of exacerbations has not been established with treatment, zanamivir is not generally recommended for patients with airways disease. The manufacturers advise that treatment should be discontinued in any patient who develops bronchospasm or 'decline in respiratory function'. It is further recommended that where a decision is made to prescribe zanamivir for a patient with asthma or COPD, he or she should be made aware of the risks and have a fast-acting bronchodilator available.

Oseltamivir

In published randomised, double-blind, placebo-controlled studies of prophylaxis, upper gastrointestinal disturbances, specifically nausea and vomiting, occurred more frequently in the oseltamivir groups in one study than in the placebo group.[297] The excess incidence of nausea was 5% and 7% in the once- and twice-daily dose groups, respectively; for vomiting it was 1.7% and 1.9%, respectively.[297] Few patients (<2% during the 6 weeks of prophylaxis) withdrew from the study because of adverse events. Most of the gastrointestinal events occurred during the first 2 days of treatment; subsequently the incidence declined to levels similar to those in the placebo group.[297]

In another study,[352] gastrointestinal tract symptoms were reported with similar frequency in recipients of oseltamivir and placebo, but nausea was reported with an excess incidence of 2.9%. Withdrawal rates were low (≤ 1%) in both groups. During one study of prophylaxis of a vaccinated frail elderly population, the number of subjects reporting at least one adverse event was similar in oseltamivir and placebo recipients.[353] However, headache was reported with a higher frequency in the oseltamivir group than the placebo group; withdrawal rates because of adverse events were similar (placebo 4% versus oseltamivir 6.5%).[353]

Vaccination

The first attempts at immunisation were made with ferrets within 2 years of the first isolation of human influenza virus in 1933. This was followed in 1936 by studies of a crude vaccine in children prepared from homogenates of infected mouse lung. Subsequent breakthroughs came with the demonstration in 1937 that influenza virus could be grown in hen's eggs and by recognition of its agglutination properties. This enabled virus to be purified and concentrated, it enabled the potency of vaccines to be measured in terms of chick cell agglutination (CCA) units and the haemagglutination inhibition test provided the means to titrate sera for virus antibody. The first licences for commercial vaccine production were granted in 1945.

A major setback occurred in 1947 when a pseudo-pandemic virus, influenza A/FM/1/47 H1N1, spread from Australia throughout the world. Antigenically it was markedly different to the A/Puerto Rico/8 (PR/8) and A/Weiss/43 vaccine strains, so vaccination was ineffective. This led ultimately to the current practice of vaccine strain selection using recent representative viruses.

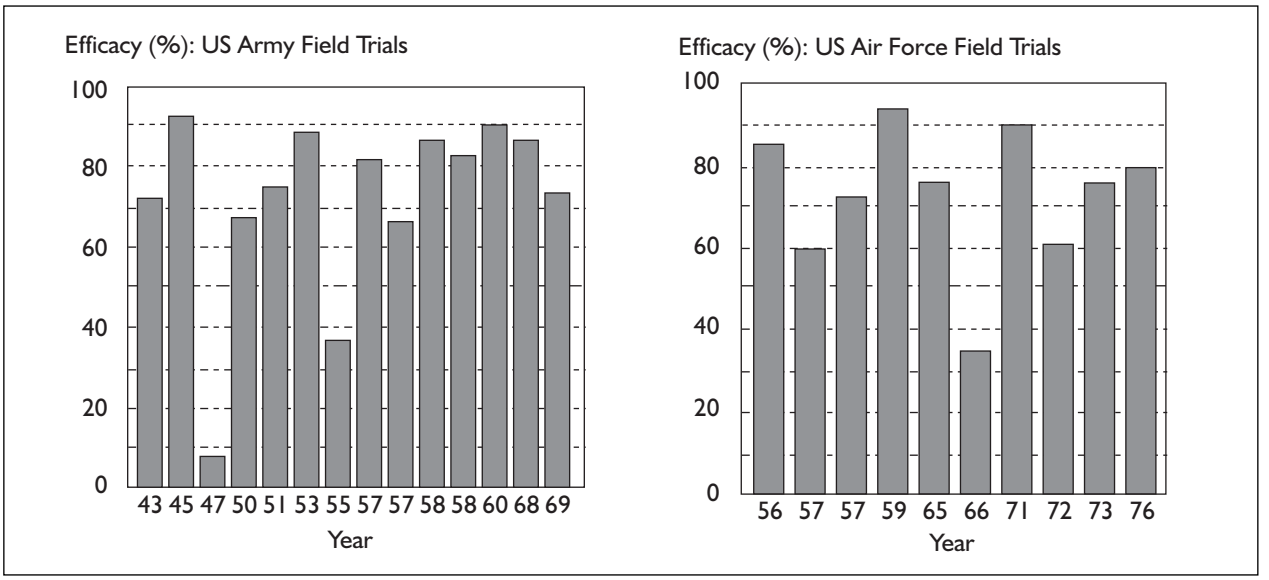

FIGURE 7 *Efficacy of influenza vaccination in healthy young adult populations in the US Army and Airforce. (Data adapted from Davenport (1973),[639] and Meiklejohn (1983).[640] Source: Nichol, 1998.[218]) Reproduced from Nicholson KG, Webster RG, Hay AJ. Textbook of influenza. Oxford: Blackwell Science; 1998, by permission of Blackwell Publishing.*

During placebo-controlled trials conducted with many thousands of military recruits in the US Army over several decades, vaccine efficacy for reducing laboratory-confirmed influenza was 80–90% during seven of 14 seasons, around 70% during five and <40% during only two (*Figure 7*). Similar trials in the US Air Force revealed vaccine efficacy of 70–95% during seven of 10 seasons, around 60% during two when there was a poorer match between vaccine and wild virus and <40% during only one when antigenic shift occurred (*Figure 7*).

Rationale for vaccination

Historically recommendations of the use of influenza vaccine were based on:

- Vaccine efficacy studies in young military recruits.
- The concentration of influenza-associated morbidity and mortality in certain 'high-risk' groups during outbreaks. As previously discussed, these include the elderly, particularly those aged >65 years, and people of any age with a chronic heart or chest complaint, including asthma, chronic kidney disease, diabetes, lowered immunity due to a disease or treatment such as steroid medication or cancer treatment and people living in a retirement home or a nursing home).
- Vaccine antigenicity studies.

Vaccine recommendations in the 'high-risk' groups have not been based on randomised, double-blind, placebo-controlled trials. In the absence of sound scientific data, the value of immunisation in the high-risk groups was questioned for various reasons: outbreaks of influenza continued to be reported among the elderly, especially in nursing homes; some high-risk medical conditions (e.g. diabetes, hypertension and asthma) were being managed better than before; living standards had improved; and antimicrobial and antiviral agents were available.

Consequently, recommendations differed considerably among countries.[354] Immunisation levels were low in many countries and vaccine distribution varied markedly even among those having the same recommendations. Clearly, there was a need to obtain better information on vaccine efficacy and effectiveness to strengthen existing recommendations.

Strategies for vaccination against influenza

Inactivated influenza virus vaccines represent the mainstay of efforts to prevent influenza and its complications. Current vaccines are produced from influenza virus grown in chick embryos and consist of either whole virion (WV), detergent-treated 'split product' (SP) or purified HA and NA surface antigen formulations. Newly isolated influenza viruses often grow poorly in hen's eggs. Because low virus yields limit the amount of material for vaccine production, it would be both difficult and expensive to produce sufficient vaccine using such strains. To overcome this problem, genetic reassortants are produced

between new isolates and a virus with excellent growth characteristics, such as influenza A/Puerto Rico/8 (PR8). A high growth reassortant is selected with the HA and NA of the new isolate and the growth characteristics of PR8. This technique is limited to influenza A viruses only.
Promising developments include the use of mammalian cell lines including Vero cells and Madin–Darby canine kidney (MDCK) cells to grow influenza virus, the use of adjuvants including liposomes and MF59 and live cold-adapted (CA) reassortant vaccines.

Whole virion vaccine
The first influenza vaccines were crude WV preparations of influenza virus grown in eggs; they frequently gave rise to local and systemic reactions. Although virion WV vaccines are purer than they used to be, they are considered unsuitable for use in young children because of adverse reactions. Some workers have found evidence that WV vaccines may be more immunogenic[355,356] than SP vaccine in elderly primed subjects, whereas others have found the converse.[357] WV vaccines are not licensed in the UK, but there is evidence that WV vaccines are more immunogenic in immunologically naive populations, so they may play an important role during pandemics.

Split product vaccine
Numerous trials have shown that SP vaccines, now the most common type of influenza vaccine, are as immunogenic as WV material in primed patients, but less reactogenic, particularly in children. However, they are not as immunogenic as WV vaccines in naive populations during antigenic shift or in young children who have not been previously infected, in which case a second dose of vaccine is required.

Surface antigen vaccine
Surface antigen vaccines contain purified HA and NA and are as immunogenic as WV and SP vaccines in primed subjects, although two doses are required in young children. Surface antigen vaccine was first licensed in the UK in 1980.

Limitations of current methods of influenza vaccine manufacture

- Current influenza vaccines are produced in embryonated hens' eggs. Because of the large numbers required, advanced planning must start nearly 1 year before vaccination.
- Chickens are susceptible to disease, so an adequate supply of eggs and vaccine cannot be guaranteed.
- In the event of a pandemic, the necessary number of high-quality fertile hens' eggs, and the capacity of manufacturers to process them, are unlikely to match global needs.
- The interval between the initial identification of a new pandemic strain and outbreaks may be insufficient to produce vaccine using current technology.
- Growth of human influenza virus in eggs can lead to the selection of variants which differ antigenically from the original.
- The requirement for high-growth reassortants can delay vaccine manufacture and reassortants may be unstable and difficult to propagate.

Current vaccine developments

Cell cultures as substrates for the production of influenza vaccine
The WHO has recognised an urgent need to develop a cell-culture technique for influenza vaccine production. Cell culture systems offer the following advantages:

- Viruses isolated and passaged exclusively in mammalian cells retain their antigenic characteristics.
- Virus growth occurs adequately in mammalian cells without the need for high-growth reassortants.
- Cell culture systems offer the possibility of increasing vaccine production at short notice to meet unexpected demand or produce supplemental vaccine should a new variant be detected after vaccine strain selection has taken place.

Two continuous cell lines, MDCK cells and African green monkey (Vero) cells, support influenza virus replication at levels sufficient to be considered for vaccine production. Candidate vaccines produced using both technologies have been evaluated in humans.

Adjuvants
Various adjuvants have been evaluated as a means of enhancing the immune response to influenza vaccine. Only one, aluminium hydroxide, has been licensed in the UK for use in humans. Although more effective than aqueous influenza vaccine in laboratory animals, their ability to enhance immune response in humans is questionable and they are currently not used.[358]

Liposomes are lipid membrane particles that can serve as delivery systems for entrapped proteins and adjuvants. Liposomes are themselves adjuvants, and other immunostimulators, such as

lipopolysaccharide, monophosphoryl A and muramyldipeptide (MDP), when encapsulated within liposomes, show enhanced adjuvanticity, with reduced side-effects.[359] Virosomes are liposomes that contain virus fusion proteins in the liposome bilayer. Virosomal vaccine containing 15 μl of influenzal HA per viral strain per dose inserted into a membrane of phosphatidylcholine and phosphatidylethanolamine has been evaluated in humans.[360–363] Seroconversion rates were significantly higher for three of three and two of three strains in two published studies.[362] After several years of licensure in Italy and Switzerland, virosomal influenza vaccine was recently licensed in Europe and became available in the UK during the winter of 2002–3.

The adjuvant MF59 is an oil-in-water emulsion containing squalene (a cholesterol metabolite) and the emulsifiers polysorbate 80 (a water-soluble surfactant) and sorbitan trioleate (an oil-soluble surfactant) that stabilise the squalene particle at a size of about 150 nm. Subunit influenza vaccine (containing 15 μl of influenzal HA per viral strain per dose) adjuvanted with MF 59 has been evaluated in more than 12,000 humans since 1992. It is currently licensed in some European countries but not the UK. The addition of MF59 to influenza vaccine is associated with significant increases in HI antibody titres to the 'interpandemic' influenza A H3N2 and influenza B antigens, but not H1N1 antigen.[364–367] MF59 greatly enhanced the serological responses to a candidate H5 surface antigen vaccine in comparison with conventional vaccine.[368] MF59 is associated with an increase in transient mild local reactions, but the incidence of systemic reactions and analgesic and antipyretic use is the same with or without MF59.

Cold-adapted (CA) live attenuated vaccines

The donor of attenuation for live CA reassortant vaccines is influenza A/Ann Arbor 6/60 (H2N2) virus.[369] Originally isolated from throat washings in primary chick embryo cells at 36°C, A/Ann Arbor 6/60 virus was adapted to grow at 25°C by passaging at progressively lower temperatures. Virus that grew well at both 25 and 33°C was then passaged repeatedly in tissue culture and in embryonated hens' eggs at 25°C. Similar methods were used to produce an influenza B donor of attenuation. Live attenuated vaccines bearing the surface antigens of recent isolates are produced by genetic reassortment. Candidate vaccine viruses are generated by co-infecting tissue culture cells with the CA, temperature sensitive (ts) donor of attenuation and the selected wild-type virus. Progeny viruses are grown in the presence of antisera to the HA and NA of the donor of attenuation, which inhibits the growth of viruses expressing the HA and NA of the donor virus. Candidate vaccine strains contain all six internal genes from the donor of attenuation and the two genes from the wild-type virus that code for the HA and NA. The six internal genes contain a number of mutations. Although not all of these confer attenuation, more than one gene is associated with attenuation, so reversion to virulence is unlikely. Only viruses that grow well at 33°C are selected as candidate vaccine strains. Vaccine virus is able to replicate well at the temperatures found in the nasopharynx, but do not replicate at the core body temperature found in the lower airway.

The goal of live vaccines is to establish a limited infection in the upper respiratory tract epithelium and induce local antibody production. Live CA vaccine is delivered by nasal drops or spray and could ultimately be delivered by parents. Live CA vaccines have been evaluated extensively during the last three decades.[369] A recent study has demonstrated excellent efficacy in young children, with reductions in both influenzal illness and otitis media.[309,370]

Potency considerations

The original potency test for HA content of vaccine was the CCA test, which attempted to standardise the haemagglutination reaction. The international unit (IU) related measurements of virus haemagglutination to an international standard. The limitations of these techniques led to highly variable results from laboratory to laboratory and even from test to test within a laboratory. The inadequacies of the CCA test, particularly for subunit vaccines, are well recognised.[371] In the mid-1970s, an improved test, the single radial diffusion (SRD) test,[372] was developed and is now used worldwide to ensure standardisation of vaccine potency.

When the SRD test was first developed, the dose of HA needed to induce a satisfactory immune response in primed individuals was found to be in the region of 7–20 μg HA per dose. In recent years, most vaccines have contained 15 μg of HA per strain per dose, and this has been formally standardised in the European Union (EU) since 1992. The quantity of antigen required to evoke satisfactory immune responses in **unprimed** individuals is unclear, since few studies have been conducted using microgram quantities of antigen in SP or surface antigen vaccines following the

emergence of a novel virus. However, two doses of vaccine are currently recommended to immunise children if receiving influenza vaccine for the first time.

Selection of vaccine strains

Virus isolates from national centres are submitted to one or more of the WHO's four Collaborating Centres for Influenza Reference and Research for antigen and genetic analyses. In February of each year, the WHO recommends which viral strains should be included in the next year's vaccine. A second review is held in the autumn to consider whether there should be a further recommendation for vaccines for the southern hemisphere.Three types of data are assessed in making the recommendation:

- Antigenic and genetic data on recent virus isolates: these data are compared with those of isolates obtained in the recent past.
- Epidemiological data: to assess whether the new isolates have the potential to spread and cause disease.
- Antibody responses: to assess the ability of the currently available vaccines to evoke antibody responses to the newly detected viruses.

How well do the WHO recommendations work?

According to Wood,[373] mismatches between vaccine and wild-type viruses are not uncommon. During the decade 1987–97, a good match (between vaccine and wild-type strains) was achieved in respect of 23 (77%) of 30 circulating strains, but, when considered on an annual basis, the epidemic strains were 'antigenically different' from the vaccine strains during five of 10 seasons.

Antibody and protection

A relationship between serum haemagglutination inhibition (HAI) antibody and protection has consistently been observed with a serum HI titre of approximately 30–40 representing a 50% protective level of antibody against infection by homologous virus.[374] Accordingly, the HAI test is widely used in assessing vaccination responses. The level of serum neutralising antibody that correlates with protection of humans has not been established, but single radial haemolysis (SRH) zone areas of 25–50 mm^2 represent a 50% protective level.[375,376] Antibody to the viral NA plays an important role in protection against influenza.[377] However, whereas current influenza vaccines are standardised to contain 15 μg of HA of each virus strain per dose, the quantity of NA is not standardised and the anti-NA antibody response is not routinely measured.

Immunogenicity studies

Since 1992 there have been EU requirements for harmonisation of influenza vaccines, which include annual clinical trials for licensing. Regular trials are also carried out in other parts of the world. In the EU, the vaccines are tested in adults (18–60 years) and elderly (>60 years), in groups of 50 subjects, and attain the following:

Adults (18–60 years):

- seroconversions or significant rises (i.e. a ≥ 4-fold increase in post-vaccination titre) by >40%
- mean fold increase in geometric mean time (GMT) post-vaccination >2.5
- significant levels of antibody (i.e. having post-vaccination HI titres >1:40) in >70%.

Elderly (≥ 60 years):

- seroconversions or significant rises (i.e. a ≥ 4-fold increase in post-vaccination titre) by >30%
- mean fold increase in GMT >2
- significant levels of antibody (i.e. having post-vaccination HI titres >1:40) in >60%.

There are as yet no specific requirements for pandemic situations.

Vaccine efficacy and effectiveness

Data on the efficacy and effectiveness of inactivated influenza vaccines that have been published in recent years on the following cohorts and study areas are presented in Appendix 20. The studies in Appendix 20, conducted by various methods in different continents, over many influenza seasons, in children, healthy adults, community-dwelling elderly and those in residential care almost always reveal influenza vaccine to be highly efficacious and effective.

Vaccine efficacy/effectiveness in children (see Appendix 20)

- vaccine efficacy – reductions in laboratory-confirmed influenza
- vaccine effectiveness – reductions in acute respiratory illness (ARI)/ILI
- reductions in school absenteeism for ARI/ILI
- reductions in otitis media in children
- reductions in asthma exacerbations complicating ILI in high-risk children
- reduction in transmission of influenza to contacts.

Vaccine efficacy/effectiveness in adults of working age (see Appendix 20)

- vaccine efficacy – reductions in laboratory-confirmed influenza

- vaccine effectiveness – reductions in acute respiratory illness/ILI
- reductions of work absenteeism for acute respiratory illnesses (URTIs, ARIs, ILIs)
- reductions in medical consultations for ILI in working adults
- reductions in medical consultations for ILI and ARI in working adults
- reductions in antibiotic use for ILI in working adults
- reductions in OTC purchase (use) of drugs for ILI in working adults
- reductions in complications of ILI in working adults.

Vaccine efficacy/effectiveness in community-dwelling elderly (see Appendix 20)

- reductions in laboratory-confirmed influenza
- reductions in acute ARI/ILI in community-dwelling elderly
- reductions in medical consultations for ILI by community-dwelling elderly
- reductions in hospital admissions for pneumonia/ILI among community-dwelling elderly
- reductions in hospital admissions for all respiratory conditions among community-dwelling elderly
- reductions in deaths (from P & I, or all-cause mortality) among community-dwelling elderly.

Vaccine efficacy/effectiveness among people with high-risk conditions (see Appendix 20)

- reductions in laboratory-confirmed influenza
- reductions in consultations among people with high-risk conditions
- reductions in exacerbations of COPD
- reductions in exacerbations of asthma
- reductions in episodes of congestive heart failure
- reductions in hospitalisations (mostly for diabetic events) among patients with diabetes
- reductions in hospital admissions for pneumonia/ILI among people with high-risk conditions
- reductions in hospital admissions for all respiratory conditions among people with high-risk conditions
- reductions in deaths among people with high-risk conditions.

Vaccine efficacy/effectiveness in residential care (see Appendix 20)

- reductions in laboratory-confirmed influenza in residential care
- reductions in febrile respiratory illness in residential care
- reductions in pneumonia complicating ILI in residential care
- reductions in hospitalisations complicating ILI in residential care
- reductions in deaths in residential care.

TABLE 4 *Incidence of adverse events after vaccination with inactivated influenza vaccines*

Adverse effects: rate (%) in vaccinees minus rate in controls (*p*-value in parentheses)						
	Margolis et *al.*, 1990[378]	**Margolis et *al.*, 1990[383]**	**Govaert et *al.*, 1993[379]**	**Nichol et *al.*, 1996[381]**	**Bridges et *al.*, 2000[380]**	**Bridges et *al.*, 2000[380]**
Population (*n*)	336	650	1806	849	1180	1177
Vaccine	Split	Split	Split	Split	Split	Split
Local reactions:	–	–	10.2 (<0.001)	–	–	–
Sore arm	15.2 (<0.001)	19.5[a]	–	39.7 (<0.001)	35 (<0.001)	31 (<0.001)
Swelling	–	–	6.4 (<0.001)	–	–	–
Itching	–	–	3.1 (<0.001)	–	–	–
Pain when touched	–	–	7.2(<0.001)	–	–	–
Constant pain	–	–	1.0 (<0.001)	–	–	–
Redness	–	–	–	–	8.0 (<0.001)	8.0 (<0.001)
Systemic reactions:	–	–	1.6 (ns)	1.1 (ns)	–	–
ILI	–	5.5 (0.03)	–	–		–
Fever(ish)	1.2 (ns)	0.2 (ns)	0.6 (ns)	0.1 (ns)	(ns)	(ns)
Tiredness	0.3 (ns)	–	–	–0.5 (ns)	(ns)	(ns)
Malaise	0.9 (ns)	–	0.9 (ns)	–1.5 (ns)	–	–
Myalgia	0.6 (ns)	–	–	0.5 (ns)	(ns)	(ns)
Headaches	–0.7 (n)	–	1.0 (ns)	–3.6 (ns)	(ns)	(ns)
Disability days	–	1.1 (ns)	–	–	–	–

ns, Not significant.
[a] No statistical comparison.

Adverse effects of inactivated vaccines

Many millions of doses of influenza vaccine are administered throughout the world each year and the overall rate of adverse reactions is low. *Table 4* summarises the adverse events reported after vaccination of adults in randomised double-blind, placebo-controlled trials,[226, 378-382] and an observational study.[383]

Table 4 shows that local reactions are significantly less common in the placebo/control groups than in vaccinees, but no difference is found in the incidence of systemic reactions. Side-effects tend to be mild in nature and of short duration.[379] Repeated vaccination does not increase the likelihood of adverse reactions,[379] and in general the difference between the effect of vaccination in vaccine and placebo groups decreases with increasing age.[379] Women report more side-effects than men.[379,382,384–387]

Rare adverse events with probable causal association with inactivated influenza vaccine

Hypersensitivity

Judging by the virtual absence of reports in the literature, allergic reactions to influenza vaccine including urticaria, angioedema, and anaphylaxis occur rarely.[388,389] Although current influenza vaccines contain only a small quantity of egg protein, allergic reactions probably result from hypersensitivity to residual egg protein. However, a history of sensitivity to eggs is not as reliable an indication of vaccine sensitivity as skin testing with vaccine.[388,390]

Smith *et al*.[384] conducted a study of reactions to influenza vaccine in almost 6000 healthy adults. In approximately 16,500 injections, only two patients had an acute reaction resembling anaphylaxis. Since July 1963 (a 37-year period), the Medicines Control Agency (MCA) has received passive reporting of 14 cases of angioedema, 34 cases of facial oedema and 14 cases of periorbital and tongue oedema. Additionally, 105 cases of urticaria, 17 cases of 'allergic reaction', 38 cases of anaphylaxis and three cases of hypersensitivity and serum sickness have been reported.

Oculo-respiratory syndrome

During the 2000–1 influenza immunisation season, Health Canada received 1735 reports of ocular or respiratory influenza vaccine-associated adverse events. Of these reports, 960 (39%) were classified as meeting the case definition for a newly recognised 'oculo-respiratory syndrome' (ORS), defined as the presence of bilateral red eyes, or at least one of the following respiratory symptoms: cough, wheeze, chest tightness, difficulty in breathing or sore throat or facial oedema, occurring within 2–24 hours of influenza vaccination and resolving within 48 hours.[391] No deaths have been reported in association with ORS.

Nine hundred and twenty-five (96%) cases of ORS occurred following receipt of Fluviral® S/F produced by BioChem Pharma (now Shire Biologics, a division of Shire BioChem), and 12 (1%) cases occurred following receipt of Fluzone® or Vaxigrip®, both produced by Aventis Pasteur. All but one of the distributed lots of Fluviral have been implicated. Analysis reveals that the persons with ORS are most frequently 40 and 59 years of age, and are more often women and persons with a history of allergies (but not asthma).[392] An average of ~12 cases per annum have been reported in the USA during a 10-year period.

The pathophysiological mechanism underlying ORS is obscure. Suggestions include a hypersensitivity reaction and an interferon-mediated immune response. However, all three vaccines licensed in Canada during the 2000–01 season used the same influenza strains and seed stocks. Fluviral S/F used deoxycholate to split the virus, whereas Fluzone and Vaxigrip used Triton X-100. Electron microscopic studies revealed a higher proportion of unsplit (whole) virus (19.4% according to Shire Biologics studies), and a higher proportion of aggregate virus particles in Fluviral S/F compared with the other two vaccines and compared with previous years.[391] All products contained thiomersal.

Guillain–Barré syndrome (GBS)

GBS occurs in the general population at a rate of 1.5–2.0 per 100,000 person-years.[393] Cases of GBS have been reported rarely after influenza[144,145] and other infectious illnesses, notably *Campylobacter jejuni*, and upper-respiratory tract infections in general.[394] A case–control study for 16 infectious agents in 154 GBS patients revealed significant associations with cytomegalovirus, Epstein–Barr virus and *Mycoplasma pneumoniae*, but infections with influenza A and B in GBS were not more frequent than in controls.[394]

The 1976 swine influenza vaccine was associated with an increased frequency of GBS.[395,396] Among recipients of swine influenza vaccine in 1976, the number of excess cases of GBS during the first 6 weeks attributed to the vaccine was 8.6 per million vaccinees in Michigan [relative risk (RR)

7.94] and 9.7 per million in Minnesota (RR 5.23).[396] However, an association of influenza vaccination with GBS in the non-military adult population was not found in studies of US military personnel,[397] residents in The Netherlands[398] or persons under the age of 18 years in the USA.[395]

Since the 1976–7 swine influenza programme, the risk of GBS associated with influenza vaccination has been very small. During two of three influenza seasons during the period 1978–81, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated [1.4 (95% CI 0.7 to 2.7) in 1978–9; 0.6 (95% CI 0.45 to 1.32) in 1979–80, 1.4 (95% CI 0.8 to 1.76) in 1980–1] but were not statistically significant in any of these studies.[399,400] For the 1990–91 influenza season, an elevated RR of 3.0 was found for persons 18–64 years of age (95 % CI 1.5 to 6.3), but not among people aged ≥ 65 years.[401] A retrospective review of 289 active duty patients with GBS (influenza vaccine coverage is approximately 80% during the army's mass vaccination program in October each year), who were admitted to US Army medical treatment facilities during the period 1980–8, revealed no temporally related increase in GBS suggesting seasonal variations.[402] These results suggested that there was no increased risk of acquiring GBS associated with the administration of influenza vaccines, and that the 'trigger agent' in the A/New Jersey/(swine) influenza vaccine in 1976 was not present in subsequent vaccine preparations.

However, a retrospective study of the 1992–3 and 1993–4 seasons in four American states revealed an overall relative risk of GBS occurring within 6 weeks after influenza vaccination, adjusted for age and sex, of 1.7 (95% CI 1.0 to 2.8; $p = 0.04$), suggesting an absolute risk of ~1 per million vaccinees (range, 0.5–2 per million vaccinees).[403]

Obtaining strong epidemiological evidence for a possible small increase in risk is difficult for such a rare condition as GBS. The available data reveal an elevated, but statistically non-significant, increase in the relative risk of GBS occurring after influenza vaccination during most seasons, and a significant increase in risk during others. Overall the data indicate that administration of influenza vaccine causes approximately one case of GBS per million vaccinees, with one in 5 million vaccinees requiring ventilation, and death from complications of GBS in one in 20 million vaccinees.

Other neurological events

Searches of the world literature reveal a number of reports describing an association between influenza vaccination and the occurrence of meningoencephalitis/encephalopathy, myelitis/myelopathy, brachial neuritis, polyradiculoneuritis and peripheral neuropathy.[404–422]

Emphasis upon cases of GBS that resulted from the 1976 swine influenza immunisation programme in the USA has obscured the fact that other neurological complications involving the CNS also occurred. Poser[414] reported 26 cases in association with swine influenza vaccination and 41 case reports described in the literature since 1956[404] and commented that the aetiological significance of the swine influenza vaccination was initially overlooked. Hence it is highly probable that a relationship between the rare occurrence of adverse neurological reactions and routine inter-pandemic influenza vaccination is often overlooked. Rapid onset after vaccination is reported[410,411,417] and patients may have prolonged disability, although others evidently respond to steroids.[416]

Since July 1963, the MCA has received passive reporting of 26 cases of encephalitis, encephalomyelitis and myelitis. It is not established that any of these events are causally related to vaccination. Additionally, the MCA has received 11 reports of Bell's palsy and 28 reports of mononeuritis, neuralgic amyotrophy and peripheral neuropathy.

Ocular events

Optic neuritis is an occasional complication of vaccination. Searches of the world literature reveal compelling evidence for a rare association between vaccination against influenza and the occurrence of ophthalmic events, including optic neuritis/neuropathy,[422–428] that may result in permanent visual loss,[428] uveitis[429,430] and corneal graft rejection.[431,432] One patient developed bilateral optic neuritis on two occasions, 1 year apart. Influenza vaccination was given two weeks before the onset of each episode and no other causes were identified.[427] Thurairajan *et al*.[433] described a patient with polyarthropathy, orbital myositis and posterior scleritis following inoculation with surface antigen vaccine. Optic atrophy has also been reported in association with acute disseminated encephalomyelitis occurring within days of influenza vaccination.[412] The MCA has received an average of less than two reports annually since 1963 of ophthalmic disorders following vaccination.

Rare adverse events with possible causal association with inactivated influenza vaccine

Cutaneous events

Several cutaneous events have been reported to the MCA following influenza vaccination, most commonly erythematous and maculopapular rashes. Excluding local injection site reactions (n = 157), 323 reports of cutaneous events have been reported to the MCA since 1963. Potentially life-threatening cutaneous events have been reported rarely (epidermal necrolysis, one case; Stevens–Johnson syndrome, two cases). Seven cases of pemphigoid after influenza vaccination were reported to the MCA, and cases of pemphigoid and pemphigus are reported in the world literature.[434–437] Both influenza vaccination and bullous pemphigoid are common in the elderly, and the association may be no more than a coincidence. However, exacerbations have been reported following further influenza vaccination.[434,436]

Vasculitis, Henoch–Schönlein purpura and 'rheumatic' complaints

A number of cases of systemic vasculitis, occurring within several weeks of influenza vaccination,[424,438–446] or simultaneous influenza and pneumococcal vaccination[447] have been described. Kelsall *et al*.[448] reported a case of vasculitis and identified 16 other cases after influenza vaccination. Three patients had similar illnesses after previous influenza vaccination or ILI. As in the case reported by Kelsall *et al*.,[448] 11 resolved without recurrence. Two of the patients died. One of two patients described by Blumberg *et al*.[424] had an illness characterised by fever, arthralgias and myalgias, and developed uveitis and optic neuritis in addition. The temporal association of these conditions suggests a common aetiology and pathogenesis.

Henoch–Schönlein purpura,[449–451] vascular purpura with cryoglobulinaemia,[452] thrombotic thrombocytopenic purpura,[453] 'rheumatoid' purpura,[454] and rheumatic complications[455] including systemic lupus erythematosus, rheumatoid arthritis and polymyalgia rheumatica[446,455,456] have all been described rarely following influenza vaccination. Interestingly, systemic vasculitis was either initiated or reactivated in a woman with polymyalgia rheumatica after influenza vaccination.[457]

Since July 1963, the MCA has received 16 reports of vasculitis, three reports of Henoch–Schönlein purpura, 10 of purpura, two of thrombotic thrombocytopenic purpura and 11 of polymyalgia rheumatica.

Pericarditis and rhabdomyolysis

Pericarditis is possible a rare complication of influenza vaccination.[458–460] Influenza vaccination has also been mentioned as a possible trigger of rhabdomyolysis-induced acute renal failure.[461] Since 1963, the MCA has been notified of six cases of pericarditis associated with the use of influenza vaccination and the Centre National de Pharmacovigilance in France has reported four cases of pericarditis after influenza vaccination.

Asthma exacerbations

One of the obstacles to the delivery of vaccine in the UK to patients with chronic airways disease has been concern that vaccine may trigger exacerbations. Broncho-provocation tests may show increased bronchial reactivity of people with asthma for several days after vaccination against influenza,[462] but not at 1 week.[463]

Anecdotal reports suggest an association between vaccination and exacerbations.[464,465] Although most observational studies suggest that inactivated vaccine is safe in people with asthma,[466–470] Bell and colleagues[471] observed a decrease in peak expiratory flow (PEF) and increased use in bronchodilators within 96 hours of vaccination of asthmatic children. A slight fall in evening PEF after vaccination was noted during a small placebo-controlled crossover study,[472] but two other placebo-controlled studies found no adverse pulmonary effects.[473,474]

Two large randomised, double-blind, placebo-controlled, crossover trials and one retrospective cohort study have been conducted recently in patients with asthma. In addition, a systematic review of the literature evaluating the safety of influenza vaccination in patients with asthma has been undertaken.

Nicholson and colleagues[475] studied 262 patients, aged 18–75 years, who recorded daily peak expiratory flow, respiratory symptoms, medication, medical consultations and hospital admissions for 2 weeks before the first injection and until 2 weeks after the second injection. The primary clinical outcome measure in this multi-centre study conducted in England was an asthma exacerbation occurring within 72 hours of injection, defined by a decline in early-morning PEF of more than 20% compared with the lowest of the best three early-morning PEF values during the 3 days before the injection. Among 255 participants with paired data, 11 recorded a fall in PEF of >20% after vaccine compared with three after placebo (McNemar's test, p = 0.06); a fall of ≥ 30% was

recorded by eight after vaccine compared with none after placebo (binomial test, $p = 0.008$). However, when participants with colds were excluded, there was no significant difference in the numbers with falls of >20% between vaccine and placebo, although the difference for PEF decreases of >30% approached significance (five versus none; binomial test, $p = 0.06$). This association was confined to first-time vaccinees.

The American Lung Association Clinical Research Centers[476] conducted a multi-centre, randomised, double-blind, placebo-controlled, crossover trial of inactivated trivalent SP influenza vaccine in 2032 patients with asthma (age range, 3–64 years). The order of injection of vaccine and placebo was assigned randomly, with a mean of 22 days between the injections. The primary outcome measure was an exacerbation of asthma in the 2 weeks after the injections [defined as one or more of the following: a decrease of at least 30% in the peak expiratory flow rate (PEFR) from the second highest PEFR measured during the study; an increase in the daily use of bronchodilator rescue medication above the average use reported in the 2 weeks before randomisation; an increase in the use of systemic steroids for asthma or the addition of systemic corticosteroids in the treatment regimen; or the unscheduled use of healthcare for the treatment of asthma]. The frequency of 'exacerbations' of asthma was similar in the 2 weeks after the influenza vaccination and after placebo injection (28.8 and 27.7%, respectively; absolute difference, 1.1%; 95% CI –1.4 to 3.6%). The exacerbation rates were similar in subgroups defined according to age, severity of asthma and other factors.

Kramarz and colleagues[477] studied the incidence of hospitalisations and emergency consultations for asthma following influenza vaccination of children, 1–6 years of age, whose medical, pharmacy prescriptions and vaccination details were accessed from the computerised databases of four large health maintenance organisations on the West Coast of the USA. In unadjusted analyses, vaccination was associated with high rates of asthma exacerbations. However, after adjusting for asthma severity using a self-control method, the incidence rate ratios of asthma exacerbations after vaccination were 0.58 (95% CI 0.36 to 0.95), 0.74 (95% CI 0.47 to 1.17) and 0.98 (95% CI 0.76 to 1.27) during the three influenza seasons. The investigators concluded that after controlling for asthma severity, influenza vaccination does not result in acute asthma exacerbations in children.

Cates and colleagues[478] evaluated the efficacy and side-effects of influenza vaccination of patients with asthma (Cochrane review). Nine trials were included. Four of these trials were considered to be of high quality. The included studies covered a wide diversity of people, settings and types of influenza vaccination, so data from the different trials were not pooled. In one trial, no protective effect of influenza vaccination against asthma exacerbation was demonstrated, but the incidence of influenza was low during the study period. A higher number of asthma exacerbations following killed influenza vaccination was found in one trial (risk difference 3.1%, 95% CI 0.3 to 5.8%). When people with URIs were excluded, this difference was no longer significant. A small trial using recombinant vaccine found no significant difference in asthma exacerbations between the vaccinated and placebo groups. The reviewers concluded that there was insufficient evidence to assess the benefits and risks of influenza vaccination for people with asthma.

The available data indicate that inactivated influenza vaccine is safe in adults and children with asthma, including those with severe asthma. The data do not suggest that administration of influenza vaccine to people with asthma evokes costs due to increased use of medication, medical consultations or hospitalisation.

Chapter 3

Systematic review and meta-analysis of the use of neuraminidase inhibitors for the treatment of influenza A and B

Introduction

This chapter describes the systematic review and meta-analyses of NIs for treatment of influenza. The first section describes the methods for reviewing the effectiveness of NIs for treatment of influenza. The results are presented in the second section, including the results of any meta-analyses performed, and the chapter concludes with a discussion section.

Methods for reviewing effectiveness

Search strategy

A number of online electronic databases were searched to ensure complete ascertainment of published reports on the NIs: MEDLINE (1966 to December 2001), EMBASE (1980 to December 2001) and the Integrated Science Citation Index (via Manchester Information and Associated Services) (1981 to December 2001). These were supplemented with searches of the National Library of Medicine (PUBMED) and the Health Economic Evaluations Database (HEED) of the Office of Health Economics. The main subject terms are given in *Table 5*, and were used to search the title, abstract and keyword sections of the references.

The search findings were checked against a number of registers and online databases (*Table 6*).

Journals whose contents and archives were searched are given in *Table 7*.

TABLE 5 *Main subject terms for searching databases for NI evidence*

- "Neuraminidase Inhibitors" AND "Influenza"
- "Zanamivir" OR "Relenza" OR "GG167"
- "Tamiflu" OR "Oseltamivir" OR "GS 4104" OR "GS4071"

TABLE 6 *Registers and online databases searched*

- Cochrane Controlled Trials Register
- National Research Register
- Meta Register of Controlled Trials
- National Institute for Clinical Evidence
- Centre for Evidence-based Medicine
- Bandolier – Evidence Based Health Care
- International Agency for Health Technology Assessment
- Canadian Coordinating Office for Health technology Assessment
- International Society of Technology Assessment in Health Care
- National Coordinating Centre for Health Technology Assessment
- Infectious Diseases Society of America
- The Medical Research Council's National Institute for Medical Research Influenza Bibliography
- NHS Centre for Reviews and Dissemination (CRD):
  - Database of Abstracts of Reviews of Effectiveness (DARE)
  - NHS Economic Evaluation Database (NHS EED)
  - Health Technology Assessment (HTA) Database
  - Systematic Reviews Commissioned
  - CRD Publications.
- The Cochrane Database of Systematic Reviews:
  - Neuraminidase inhibitors for preventing and treating influenza in healthy adults

TABLE 7 *Journals searched*

- *Annals of Internal Medicine*
- *Antimicrobial Agents and Chemotherapy*
- *Archives of Internal Medicine*
- *British Medical Journal*
- *Clinical Drug Investigation*
- *Clinical Pharmacokinetics*
- *Drug Safety*
- *Drugs*
- *Epidemiology and Infection*
- *Health Economics*
- *Journal of Antimicrobial Chemotherapy*
- *Journal of Infection*
- *Journal of Infectious Diseases*
- *Journal of the American Medical Association*
- *The Lancet*
- *New England Journal of Medicine*
- *Pharmacoeconomics*

In addition to the electronic database search strategy, the following further measures were taken in order to maximise our chances of finding all the relevant studies.

1. Scrutiny of reference lists of identified articles.
2. Scrutiny of reference sections of the major textbook Nicholson KG, Webster RG, Hay AJ. *Textbook of influenza*. Oxford: Blackwell Science; 1998.[479]
3. Scrutiny of reference lists of two NICE reports on the use of zanamivir[2,480] and also the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) reports on the use of oseltamivir[7] and zanamivir[6] for the treatment of influenza.
4. Meetings with representatives from both Hoffman La Roche and GlaxoSmithKline were set up to ascertain if any additional trials, not identified through other methods, existed (i.e. 'unpublished' or 'in press' or 'on-going'). Also to gain further information where the published information on known trials was unclear.
5. Searching of pre-existing personal databases.

Inclusion and exclusion criteria

All trials evaluating the treatment of influenza by NIs (zanamivir or ostletamivir) were considered for inclusion in this systematic review. To be selected for the systematic review, leading to further examination for inclusion in the meta-analyses, trials had to meet the criteria outlined in *Table 8*.

Table 8 *Inclusion criteria for NI systematic review*

1. It had to be a randomised, double-blind trial
2. Patients had to have contracted (or suspected to have contracted) naturally occurring influenza (i.e. all trials where patients were deliberately given experimental influenza were excluded, since this does not relate to the efficacy of NIs in clinical practice, of interest here)
3. At least one clinical outcome measure of relevance had to be reported. Those considered relevant are:
   - time to alleviation of symptoms
   - time to alleviation of major influenza symptoms
   - time to eradication of major signs and symptoms
   - time to return to normal activities
   - number of days symptoms scored none/mild
   - complications requiring use of antibiotics
   - adverse events due to treatment
   - hospitalisations
4. The NI had to be administered using the formulation submitted for licensing approval
5. Data had to be available before 31 December 2001
6. Necessary trial information had to be available in English

Data extraction strategy

Data from the studies identified for inclusion in the systematic review were extracted using a data extraction form. Data were extracted on the patient groups considered by each trial and the summary statistics for the efficacy outcomes of interest (all described in detail below). Data were obtained from a variety of sources including the published literature, FDA reports (http://www.fda.gov/cder/approval/index.htm), previous health technology assessments[2,6,7,480] and directly from pharmaceutical companies.

Patient groups

For this report, in addition to an analysis of all study individuals regardless of their risk status, four broad categories of patients were considered:

- 'healthy' aged 12–65 years
- 'high-risk' aged ≥ 12 years
- 'healthy' children aged ≤ 12 years
- 'high-risk' children aged ≤ 12 years.

'High-risk' individuals were defined as individuals of any age with a concurrent disease severe enough to require regular medical follow-up or hospital care (for example, chronic disorders such as chronic respiratory disease, cardiovascular disease and pulmonary disorders) plus otherwise healthy elderly individuals ≥ 65 years. For the purposes of this review, 'high-risk' individuals were divided into children ≤ 12 years and other individuals ≥ 12 years as defined by the studies identified. Note that for trials which included individuals from more than one of the groups listed above, results were requested from the pharmaceutical companies stratified into these groups. Note: zanamivir is only licensed for persons ≥ 12 years, whereas Hoffman La Roche have announced that they have received a positive recommendation from the Committee for Proprietary Medicinal Products (CPMP) for the approval of oseltamivir for the treatment of influenza A and B in adults and children over the age of 1 year, and also for the prevention of influenza in adolescents and adults. Hoffman La Roche expected to receive marketing authorisation in July 2002.

Results from the different studies were reported in terms of two patient populations:

- intention-to-treat (ITT) – all individuals recruited into the study (i.e. with influenza and ILI)
- influenza positive – only individuals with clinically confirmed influenza.

Efficacy end-points

Time to symptoms alleviated

There was no unanimous definition of time to symptoms alleviated. In each study, relevant influenza symptoms were identified (as listed in *Tables 9* and *10*) and usually rated by study participants on a four-point scale (0 absent, 1 mild, 2 moderate, 3 severe) for up to 21 days. Different definitions of symptoms alleviated were used by the two companies and also for adults and children (*Tables 9* and *10*). Note that in GlaxoSmithKline's re-analysis of the data, definition of time to symptoms alleviated was made consistent across all their studies by, for example, adding temperature where it was previously omitted.

Time to return to normal activities

The time to return to normal activities, where considered, was defined as the first day on which subjects recorded that they were able to carry out usual daily activities. The Hoffman La Roche criteria required that this remained the case for 24 hours and was based on an 11-point visual analogue scale (0 unable to perform normal activity, 10 fully able to perform normal activity). For the Hoffman La Roche children's trial (aged ≤ 12 years) time to return to normal activity was a component of the primary end-point – time to symptoms alleviated.

Other efficacy end-points

Other end-points considered in this review are adverse events due to treatment, hospitalisations and complications requiring the use of antibiotics (e.g. otitis, bronchitis, sinusitis, pneumonia).

Statistical issues

For time to event data (i.e. time to symptoms alleviated and time to return to normal activities), the descriptive statistic of most clinical interest is the **median** time. In the majority of publications identified, the median time to the event of interest was reported. However, there were inconsistencies in the method used to calculate the median time to the event of interest (i.e. whether or not to allow for censored observations – those individuals who were still ill at the end of the trial follow-up

TABLE 9 *Adults: definition of symptoms alleviated for the different NI trials*

Symptoms alleviated occurs when the following hold for at least 24 hours		
	GlaxoSmithKline	**Hoffman La Roche**
Feverishness	None	None or mild
Headache	None or mild	None or mild
Sore throat	None or mild	None or mild
Cough	None or mild	None or mild
Muscle aches (myalgia)	None or mild	None or mild
Fatigue		None or mild
Nasal congestion		None or mild
Loss of appetite		
Return to usual activities		
Temperature	<37.8°C (100°F)	

TABLE 10 *Children: definition of symptoms alleviated for the different NI trials*

Symptoms alleviated occurs when the following hold for at least 24 hours		
	GlaxoSmithKline	**Hoffman La Roche**
Feverishness	Absent or minimal	
Headache	Absent or minimal	
Sore throat	Absent or minimal	
Cough	None or mild	None or mild
Muscle aches (myalgia)	Absent or minimal	
Fatigue		
Nasal congestion		None or mild
Loss of appetite		
Return to usual activities		Yes
Temperature	<37.8°C (100°F)	≤ 37.2°C (98.9°F)

period). Also, to enable the results from different studies to be combined in a meta-analysis the standard error (SE) of the median is required, which was not reported in the majority of cases. Therefore, it was necessary to request additional information from the two pharmaceutical companies. In all cases the SE of the median was calculated using the method advocated by Collett.[481] Meta-analyses were performed on the median time difference between the treatment and placebo groups.

Finally, as economic evaluation is concerned with assessing the expected outcomes and costs of the treatments compared, it was necessary to obtain, or derive, the mean time to the event of interest as it is difficult to give a meaningful economic interpretation to the common practice of relating a difference in median outcome to the difference in mean cost.[482] Owing to censored data, the time to the event of interest for all individuals in the trial is not known and therefore the mean is undefined. The mean data supplied by the pharmaceutical companies were inconsistent either using a so-called 'restricted mean method'[483] or ignoring censored observations. It was therefore decided, for consistency, to derive a mean time and its corresponding SE for each trial from the median time by assuming the distribution for time to recovery outcomes follows an exponential distribution (see Appendix 3 for further details).

Other end-points considered in this review (i.e. adverse events due to treatment, hospitalisations and complications requiring use of antibiotics) were expressed as either the number of individuals incurring the event or the proportion of individuals incurring the event out of the total study population.

Assessment of study validity

Previous reports[2,6,7] have applied the Jadad trial quality scoring[484] system to assess study validity (see Appendix 2). This was considered problematical to the point of misleading because:

1. Varying degrees of published information were available in English (i.e. conference abstracts, FDA reports, formal publications, personal correspondence with pharmaceutical companies).
2. Where necessary, data were re-analysed at our request by the pharmaceutical companies. ITT (total population and influenza positive population) analyses were always requested irrespective of any results that may have been published previously.

For the reasons outlined above, in this review low Jadad scores primarily indicate lack of clarity in the trial descriptions available (we used whatever data sources available to calculate these scores – see point 1 above). Therefore, no Jadad cut-off point was applied as an additional exclusion criterion. However, since all trials had to be randomised and double-blinded for inclusion in this review, a quality threshold is maintained.

Data analysis

Where sufficient information was available, results from different studies were combined using meta-analysis for each NI compound separately using the outcome measures defined in the section 'Data extraction strategy' (p. 42). Separate analyses were carried out on ITT populations for each patient subgroup and for all individuals and those confirmed influenza positive. Random effects models[485] were used throughout to take into account any statistical heterogeneity that may exist. All meta-analyses were performed using the STATA software package (http://www.stata.com). Note that the practice of combining medians rather than means is non-standard, but justified for time to event data, as it is the more clinically relevant outcome in this case (as discussed in the section 'Statistical issues', p. 43). For the complication end-points considered in this review, previous pooled analyses were used since these contained more data than available to ourselves. Note that these analyses were conducted by pooling the individual patient level data from the different studies (rather than combining effect sizes from each study in a meta-analysis). Since such analyses are marginal (i.e. equivalent to constructing one large 2×2 table of all the data combined), they have the potential to be misleading.[485,486] As a safeguard against this, meta-analyses were carried out on the limited data available to us, which produced results that were consistent with the marginal analyses results in all cases.

Sensitivity analyses were performed to test the robustness of the results to various assumptions made in the analysis. Hence additional meta-analyses were performed on the subsets defined by (i) data published in peer-reviewed journals only and (ii) a Jadad quality score of 4 or 5 only (see *Tables 12* and *15*). Ideally, a further subgroup analysis on European studies only would have been performed, but this was not possible owing to many of the required data being combined with those from other continents in multi-centre trials (see Appendix 1, *Tables 105* and *107*).

TABLE 11 *Excluded zanamivir treatment and related studies with reasons for exclusion*

Study ID	Reason for exclusion from systematic review
JNAI-01[a]	Japanese only; different primary end-point; different symptoms and severity scales; data difficult to obtain/translate
JNAI-04[a]	Japanese only; different primary end-point; different symptoms and severity scales; data difficult to obtain/translate
JNAI-07[a]	Japanese only; different primary end-point; different symptoms and severity scales; data difficult to obtain/translate
NAI10901	No relevant outcome; interaction study with vaccination; end-point is serology
NAI10902	No relevant outcome. Measured concentrations in respiratory tract
NAIA1001	Experimental influenza
NAIA1002	Experimental influenza
NAIA1003	Experimental influenza
NAIA1004	Experimental influenza
NAIA1005	Experimental influenza
NAIA1006	Experimental influenza
NAIA1008	Experimental influenza
NAIA1009	PK, safety and tolerability, no relevant outcome
NAIA1010	Experimental influenza
NAIB1001	PK, safety and tolerability, no relevant outcome
NAIB1002	PK, safety and tolerability, no relevant outcome
NAIB1003	PK, safety and tolerability, no relevant outcome
NAIB1004	PK, safety and tolerability, no relevant outcome
NAIB1005	PK, safety and tolerability, no relevant outcome
NAIB1007	PK, safety and tolerability, no relevant outcome
NAIB1008	PK, safety and tolerability, no relevant outcome
NAIB1009	PK, safety and tolerability, no relevant outcome
NAIB2001	No data available
NAIB2003	No data available – dosages 16 and 32 mg twice daily
NAI30011	Analysis not published but study report available in GSK NICE submission (unfortunately data not available in appropriate format)
NAI30012	Analysis not published but study report available in GSK NICE submission (unfortunately data not available in appropriate format)
NAI30015	Analysis not published but study report available in GSK NICE submission (unfortunately data not available in appropriate format)
NAI30020	Study ongoing
NAI30028	Study ongoing
NAI40003	Information leaflet study, no relevant outcome
NAI40004	Lung capacity outcomes only, not randomised
NAI40012	Leaflet study, no relevant outcome
NAI40015	Open study, no comparable endpoint

[a] Owing to lack of information published in English on these studies, it has been necessary to rely on the judgement of representatives at GlaxoSmithKline for this information.

Results

Quantity and quality of research available

Below, the trials included in the NI treatment systematic review are described; they are categorised by specific NI and the target population.

Zanamivir

Forty-four different trials evaluating zanamivir for the treatment of influenza were identified. Since the results of trials (i) NAIA2008 and NAIB2008 and (ii) NAIA2005 and NAIB2005 are reported as combined in most data sources,[487–489] they are treated as two rather than four trials (i.e. NAIA/B2008 and NAIA/B2005) in this review, reducing the number of trials to 42. The excluded studies/trials, together with the reason for the exclusion, are provided in *Table 11*. In addition, a reference list relating to all the excluded trials is provided in Appendix 1. Eleven trials had data available and met the criteria for inclusion in the systematic review. These are summarised in *Table 12* together with a Jadad score of study quality.

A reference list for the 11 trials included in the NI treatment systematic review, including their

TABLE 12 *Characteristics of zanamivir treatment trials included in meta-analyses*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Follow-up (days)	Jadad score	Data source + extra information
NAIA2005 NAIB2005	Previously healthy adults of at least 13 years of age. Present within 48 hours after onset of symptoms. Influenza was confirmed to be circulating before recruitment started in each centre. There were no 'high-risk' individuals. Vaccinated individuals were excluded from the study	144 placebo (inhaled + intranasal) 132 10 mg inhaled + placebo intranasal twice daily 141 10 mg inhaled + 6.4 mg intranasal twice daily	5	28	4	Considered as one trial. [Ref.: Hayden *and colleagues*., 1997[488]]
NAIB2007	At least 13, 16 or 18 years old (depending on centre). Present within 48 hours after onset of symptoms. Note that ~13% of participants considered 'high risk'	183 placebo 188 10 mg inhaled twice daily 183 10 mg inhaled + 6.4 mg intranasal twice daily	5	5	2	[Ref.: GlaxoSmithKline database]
NAIA2008 NAIB2008	Previously healthy persons at least 13 or 18 years old (depending on centre). Present within 48 hours after onset of symptoms. Note that 13% of participants considered 'high risk'. 0.8% of the study population were vaccinated	422 Placebo 419 10 mg inhaled + 6.4 mg intranasal twice daily 415 10 mg inhaled + 6.4 mg intranasal four times daily	5	21	4	Considered as one trial. Placebo group is 2 combined arms of placebo twice and placebo four times daily. [Ref.: Monto *et al*., 1999[487]]
NAIB3001	Previously healthy persons at least 12 years old. Present within 36 hours after onset of symptoms. Influenza activity in area confirmed. Recruitment started when influenza activity was seen to be increasing. Note that 17% of participants considered 'high risk'. 6% of the study population were vaccinated	228 placebo 227 10 mg inhaled twice daily	5	28	5	[Ref.: MIST, 1998[490]]
NAIA3002	Previously healthy persons at least 12 years old. Present within 48 hours after onset of symptoms. Note that 14% of participants considered 'high risk'.	365 placebo 412 10 mg inhaled twice daily	5	28	2	[Ref.: GlaxoSmithKline database]

continued

TABLE 12 *Characteristics of zanamivir treatment trials included in meta-analyses (cont'd)*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Follow-up (days)	Jadad score	Data source + extra information
NAIB3002	At least 12 years old. Present within 48 hours after onset of symptoms. Recruitment started when influenza was known to be circulating locally. Note that 9% of participants considered 'high risk'. 4% of the study population were vaccinated	182 placebo 174 10 mg inhaled twice daily	5	28	5	[Ref.: Makela *et al*., 2000[491]]
NAI30008	Persons with asthma or COPD, at least 12 years old. Recruitment started when influenza was known to be circulating in the community. Present within 36 hours after onset of symptoms. 23% of the study population were vaccinated	263 placebo 262 10 mg inhaled twice daily	5	28	5	[Ref.: Murphy *et al*., 2000[492]]
NAI30009	Previously healthy children 5–12 years old. Present within 36 hours after onset of symptoms. Recruitment started when influenza was known to be circulating in the community. Influenza was confirmed to be circulating before recruitment started in each centre. Note that 8% of participants considered 'high risk'. 2% of study population were vaccinated	247 placebo 224 10 mg inhaled twice daily	5	28	3	[Ref.: Hedrick *et al*., 2000[493]]
NAI30010	Eligible families were those with two to five members, including at least one adult and at least one child between 5 and 17 years old. Once laboratory confirmed influenza activity had been documented in the community, families in which one member contracted an ILI (the 'index case') began to take the study drug. The treatment trial consisted of the 'index cases' only. Present within 36 hours after onset of symptoms. Note that 7% of participants considered 'high risk'. 10% of the study population were vaccinated	158 placebo 163 10 mg inhaled twice daily	5	28	3	Analysis of index cases from a study set up to examine the prevention of transmission of influenza A and B within families [Ref.: Hayden *et al*., 2000[332]]

TABLE 13 *Relevant data extracted from different studies*

Trial	Time to symptoms alleviated	Time to return to normal activities	Pneumonia	Complications requiring use of antibiotics	Adverse events
NAIA2005					
NAIB2005	✓	✓		✓	
NAIB2007	[a]	[a]	✓	✓	
NAIA2008					
NAIB2008				✓	
NAIB3001	✓	✓	✓	✓	
NAIA3002	✓	✓	✓	✓	
NAIB3002	✓	✓	✓	✓	
NAI30008	✓	✓			
NAI30009	✓	✓	✓	✓	
NAI30010	✓	✓	✓	✓	

[a] Short follow-up of 5 days, therefore median undefined (>3.5 days).

respective participating centres, is also provided in Appendix 1. For clarity, and to ease comparability with other sources, the original study code numbers assigned by GlaxoSmithKline to their trials are reported here and in the reference lists.

Note on Burls systematic review

When carrying out a review of the same topic, Burls and colleagues[2] included all the studies considered here (listed in *Table 13*), in addition to eight other studies (JNAI-01, NAIA1001, NAIA1002, NAIA1003, NAIA1004, NAIA1005, NAIB2001, NAIB2003) rejected here for reasons given in *Table 11*. No data were available to either ourselves or Burls and colleagues[2] for two of these trials (NAIB2001, NAIB2003), and the remaining five trials (NAIA1005, NAIA1001, NAIA1002, NAIA1003, NAIA1004) did not report any of the outcomes examined in this review, hence contrary to initial appearances there is broad agreement of the evidence base on which the two systematic reviews are based.

Table 13 indicates which studies provide data on the outcomes of interest. Note that although sometimes available, adverse event data were not considered from the treatment trials because the reporting of adverse events varied between trials, and it was often difficult to separate from certain complications. Therefore, for the purposes of the economic model, adverse events data were obtained from trials designed to evaluate the prophylactic use of NIs for the prevention of influenza (see Chapter 4).

TABLE 14 *Excluded oseltamivir studies*

Study ID	Reason for exclusion from systematic review
M76001[a]	No data available
M76006	Uncontrolled
WV15759	No data (asthmatic children)
WV15871	No data (asthmatic children)
WV15707[a]	No data available
Gubareva *et al.*, 2000[494]	Experimental Influenza
Kashiwagi *et al.*, 2000[495]	No data available – abstract in English but article in Japanese
Hayden *et al.*, 1999[312] (reports two different studies)	Both trials examine experimental influenza

[a] Data from trials M76001 and WV15707 were included in the combined analysis of complication rates provided by Roche Pharmaceuticals[496] (see below).

Oseltamivir

Seventeen different trials evaluating oseltamivir for the treatment of influenza were identified. The excluded studies/trials, together with the reason for the exclusion, are provided in *Table 14*. In addition, a reference list relating to all the excluded trials, is provided in Appendix 1. Nine had data available and met the criteria for inclusion in the systematic review. These are summarised in *Table 15* together with a Jadad score of study quality.

TABLE 15 *Characteristics of oseltamivir treatment trials included in the healthy adults meta-analysis*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Follow-up (days)	Jadad score	Data source + extra information
WV15670	Previously healthy, aged 18–65 years. Present within 36 hours after onset of symptoms. Persons vaccinated in the previous 12 months were excluded. There were no 'high-risk' individuals	238 placebo 243 75 mg/dose twice daily 245 150 mg/dose twice daily	5	21	5	[Ref.: Nicholson *et al*., 2000[497]]
WV15671	Previously healthy, aged 18–65 years. Present within 36 hours after onset of symptoms. Persons vaccinated in the previous 12 months were excluded. There were no 'high-risk' individuals	209 placebo[a] 210 75 mg/dose twice daily 208 150 mg/dose twice daily	5	21	5	[Ref.: Treanor *et al*., 2000[498]]
WV15730	Previously healthy, aged 18–65 years. Present within 36 hours after onset of symptoms. Persons vaccinated in the previous 12 months were excluded. There were no 'high-risk' individuals	27 placebo 31 75 mg/dose twice daily	5	21	5	[Ref.: http://www.fda.gov/cder/approval/index.htm]
WV15812	Persons with chronic and/or respiratory disease[b], aged ≥ 13 years. Present within 36 hours after onset of symptoms. Approx. 30% of the study population were vaccinated	149 placebo 152 75 mg/dose twice daily	5	21	4	[Ref.: http://www.fda.gov/cder/approval/index.htm]
WV15872	Persons with chronic and/or respiratory disease aged ≥ 13 years	53 placebo 47 75 mg/dose twice daily	Not available	Not available	2	[Ref.: not published]
WV15819	Previously healthy, aged ≥ 65 years. Present within 36 hours after onset of symptoms. Approx. 46% of the study population were vaccinated	93 placebo 76 75 mg/dose twice daily	5	21	4	[Ref.: http://www.fda.gov/cder/approval/index.htm]
WV15876	Previously healthy, ≥ 65 years	44 placebo 54 75 mg/dose twice daily	5	21	2	[Ref.: not published]

continued

TABLE 15 *Characteristics of oseltamivir treatment trials included in the healthy adults meta-analysis (cont'd)*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Follow-up (days)	Jadad score	Data source + extra information
WV15978	Previously healthy, aged ≥ 65 years	238 placebo 228 75 mg/dose twice daily	Not available	Not available	2	[Ref.: not published]
WV15758	Previously healthy children aged 1–12 years. Present <48 hours after onset of symptoms. Influenza immunisation was not an exclusion criterion. There were no 'high-risk' individuals	351 placebo 344 2 mg/kg/dose twice daily (to a max. of 100 mg/dose)	5	28	4	[Ref.: Whitley *et al*., 2001[499]]

[a] Two persons in this study were excluded before treatment given and analysis is reported excluding these persons.
[b] Patients with chronic cardiac (excluding chronic idiopathic hypertension) or pulmonary disorders (including bronchopulmonary dysplasia and asthma but excluding cystic fibrosis) severe enough to require regular medical follow-up or hospital care. In study WV15872 the following clarification was also given: pulmonary disorders were defined as COAD (chronic obstructive airway disease), which permanently reduces the FEV_1. Asymptomatic patients with a previous valve replacement or bypass surgery were also eligible.

TABLE 16 *Relevant data extracted from different studies*

Trial	Time to symptoms alleviated	Time to return to normal activities	Pneumonia	Complications requiring use of antibiotics	Adverse events
M76001[a]			✓	✓	
WV15670	✓	✓	✓	✓	
WV15671	✓	✓	✓	✓	
WV15707[a]			✓	✓	
WV15730	✓	✓	✓	✓	
WV15812	✓	✓	✓	✓	
WV15872	✓	✓	✓	✓	
WV15819	✓	✓	✓	✓	
WV15876	✓	✓	✓	✓	
WV15978	✓	✓	✓	✓	
WV15758	✓	✓			

[a] Although no data were available for these studies separately, combined data with other studies were available for complication rates.

Table 16 indicates which studies provide data on the outcomes of interest. Note that although sometimes available, adverse event data were not considered from the treatment trials because the definition of adverse events varied between trials, and it was often difficult to separate from certain complications. Therefore, for the purposes of the economic model, adverse events data were obtained from trials designed to evaluate the prophylactic use of NIs for the prevention of influenza (see Chapter 4).

Assessment of effectiveness

Zanamivir

For time to event outcomes, two estimates of the median time are reported in the tables below. The statistic labelled 'published' is the median reported in the published literature, which makes no allowance for censoring. The statistic labelled 'published re-analysis' is the median provided on request from GlaxoSmithKline, which does allow for censored observations and is consistent with the Hoffman La Roche trial results (see the section 'Oseltamivir', p. 69). For each subgroup, the difference between the placebo group and the dosage licensed (inhaled 10 mg twice daily group) is reported. Where other dosage levels were evaluated in a trial, these data were also reported for completeness, although no formal comparisons were made. It is important to note that the time to outcome end-points are measured in days. Since these are calculated from diary entries completed twice daily by study participants, they are always rounded upwards to the nearest half-day.

Time to symptoms alleviated

'Healthy' subgroup of individuals aged 12–65 years in the zanamivir treatment trials (ITT). Table 17 reports the median time to alleviation of symptoms in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 8* displays the results from the random effects meta-analysis, which shows a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –0.78 days (95% CI –1.31 to –0.26).

'Healthy' subgroup of individuals aged 12–65 years in the zanamivir treatment trials (influenza positive). Table 18 reports the median time to alleviation of symptoms in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 9* displays the results from the random effects meta-analysis, which shows a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –1.26 days (95% CI –1.93 to –0.59).

'High-risk' subgroup of individuals aged ≥ 12 years in the zanamivir treatment trials (ITT). Table 19 reports the median time to alleviation of symptoms in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 10* displays the results from the random effects meta-analysis, which shows a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –0.93 days (95% CI –1.90 to 0.05) that is not formally significant at the 5% level. Note that the trial

TABLE 17 *Median number of days to the alleviation of symptoms for 'healthy' individuals in the zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
NAIA/B2005	[*N* = 144; *R* = 134]	[*N* = 132; *R* = 123]	[*N* = 141; *R* = NDA]	
Published	5.0 (NDA)	5.0 (NDA)	4.0 (NDA)	NDA
Published re-analysis	4.5 (0.3)	3.5 (0.3)	NDA	–1.0 (–1.8 to –0.2)
NAIB2007	[*N* = 159; *R* = 35]	[*N* = 165; *R* = 57]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	>3.5 (NDA)	>3.5 (NDA)	NDA	NDA
NAIA/B2008[a]	[*N* = NDA; *R* = NDA]		[*N* = NDA; *R* = NDA]	
Published	NDA		NDA	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 189; *R* = 146]	[*N* = 190; *R* = 156]		
Published	NDA	NDA		NDA
Published re-analysis	6.0 (0.3)	5.0 (0.4)		–1.0 (–1.9 to –0.1)
NAIA3002	[*N* = 305; *R* = 266]	[*N* = 363; *R* = 323]		
Published	NDA	NDA		NDA
Published re-analysis	5.0 (0.3)	5.0 (0.2)		0.0 (–0.7 to 0.7)
NAIB3002	[*N* = 163; *R* = 133]	[*N* = 161; *R* = 142]		
Published	NDA	NDA		NDA
Published re-analysis	6.5 (0.6)	5.0 (0.4)		–1.5 (–2.9 to –0.1)
NAI30010	[*N* = 149; *R* = 136]	[*N* = 151; *R* = 139]		
Published	NDA	NDA		NDA
Published re-analysis	5.5 (0.4)	4.5 (0.2)		–1.0 (–1.9 to –0.1)
Pooled meta-analysis results				–0.8 (–1.3 to –0.3)

NDA, no data available; b.d., twice daily (*bis die*); *N*, no. of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.

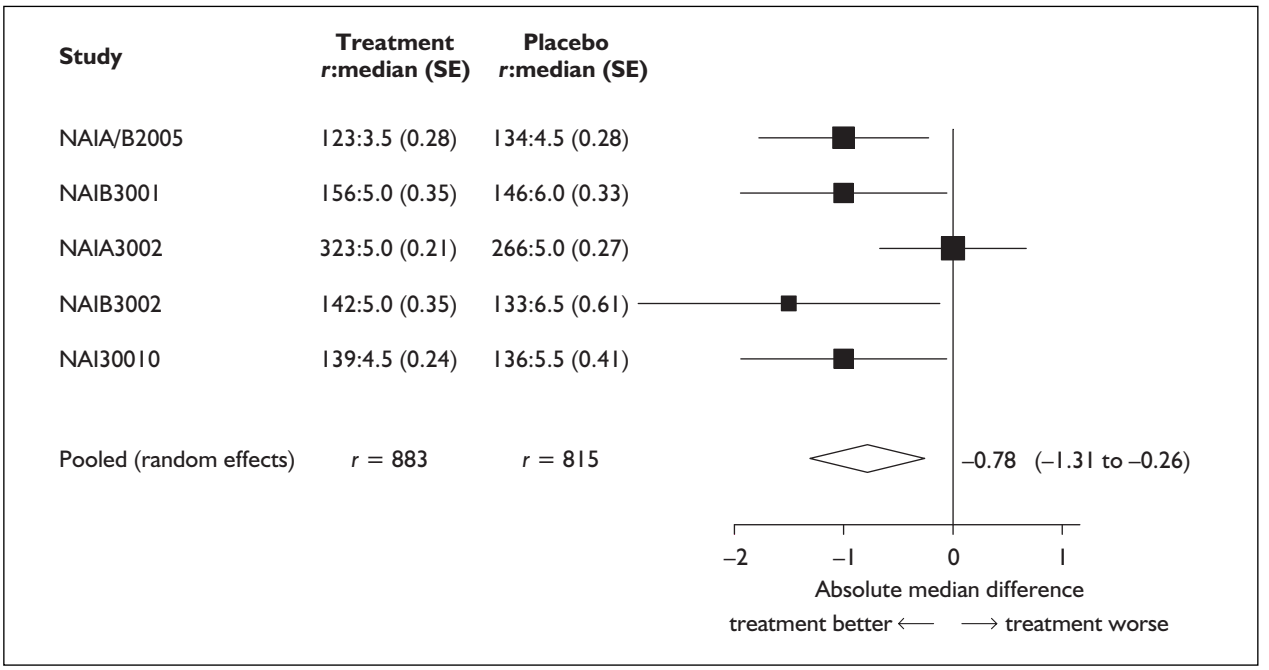

FIGURE 8 *Time to symptoms alleviated (random effects). ITT 'non-risk', 12–65-year-olds. Estimates with 95% CIs.*

TABLE 18 *Median number of days to the alleviation of symptoms for 'healthy' individuals in the zanamivir treatment trials (influenzap positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
NAIA/B2005	[*N* = 89; *R* = 83]	[*N* = 85; *R* = 80]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	4.5 (0.5)	3.5 (0.3)	NDA	–1.0 (–2.6 to 0.6)
NAIB2007	[*N* = 101; *R* = 22]	[*N* = 96; *R* = 33]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	>3.5 (NDA)	>3.5 (NDA)	NDA	NDA
NAIA/B2008[a]	[*N* = NDA; *R* = NDA]		[*N* = NDA; *R* = NDA]	
Published	NDA		NDA	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 132; *R* = 104]	[*N* = 137; R = 117]		
Published	NDA	NDA		NDA
Published re-analysis	6.0 (0.4)	4.5 (0.2)		–1.5 (–2.7 to –0.3)
NAIA3002	[*N* = 214; *R* = 190]	[*N* = 276; *R* = 245]		
Published	NDA	NDA		NDA
Published re-analysis	6.0 (0.3)	5.0 (0.2)		–1.0 (–5.3 to 3.3)
NAIB3002	[*N* = 123; *R* = 101]	[*N* = 124; *R* = 111]		
Published	NDA	NDA		NDA
Published re-analysis	6.5 (0.7)	5.0 (0.4)		–1.5 (–3.0 to 0.0)
NAI30010	[*N* = 75; *R* = 71]	[*N* = 72; *R* = 68]		
Published	NDA	NDA		NDA
Published re-analysis	5.5 (0.3)	4.5 (0.2)		–1.0 (–2.3 to 0.3)
Pooled meta-analysis results				–1.3 (–1.9 to –0.6)

NDA = no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.

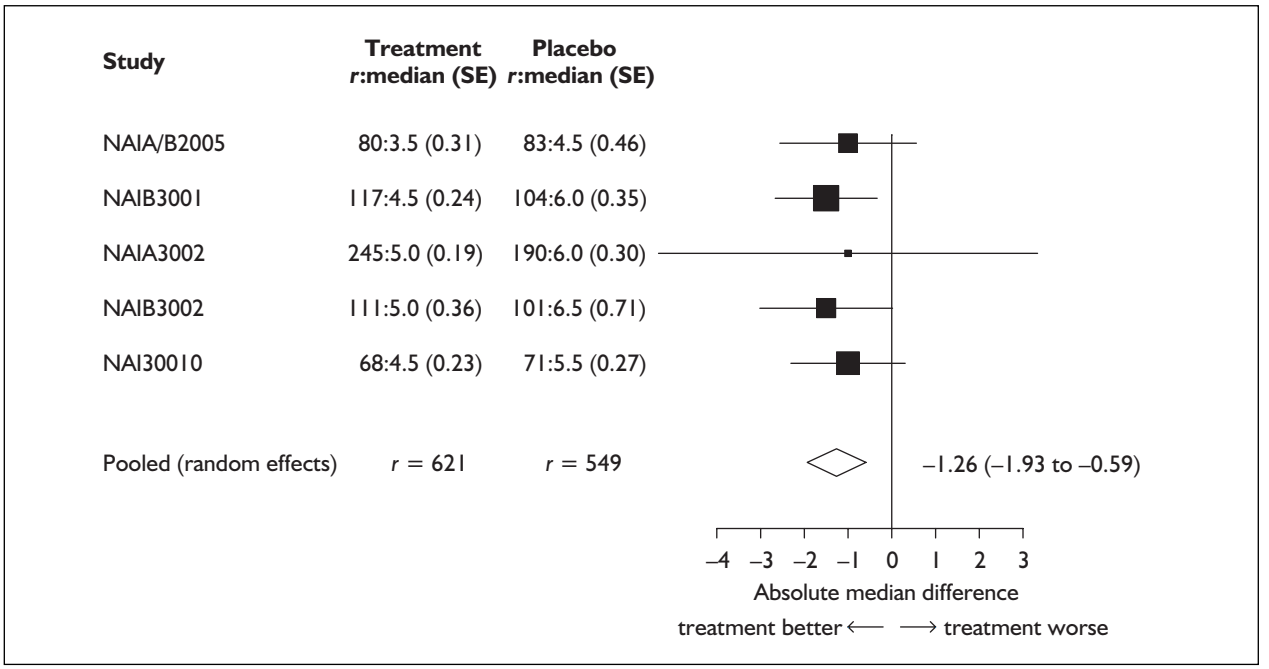

FIGURE 9 *Time to symptoms alleviated. Influenza-positive 'non-risk', 12–65-year-olds. Estimates with 95% CIs.*

TABLE 19 *Median number of days to the alleviation of symptoms for 'high-risk' individuals in the zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
NAIB2007	[*N* = 24; *R* = 8]	[*N* = 23; *R* = 13]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	>3.5 (NDA)	3.5 (0.4)	NDA	NDA
NAIA/B2008[a]	[*N* = 68; *R* = NDA]		[*N* = 48; *R* = NDA]	
Published	7.8 (NDA)		6.3 (NDA)	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 39; *R* = 24]	[*N* = 37; *R* = 32]		–2.5 (–8.0 to 1.0);
Published	8.0 (NDA)	5.5 (NDA)		*p* = 0.048
Published re-analysis	7.0 (1.4)	5.0 (0.5)		–2.0 (–5.0 to 1.0)
NAIA3002	[*N* = 60; *R* = 53]	[*N* = 49; *R* = 42]		
Published	NDA	NDA		NDA
Published re-analysis	6.0 (0.9)	7.5 (1.5)		1.5 (–1.9 to 4.9)
NAIB3002	[*N* = 19; *R* = 15]	[*N* = 13; *R* = 12]		
Published	NDA	NDA		NDA
Published re-analysis	11.5 (1.4)	9.0 (3.0)		–2.5 (–9.0 to 4.0)
NAI30008	[*N* = 263; *R* = 222]	[*N* = 262; *R* = 226]		
Published	7.0 (NDA)	6.0 (NDA)		NDA
Published re-analysis	6.5 (0.5)	5.5 (0.3)		–1.0 (–2.1 to 0.1)
NAI30010	[*N* = 11; *R* = 11]	[*N* = 10; *R* = 9]		
Published	NDA	NDA		NDA
Published re-analysis	6.5 (2.5)	5.8 (1.2)		–0.8 (–6.0 to 4.5)
Pooled meta-analysis result				–0.9 (–1.9 to 0.1)

NDA. no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal (*N* = 42): median 5.0 [difference: –2.8 (–3.5 to –0.3)].

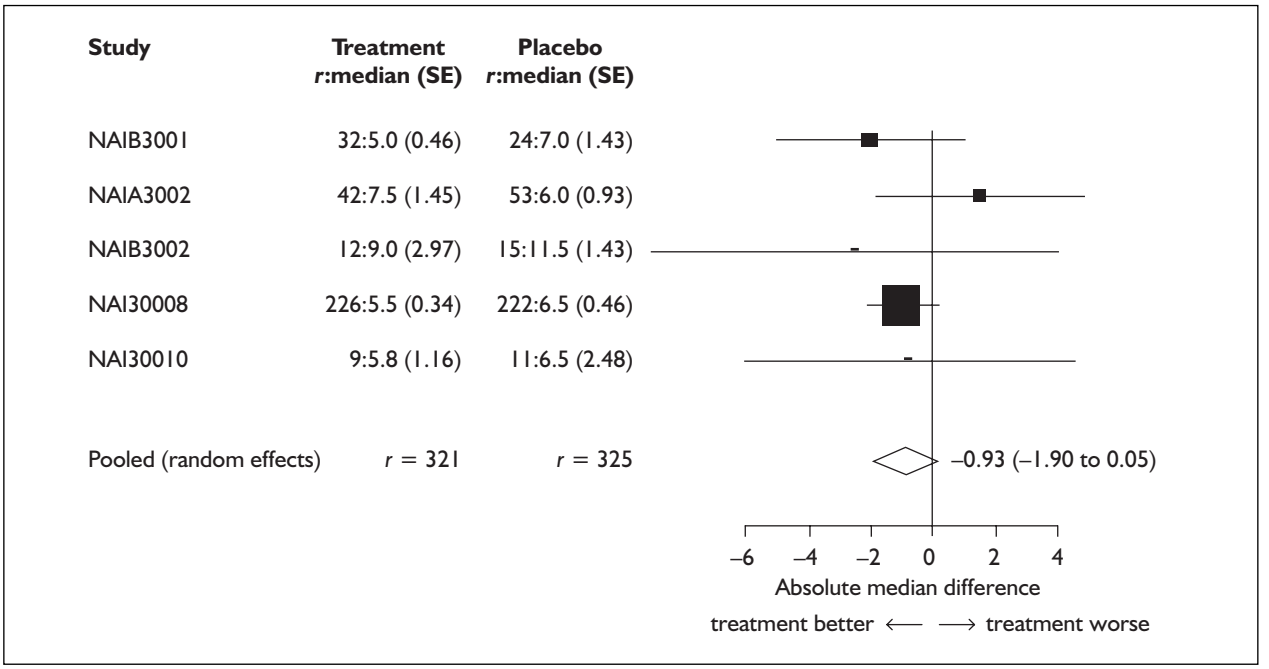

FIGURE 10 *Time to symptoms alleviated. ITT 'at-risk' including over 65-year-olds. Estimates with 95% CIs.*

NAI30008 dominates this analysis since the trial recruited only 'high-risk' individuals whereas only the relatively small subgroup of 'high-risk' individuals are included from the other trials.

'High-risk' subgroup of individuals aged ≥ 12 years in the zanamivir treatment trials (influenza positive). *Table 20* reports the median time to alleviation of symptoms in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 11* displays the results from the random effects meta-analysis, which shows a difference in the time with symptoms alleviated in the treatment group compared with the placebo group of –1.99 days (95% CI –3.08 to –0.90). Note that the trial NAI30008 dominates this analysis since the trial recruited only 'high-risk' individuals whereas only the relatively small subgroup of 'high-risk' individuals are included from the other trials.

Children aged 5–12 years in the zanamivir treatment trials (ITT). *Table 21* reports the median time to alleviation of symptoms in days and the difference between the placebo group and inhaled 10 mg twice-daily group for both the 'healthy' and 'high-risk' individuals separately. For the 'healthy' subgroup a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –1.0 days (95% CI –1.5 to –0.5) was observed. For the 'high-risk' subgroup a difference of –2.0 days (95% CI –6.9 to 2.9) was found. Note the small number of individuals in the 'high-risk' analysis and hence the large uncertainty in the estimated treatment difference.

Children aged 5–12 years in the zanamivir treatment trials (influenza positive). *Table 22* reports the median time to alleviation of symptoms in days and the difference between the placebo group and inhaled 10 mg twice-daily group for both the 'healthy' and 'high-risk' individuals separately. For

TABLE 20 *Median number of days to the alleviation of symptoms for 'high-risk' individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI); *p*-value
NAIB2007	[*N* = 17; *R* = 5]	[*N* = 17; *R* = 9]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	>3.5 (NDA)	3.5 (0.5)	NDA	NDA
NAIA/B2008[a]	[*N* = NDA; *R* = NDA]		[*N* = NDA; *R* = NDA]	
Published	NDA		NDA	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 28; *R* = 17]	[*N* = 24; *R* = 21]		–3.3 (–8.5 to 1.8);
Published	8.3 (NDA)	5.0 (NDA)		*p* = 0.161
Published re-analysis	8.0 (2.8)	5.0 (0.6)		–3.0 (–8.5 to 2.5)
NAIA3002	[*N* = 43; *R* = 38]	[*N* = 36; *R* = 32]		
Published	NDA	NDA		NDA
Published re-analysis	6.0 (1.1)	5.5 (1.8)		–0.5 (–4.7 to 3.7)
NAIB3002	[*N* = 18; *R* = 14]	[*N* = 12; *R* = 11]		
Published	NDA	NDA		NDA
Published re-analysis	11.5 (1.6)	9.0 (2.2)		–2.5 (–7.8 to 2.8)
NAI30008	[*N* = 153; *R* = 134]	[*N* = 160; *R* = 142]		
Published	7.0 (NDA)	5.5 (NDA)		–1.5 (–3.3 to 0.5)
Published re-analysis	7.0 (0.5)	5.0 (0.3)		–2.0 (–3.2 to –0.8)
NAI30010	[*N* = 6; *R* = 6]	[*N* = 4; *R* = 4]		
Published	NDA	NDA		NDA
Published re-analysis	10.5 (6.4)	4.3 (0.7)		–6.3 (–18.8 to 6.3)
Pooled meta-analysis result				–2.0 (–3.1 to –0.9)

NDA, no data available; *N* = Number of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal (*N* = NDA): median NDA [difference: –3.0, *p* = 0.009].

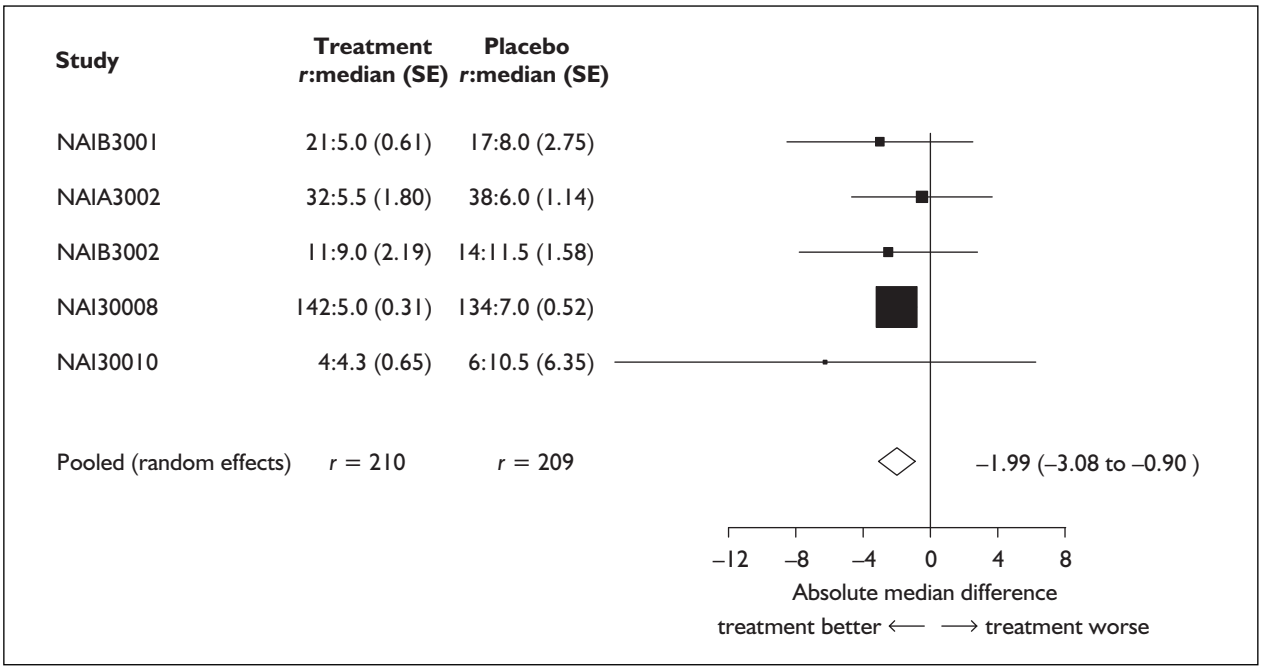

FIGURE 11 *Time to symptoms alleviated. Influenza positive 'at risk' including over 65-year-olds. Estimates with 85% CIs.*

TABLE 21 *Median number of days to the alleviation of symptoms for children in the zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
NAI30009	**Median (SE)**	**Median (SE)**	**Median difference (95% CI)**
'Healthy'	[*N* = 233; *R* = 205]	[*N* = 202; *R* = 193]	
Published	NDA	NDA	NDA
Published re-analysis	5.0 (0.2)	4.0 (0.2)	–1.0 (–1.5 to –0.5)
'High-risk'	[*N* = 14; *R* = 12]	[*N* = 22; *R* = 20]	
Published	NDA	NDA	NDA
Published re-analysis	5.8 (2.3)	3.8 (1.0)	–2.0 (–6.9 to 2.9)

NDA, no data available; *N* = no. of individuals, *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

TABLE 22 *Median number of days to the alleviation of symptoms for children in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI)**
'Healthy'	[*N* = 172; *R* = 152]	[*N* = 152; *R* = 146]	
Published	NDA	NDA	NDA
Published re-analysis	5.0 (0.2)	4.0 (0.2)	–1.0 (–1.6 to –0.4)
'High-risk'	[*N* = 10; *R* = 9]	[*N* = 12; *R* = 12]	
Published	NDA	NDA	NDA
Published re-analysis	5.8 (1.9)	2.0 (0.3)	–3.8 (–7.6 to 0.1)

NDA, no data available; *N*, no. of individuals; *R* = no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

the 'healthy' subgroup a difference in the time with symptoms alleviated in the treatment group compared with the placebo group of –1.0 days (95% CI –1.6 to –0.4) was observed. For the 'high-risk' subgroup a difference of –3.8 days (95% CI –7.6 to 0.1) was found. Note again the small number of individuals in the 'high-risk' analysis and hence the large uncertainty in the estimated treatment difference.

All ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (ITT). For completeness, *Table 23* reports the median time to alleviation of symptoms in days and the difference between the placebo group and inhaled 10 mg twice-daily group for all individuals regardless of age and risk status. *Figure 12* displays the results from the random effects meta-analysis, which shows a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –0.94 days (95% CI –1.23 to –0.65).

All ('high-risk' and 'healthy') individuals in the Zanamivir treatment trials (influenza positive). For completeness, *Table 24* reports the median time to alleviation of symptoms in days and the difference between the placebo group and inhaled 10 mg twice-daily group for all individuals regardless of age and risk status. *Figure 13* displays the results from the random effects meta-analysis, which shows

TABLE 23 *Median number of days to the alleviation of symptoms for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI) *p*-value
NAIA/B2005	[*N* = 144; *R* = 134]	[*N* = 132; *R* = 123]	[*N* = 141; *R* = NDA]	
Published	5.0 (NDA)	5.0 (NDA)	4.0 (NDA)	0.0 (NDA)
Published re-analysis	4.5 (0.3)	3.5 (0.3)	NDA	–1.0 (–1.8 to –0.2)
NAIB2007	[*N* = 183; *R* = 43]	[*N* = 188; *R* = 70]	[*N* = 183; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	>3.5 (NDA)	>3.5 (NDA)	NDA	NDA
NAIA/B2008[a]	[*N* = 422; *R* = NDA]		[*N* = 419; *R* = NDA]	
Published	7.0 (NDA)		6.0 (NDA)	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 228; *R* = 170]	[*N* = 227; *R* = 188]		–1.5 (–2.3 to –0.5);
Published	6.5 (NDA)	5.0 (NDA)		*p* = 0.011
Published re-analysis	6.0 (0.3)	5.0 (0.3)		–1.0 (–1.9 to –0.1)
NAIA3002	[*N* = 365; *R* = 319]	[*N* = 412; *R* = 365]		
Published	NDA	NDA		NDA
Published re-analysis	5.5 (0.3)	5.0 (0.2)		–0.5 (–1.1 to 0.1)
NAIB3002	[*N* = 182; *R* = 148]	[*N* = 174; *R* = 154]		–2.5 (–3.5 to –0.8);
Published	7.5 (NDA)	5.0 (NDA)		*p* < 0.001
Published re-analysis	7.0 (0.6)	5.0 (0.3)		–2.0 (–3.3 to –0.7)
NAI30008	[*N* = 263; *R* = 222]	[*N* = 262; *R* = 226]		–1.0 (NDA);
Published	7.0 (NDA)	6.0 (NDA)		*p* = 0.123
Published re-analysis	6.5 (0.5)	5.5 (0.3)		–1.0 (–2.0 to 0.1)
NAI30009	[*N* = 247; *R* = 217]	[*N* = 224; *R* = 213]		–0.5 (–1.5 to 0.0);
Published	5.0 (NDA)	4.5 (NDA)		*p* = 0.011
Published re-analysis	5.0 (0.2)	4.0 (0.2)		–1.0 (–1.5 to –0.5)
NAI30010	[*N* = 158; *R* = 145]	[*N* = 163; *R* = 150]		
Published	NDA	NDA		NDA
Published re-analysis	5.5 (0.4)	4.5 (0.3)		–1.0 (–2.0 to 0.0)
Pooled meta-analysis result				–0.9 (–1.2 to –0.7)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal (*N* = 415): median 6.0 [difference: –1.0 (–2.0 to 0.0)].

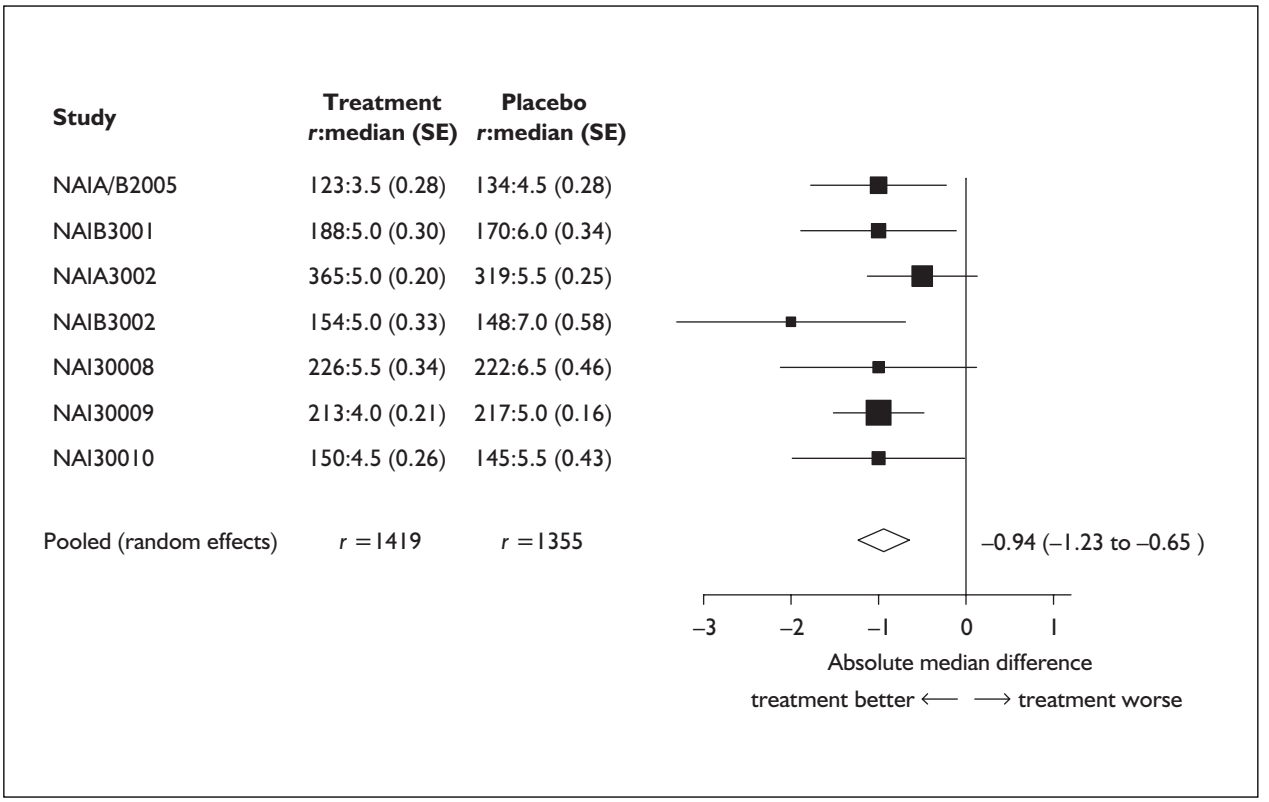

FIGURE 12 *Time to symptoms alleviated (random effects). ITT, all data ('non-risk' and 'at-risk'). Estimates with 95% CIs.*

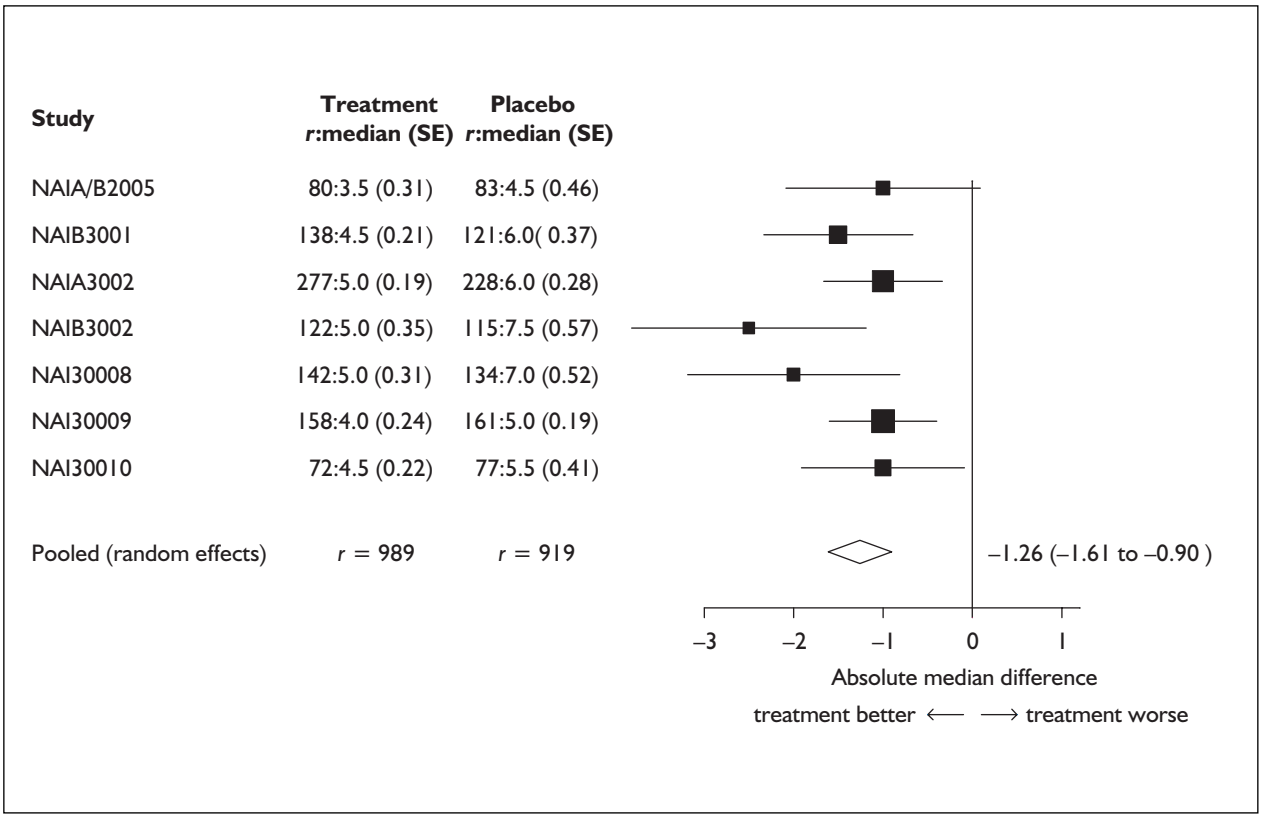

FIGURE 13 *Time to symptoms alleviated (random effects). Influenza positive, all data ('non-risk' and 'at-risk'). Estimates with 95% CIs.*

TABLE 24 *Median number of days to the alleviation of symptoms for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI) *p*-value
NAIA/B2005	[*N* = 89; *R* = 83]	[*N* = 85; *R* = 80]	[*N* = 88; *R* = NDA]	–1.0 (NDA);
Published	5.0 (NDA)	4.0 (NDA)	4.0 (NDA)	*p* = 0.05
Published re-analysis	4.5 (0.5)	3.5 (0.3)	NDA	–1.0 (–2.1 to 0.1)
NAIB2007	[*N* = 118; *R* = 27]	[*N* = 113; *R* = 42]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	>3.5 (NDA)	>3.5 (NDA)	NDA	NDA
NAIA/B2008[a]	[*N* = 240; *R* = NDA]		[*N* = 241; *R* = NDA]	
Published	7.0 (NDA)		5.5 (NDA)	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 160; *R* = 121]	[*N* = 161; *R* = 138]		–1.5 (–2.3 to –0.5);
Published	6.0 (NDA)	4.5 (NDA)		*p* = 0.004
Published re-analysis	6.0 (0.4)	4.5 (0.2)		–1.5 (–2.3 to –0.7)
NAIA3002	[*N* = 257; *R* = 228]	[*N* = 312; *R* = 277]		
Published	NDA	NDA		NDA
Published re-analysis	6.0 (0.3)	5.0 (0.2)		–1.0 (–1.7 to –0.3)
NAIB3002	[*N* = 141; *R* = 115]	[*N* = 136; *R* = 122]		–2.5 (–4.0 to –1.0);
Published	7.5 (NDA)	5.0 (NDA)		*p* < 0.001
Published re-analysis	7.5 (0.6)	5.0 (0.4)		–2.5 (–3.8 to –1.2)
NAI30008	[*N* = 153; *R* = 134]	[*N* = 160; *R* = 142]		–1.5 (–3.3 to –0.5);
Published	7.0 (NDA)	5.5 (NDA)		*p* = 0.009
Published re-analysis	7.0 (0.5)	5.0 (0.3)		–2.0 (–3.2 to –0.8)
NAI30009	[*N* = 182; *R* = 161]	[*N* = 164; *R* = 158]		–1.3 (–2.0 to –0.5);
Published	5.3 (NDA)	4.0 (NDA)		*p* < 0.001
Published re-analysis	5.0 (0.2)	4.0 (0.2)		–1.0 (–1.6 to –0.4)
NAI30010	[*N* = 81; R = 77]	[*N* = 76; *R* = 72]		
Published	7.5 (NDA)	5.0 (NDA)		*P* = 0.01
Published re-analysis	5.5 (0.4)	4.5 (0.2)		–1.0 (–1.9 to –0.1)
Pooled meta-analysis result				–1.3 (–1.6 to –0.9)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal (*N* = 241): median 5.5 [difference: –1.5 (–2.0 to 0.0)].

a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –1.26 days (95% CI –1.61 to –0.90).

Sensitivity analysis. Sensitivity analyses were performed to test the robustness of the meta-analyses results reported above to differential study quality (excluding studies with a Jadad score of <4) and publication status (excluding unpublished trials). Although the magnitude of the results did change slightly, the direction of the pooled estimates for the difference between the interventions remained consistent.

Time to return to normal activities

'Healthy' subgroup of individuals aged 12–65 years in the zanamivir treatment trials (ITT). Table 25 reports the median time to return to normal activities in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 14* displays the results from the random effects meta-analysis, which shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –0.51 days (95% CI –1.04 to 0.02) and hence not formally statistically significant at the 5% level.

TABLE 25 *Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
NAIA/B2005	[*N* = 144; *R* = 129]	[*N* = 132; *R* = 121]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)
NAIB2007	[*N* = 159; *R* = 88]	[*N* = 165; *R* = 94]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)
NAIA/B2008[a]	[*N* = NDA; *R* = NDA]		[*N* = 239; *R* = NDA]	
Published	NDA		NDA	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 189; *R* = 128]	[*N* = 190; *R* = 150]		
Published	NDA	NDA		NDA
Published re-analysis	8.0 (0.4)	7.0 (0.3)		–1.0 (–2.0 to 0.0)
NAIA3002	[*N* = 305; *R* = 233]	[*N* = 363; *R* = 292]		
Published	NDA	NDA		NDA
Published re-analysis	6.5 (0.3)	6.5 (0.3)		0.0 (–0.8 to 0.8)
NAIB3002	[*N* = 163; *R* = 113]	[*N* = 161; *R* = 123]		
Published	NDA	NDA		NDA
Published re-analysis	8.0 (0.6)	6.0 (0.4)		–2.0 (–3.4 to –0.6)
NAI30010	[*N* = 149; *R* = 145]	[*N* = 151; *R* = 146]		
Published	NDA	NDA		NDA
Published re-analysis	4.5 (0.3)	3.5 (0.3)		–1.0 (–1.8 to –0.2)
Pooled meta-analysis result				–0.5 (–1.0 to 0.0)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.

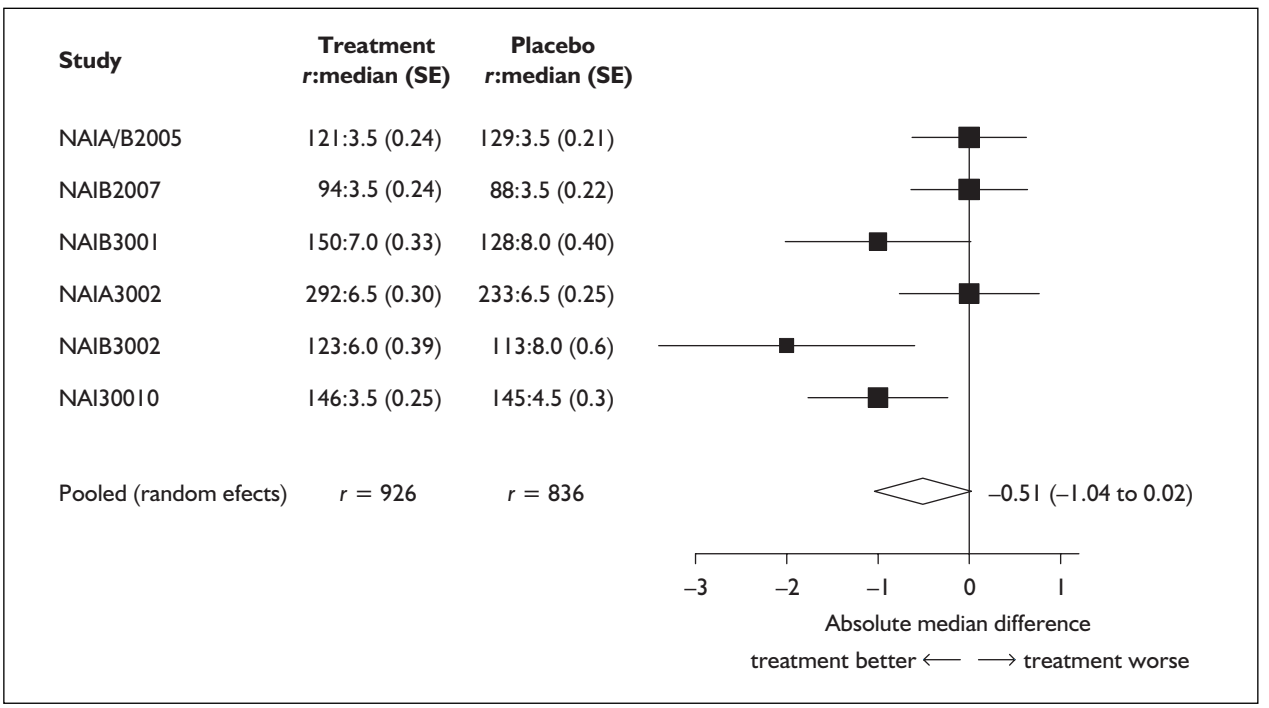

FIGURE 14 *Time to return to normal activities. ITT 'non-risk', 12–65-year-olds. Estimates with 95% CIs.*

TABLE 26 *Median number of days to return to normal activities for 'healthy' individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
NAIA/B2005	[*N* = 89; *R* = 78]	[*N* = 85; *R* = 76]	[*N* = NDA; *R* = NDA]	
Published	4.0 (NDA)	4.0 (NDA)	NDA	0.0 (NDA)
Published re-analysis	3.5 (0.3)	3.5 (0.4)	NDA	0.0 (–0.9 to 0.9)
NAIB2007	[*N* = 101; *R* = 53]	[*N* = 96; *R* = 52]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published adjusted	3.5 (0.3)	3.5 (0.3)	NDA	0.0 (–0.8 to 0.8)
NAIA/B2008[a]	[*N* = NDA; *R* = NDA]		[*N* = NDA; *R* = NDA]	
Published	NDA		NDA	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 132; *R* = 93]	[*N* = 137; *R* = 112]		
Published	NDA	NDA		NDA
Published re-analysis	8.0 (0.5)	7.0 (0.3)		–1.0 (–2.2 to 0.2)
NAIA3002	[*N* = 214; *R* = 165]	[*N* = 276; *R* = 222]		
Published	NDA	NDA		NDA
Published re-analysis	7.0 (0.3)	6.5 (0.3)		–0.5 (–1.4 to 0.4)
NAIB3002	[*N* = 123; *R* = 87]	[*N* = 124; *R* = 96]		
Published	NDA	NDA		NDA
Published re-analysis	8.5 (0.7)	6.5 (0.5)		–2.0 (–3.6 to –0.4)
NAI30010	[*N* = 75; *R* = 74]	[*N* = 72; *R* = 71]		
Published	NDA	NDA		NDA
Published re-analysis	5.0 (0.3)	4.5 (0.3)		–0.5 (–1.3 to 0.3)
Pooled meta-analysis result				–0.5 (–0.9 to 0.0)

NDA, no data available; *N*, no. of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.

'Healthy' subgroup of individuals aged 12–65 years in the zanamivir treatment trials (influenza positive). *Table 26* reports the median time to return to normal activities in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 15* displays the results from the random effects meta-analysis, which shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –0.46 days (95% CI –0.90 to –0.02).

'High-risk' subgroup of individuals aged ≥ 12 years in the zanamivir treatment trials (ITT). *Table 27* reports the median time to return to normal activities in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure16* displays the results from the random effects meta-analysis, which shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –0.09 days (95% CI –0.95 to 0.78) and hence not statistically significant at the 5% level. Since study NAIB2007 only included a 5-day follow-up period, the analysis was redone excluding this study [–0.22 days (95% CI –1.58 to 1.14)] but the meta-analysis result remains relatively consistent.

'High-risk' subgroup of individuals aged ≥ 12 years in the zanamivir treatment trials (influenza positive). *Table 28* reports the median time to return to normal activities in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 17* displays the results from the random effects meta-analysis, which shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –0.20 days (95% CI –1.19 to 0.79) and hence not statistically significant at the 5% level. Thus little difference is observed between groups in the time to return to normal activities in the 'high-risk' groups for both ITT and influenza positive populations.

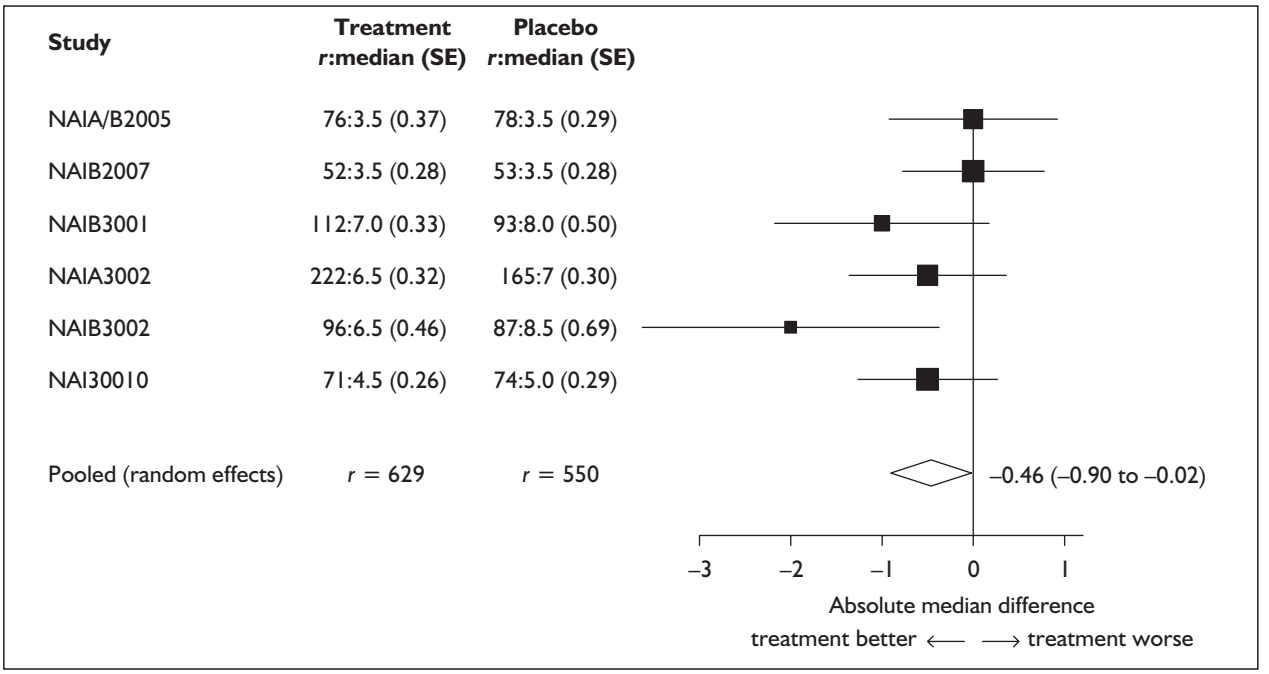

FIGURE 15 *Time to return to normal activities. Influenza positive 'non-risk' 12–65-year-olds. Estimates with 95% CIs.*

TABLE 27 *Median number of days to return to normal activities for 'high-risk' individuals in the zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
NAIB2007	[*N* = 24; *R* = 11]	[*N* = 23; *R* = 19]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	3.5 (0.5)	3.5 (0.2)	NDA	0.0 (–1.1 to 1.1)
NAIA/B2008[a]	[*N* = NDA; *R* = NDA]		[*N* = NDA; *R* = NDA]	
Published	NDA		NDA	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 39; *R* = 16]	[*N* = 37; *R* = 25]		
Published	NDA	NDA		NDA
Published re-analysis	>12.5 (NDA)	7.0 (1.2)		NDA
NAIA3002	[*N* = 60; *R* = 39]	[*N* = 49; *R* = 30]		
Published	NDA	NDA		NDA
Published re-analysis	9.5 (1.1)	11.0 (3.3)		1.5 (–5.3 to 8.3)
NAIB3002	[*N* = 19; *R* = 11]	[*N* = 13; *R* = 11]		
Published	NDA	NDA		NDA
Published re-analysis	14.5 (5.9)	9.0 (0.9)		–5.5 (–17.1 to 6.1)
NAI30008	[*N* = 263; *R* = 201]	[*N* = 262; *R* = 200]		
Published	NDA	NDA		NDA
Published re-analysis	9.0 (0.6)	8.5 (0.5)		–0.5 (–2.0 to 1.0)
NAI30010	[*N* = 11; *R* = 10]	[*N* = 10; *R* = 8]		
Published	NDA	NDA		NDA
Published re-analysis	4.0 (1.7)	5.5 (0.9)		1.5 (–2.2 to 5.2)
Pooled meta-analysis result				–0.1 (–1.0 to 0.8)

NDA, no data available; *N*, no. of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.

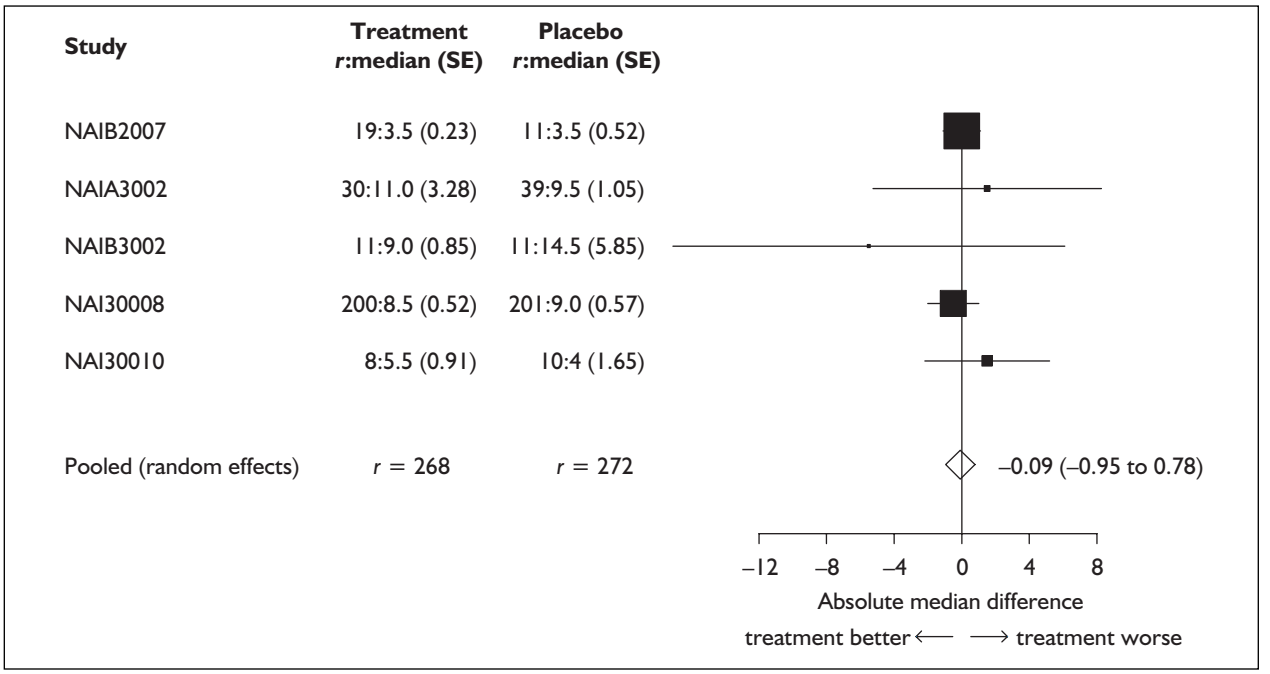

FIGURE 16 *Time to return to normal activities. ITT 'at risk' including over 65-year-olds. Estimates with 95% CIs.*

TABLE 28 *Median number of days to return to normal activities for 'high-risk' individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
NAIB2007	[*N* = 17; *R* = 8]	[*N* = 17; *R* = 13]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	3.5 (0.5)	3.5 (0.2)	NDA	0.0 (–1.0 to 1.0)
NAIA/B2008[a]	[*N* = NDA; *R* = NDA]		[*N* = NDA; *R* = NDA]	
Published	NDA		NDA	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 28; *R* = 11]	[*N* = 24; *R* = 18]		
Published	NDA	NDA		NDA
Published re-analysis	>12.5 (NDA)	7.0 (1.2)		NDA
NAIA3002	[*N* = 43; *R* = 28]	[*N* = 36; *R* = 22]		
Published	NDA	NDA		NDA
Published re-analysis	9.5 (1.6)	11.0 (3.3)		1.5 (–5.7 to 8.7)
NAIB3002	[*N* = 18; *R* = 11]	[*N* = 12; *R* = 10]		
Published	NDA	NDA		NDA
Published re-analysis	14.5 (6.1)	8.5 (1.1)		–6.0 (–18.1 to 6.1)
NAI30008	[*N* = 153; *R* = 120]	[*N* = 160; *R* = 125]		
Published	NDA	NDA		NDA
Published re-analysis	9.0 (0.8)	8.5 (0.6)		–0.5 (–2.5 to 1.5)
NAI30010	[*N* = 6; *R* = 5]	[*N* = 4; *R* = 3]		
Published	NDA	NDA		NDA
Published re-analysis	16.5 (6.1)	6.0 (0.4)		–10.5 (–22.5 to 1.5)
Pooled meta-analysis result				–0.2 (–1.2 to 0.8)

NDA, no data available; *N*, no. of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.

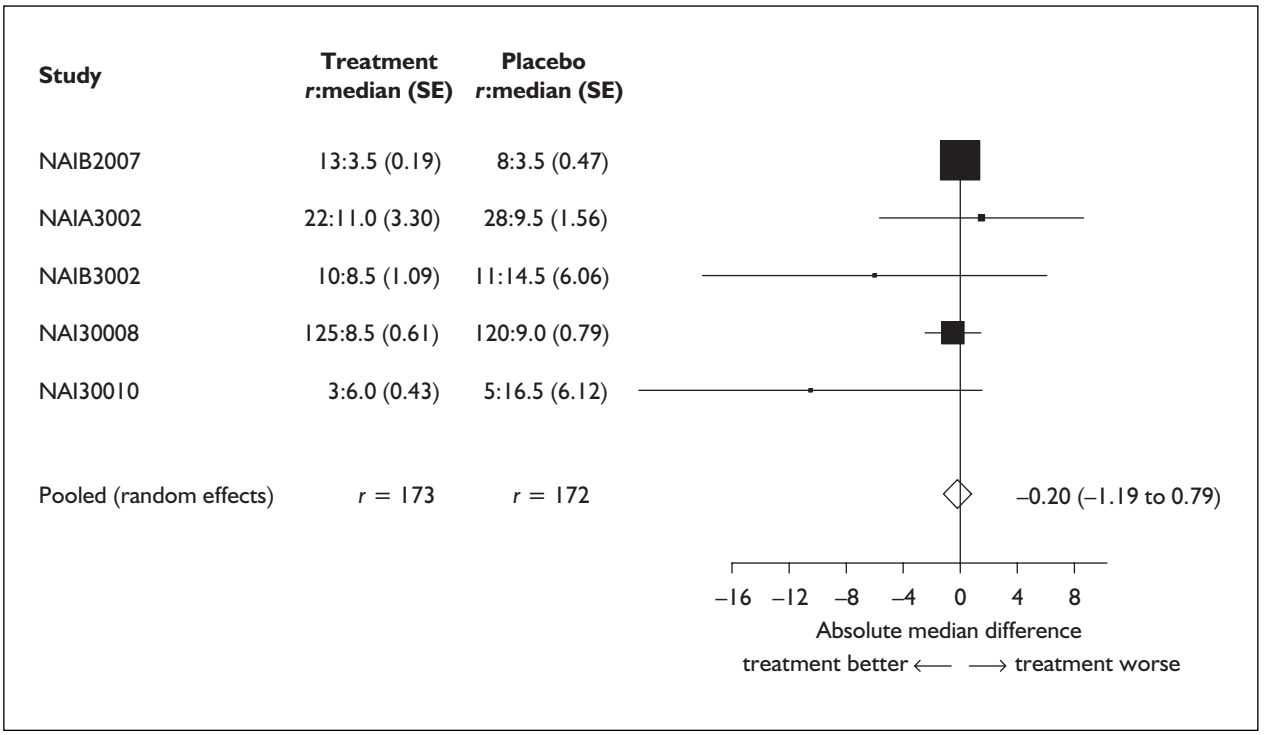

FIGURE 17 *Time to return to normal activities. Influenza positive 'at-risk' including over 65-years-olds. Estimates with 95% CIs.*

TABLE 29 *Median number of days to return to normal activities for children in the zanamivir treatment trials. (ITT group)*

Trial	Placebo			Inhaled 10 mg b.d.			Inhaled 10 mg b.d. vs placebo
NAI30009	***N***	***R***	**Median (SE)**	***N***	***R***	**Median (SE)**	**Median difference (95%CI)**
'Healthy'							
Published	233	200	NDA	202	184	NDA	NDA
Published re-analysis	233	200	6.0 (0.3)	202	184	5.5 (0.3)	–0.5 (–1.3 to 0.3)
'High-risk'							
Published	14	11	NDA	22	21	NDA	NDA
Published re-analysis	14	11	7.0 (0.5)	22	21	6.0 (1.2)	–1.0 (–3.5 to 1.5)

NDA, no data available; *N*, no. of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

Children aged 5–12 years in the zanamivir treatment trials (ITT). *Table 29* reports the median time to return to normal activities in days and the difference between the placebo group and inhaled 10 mg twice-daily group for both the 'healthy' and 'high-risk' subgroups of individuals. The results show a difference in the time to return to normal activities in the treatment group compared with the placebo group of –0.5 days (95% CI –1.3 to 0.3) for the 'healthy' subgroup and –1.0 days (95% CI –3.5 to 1.5) for the 'high-risk' subgroup. Note the small number of individuals in the 'high-risk' subgroup.

Children aged ≤ 12 years in the zanamivir treatment trials (influenza positive). *Table 30* reports the median time to return to normal activities in days and the difference between the placebo group and inhaled 10 mg twice-daily group for both the 'healthy' and 'high-risk' subgroups of individuals. The results show a difference in the time to return to normal activities in the treatment group compared with the placebo group of –0.5 days (95% CI –1.4 to 0.4) for the 'healthy' subgroup and –2.5 days (95% CI –4.4 to –0.6) for the 'high-risk' subgroup. Note again the small number of individuals in the 'high-risk' subgroup.

TABLE 30 *Median number of days to return to normal activities for children in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo			Inhaled 10 mg b.d.			Inhaled 10 mg b.d. vs placebo
NAI30009	***N***	***R***	**Median (SE)**	***N***	***R***	**Median (SE)**	**Median difference (95%CI)**
'Healthy'							
Published	172	147	NDA	154	139	NDA	NDA
Published re-analysis	172	147	6.0 (0.3)	154	139	5.5 (0.3)	–0.5 (–1.4 to 0.4)
'High-risk'							
Published	10	8	NDA	12	12	NDA	NDA
Published re-analysis	10	8	7.0 (0.4)	12	12	4.5 (0.9)	–2.5 (–4.4 to –0.6)

NDA, no data available; *N*, no. of individuals; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

TABLE 31 *Median number of days to return to normal activities for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median (SE)**	**Median difference (95% CI) *p*-value**
NAIA/B2005	[*N* = 144; *R* = 129]	[*N* = 132; *R* = 121]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)
NAIB2007	[*N* = 183; *R* = 99]	[*N* = 188; *R* = 113]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)
NAIA/B2008[a]	[*N* = 422; *R* = NDA]		[*N* = 415; *R* = NDA]	
Published	6.0 (NDA)		5.0 (NDA)	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 228; *R* = 144]	[*N* = 227; *R* = 175]		–2.0 (–4.0 to 0.0);
Published	9.0 (NDA)	7.0 (NDA)		$p < 0.001$
Published re-analysis	8.0 (0.5)	7.0 (0.3)		–1.0 (–2.1 to 0.1)
NAIA3002	[*N* = 365; *R* = 272]	[*N* = 412; *R* = 322]		
Published	NDA	NDA		NDA
Published re-analysis	7.0 (0.3)	7.0 (0.3)		0.0 (–0.8 to 0.8)
NAIB3002	[*N* = 182; *R* = 124]	[*N* = 174; *R* = 134]		–1.5 (–4.0 to 0.0);
Published	8.5 (NDA)	7.0 (NDA)		$p = 0.025$
Published re-analysis	8.5 (0.6)	6.5 (0.4)		–2.0 (3.4 to –0.6)
NAI30008	[*N* = 263; *R* = 201]	[*N* = 262; *R* = 200]		
Published	NDA	NDA		NDA
Published re-analysis	9.0 (0.6)	8.5 (0.5)		–0.5 (–2.0 to 1.0)
NAI30009	[*N* = 247; *R* = 211]	[*N* = 224; *R* = 205]		–1.0 (NDA);
Published	NDA	NDA		$p = 0.019$
Published re-analysis	6.0 (0.3)	5.5 (0.3)		–0.5 (–1.2 to 0.2)
NAI30010	[*N* = 158; *R* = 153]	[*N* = 163; *R* = 156]		
Published	NDA	NDA		NDA
Published re-analysis	4.5 (0.3)	4.0 (0.3)		–0.5 (–1.3 to 0.3)
Pooled meta-analysis result				–0.4 (–0.7 to 0.0)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal (*N* = 415): median 4.5 [difference = –1.5; $p < 0.001$].

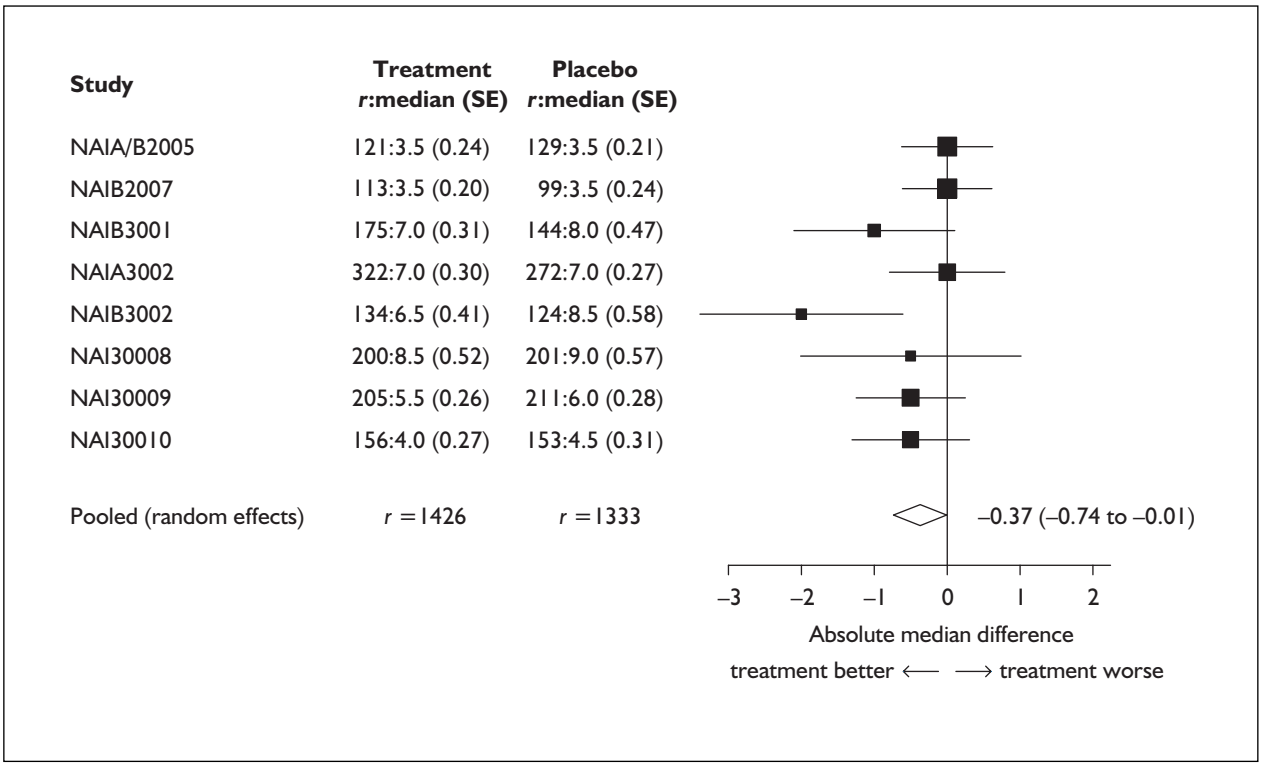

FIGURE 18 *Time to return to normal activities (random effects). Influenza positive, all data ('non-risk' and 'at-risk'). Estimates with 95% CIs.*

All ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (ITT). *Table 31* reports the median time to return to normal activities in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 18* displays the results from the random effects meta-analysis, which shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –0.37 days (95% CI –0.74 to –0.01).

All ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive). *Table 32* reports the median time to return to normal activities in days and the difference between the placebo group and inhaled 10 mg twice-daily group. *Figure 19* displays the results from the random effects meta-analysis, which shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –0.37 days (95% CI –0.72 to –0.02).

Sensitivity analysis. Sensitivity analyses were performed to test the robustness of the meta-analyses results reported above to differential study quality (excluding studies with a Jadad score of <4) and publication status (excluding unpublished trials). Although the magnitude of the results did change slightly, the direction of the pooled estimates for the difference between the interventions remained consistent.

Complications of influenza

Some data were available from the individual studies regarding the use of antibiotics for complications in those treated with zanamivir compared with those receiving placebo, but this was limited. However, two previous pooled analyses of these data were available[489,500] and are summarised below.

Monto and colleagues[489] performed a pooled/marginal analysis by combining the number of individuals requiring antibiotics for complications from each of the following trials for each arm of the trial: NAIA/B2005, NAIB2007, NAIA/B2008, NAIB3001, NAIA3002 and NAIB3002. *Table 33* shows a reduction in the complications requiring the use of antibiotics in the zanamivir group, which is statistically significant for ITT all individuals and influenza positive 'healthy' individuals.

A more recent study[500] performed a similar analysis focusing on the 'high-risk' individuals (children and adults combined) recruited into the trials. This analysis used data from NAIB2007,

TABLE 32 *Median number of days to return to normal activities for all ('high-risk' and 'healthy') individuals in the zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. and intranasal	Inhaled 10 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI) *p*-value
NAIA/B2005	[*N* = 89; *R* = 78]	[*N* = 85; *R* = 76]	[*N* = NDA; *R* = NDA]	
Published	4.0 (NDA)	4.0 (NDA)	NDA	0.0 (NDA)
Published re-analysis	3.5 (0.3)	3.5 (0.4)	NDA	0.0 (–0.9 to 0.9)
NAIB2007	[*N* = 118; *R* = 61]	[*N* = 113; *R* = 65]	[*N* = NDA; *R* = NDA]	
Published	NDA	NDA	NDA	NDA
Published re-analysis	3.5 (0.2)	3.5 (0.2)	NDA	0.0 (–0.6 to 0.6)
NAIA/B2008[a]	[*N* = 240; *R* = NDA]		[*N* = NDA; *R* = NDA]	
Published	NDA		NDA	
Published re-analysis	NDA		NDA	
NAIB3001	[*N* = 160; *R* = 104]	[*N* = 161; *R* = 130]		–2.0 (–4.0 to –0.3);
Published	9.0 (NDA)	<7.0 (NDA)		*p* < 0.001
Published re-analysis	8.0 (0.8)	7.0 (0.3)		–1.0 (–2.6 to 0.6)
NAIA3002	[*N* = 257; *R* = 193]	[*N* = 312; *R* = 244]		
Published	NDA	NDA		NDA
Published re-analysis	7.0 (0.4)	7.0 (0.3)		0.0 (–0.9 to 0.9)
NAIB3002	[*N* = 141; *R* = 98]	[*N* = 136; *R* = 106]		
Published	NDA	NDA		NDA
Published re-analysis	8.5 (0.6)	7.0 (0.5)		–1.5 (–3.0 to 0.0)
NAI30008	[*N* = 153; *R* = 120]	[*N* = 160; *R* = 125]		
Published	NDA	NDA		NDA
Published re-analysis	9.0 (0.8)	8.5 (0.6)		–0.5 (–2.5 to 1.5)
NAI30009	[*N* = 182; *R* = 155]	[*N* = 164; *R* = 151]		–1.0 (NDA);
Published	NDA	NDA		*p* = 0.022
Published re-analysis	6.0 (0.3)	5.5 (0.3)		–0.5 (–1.3 to 0.3)
NAI30010	[*N* = 81; *R* = 79]	[*N* = 76; *R* = 74]		
Published	NDA	NDA		NDA
Published re-analysis	5.5 (0.3)	4.5 (0.4)		–1.0 (–1.9 to –0.1)
Pooled meta-analysis result				–0.4 (–0.7 to 0.0)

NDA, no data available; *N*, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Also compared with 40 mg inhaled + 25.6 mg intranasal: no data available.

NAIB3001, NAIA3002, NAIB3002, NAI30009 and NAI30010 and observed similar results (*Table 34*).

From the single children trial (NAI30009), the number of individuals with complications requiring use of antibiotics in those confirmed as influenza positive was 27 out of 182 (15%) for the placebo group compared with 20 out of 164 (12%) for the treatment group.

The data used in the economic model are highlighted in bold in *Tables 33* and *34*. Note that although data in *Table 34* are more up-to-date than those in *Table 33*, they are limited to high-risk individuals and therefore it was necessary to rely on the results in *Table 33* for 'healthy' individuals. Antibiotics use for children was taken from trial NAI30009 as reported above.

A severe complication of influenza is pneumonia. Unfortunately, only limited information on this outcome was available from individual trial reports, but a previously published marginal pooled analysis[501] did report clinically confirmed pneumonia for a combined analysis of trials NAIB2007, NAIB3001, NAIA3002, NAIB3002, NAI30009 and NAI30010. The results of this are reported in *Table 35*. Note: a common complication of influenza in young children is otitis media, but this outcome was not reported in the trials.

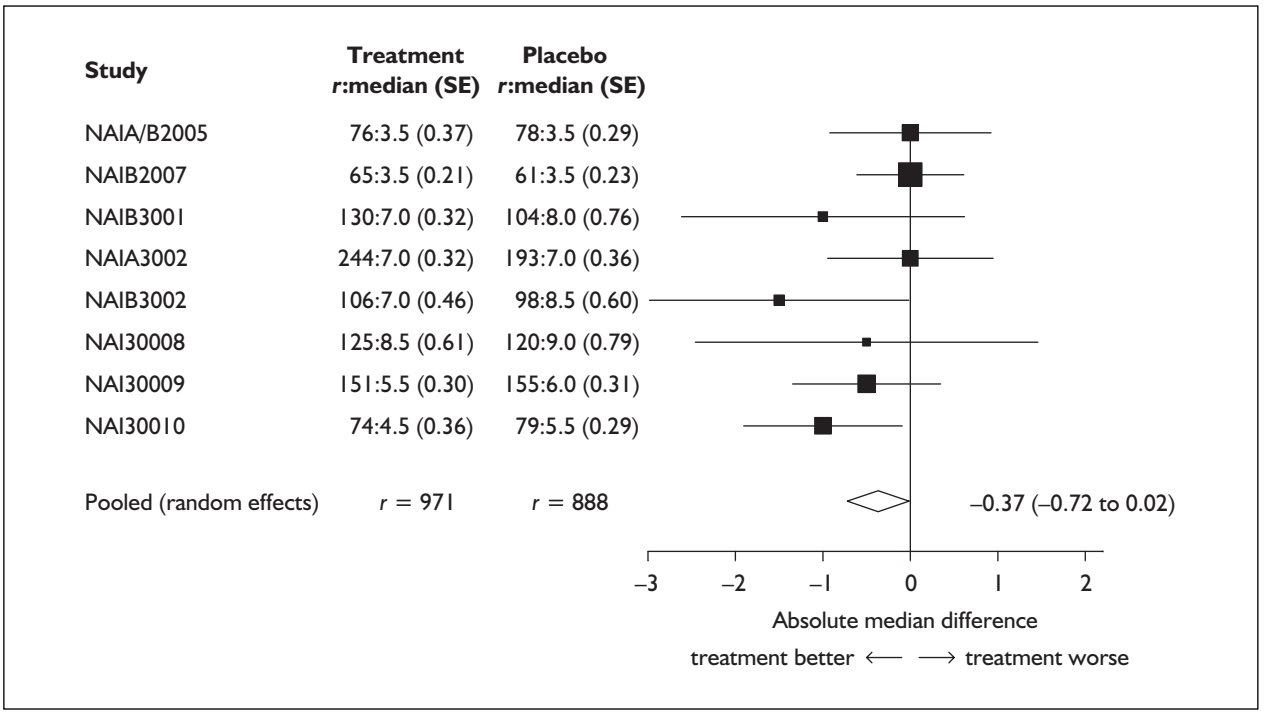

FIGURE 19 *Time to return to normal activities (random effects). Influenza positive, all data ('non-risk' and 'at-risk'). Estimates with 95% CIs.*

TABLE 33 *Complications requiring use of antibiotics*[489]

	Placebo		Zanamivir (10 mg inhaled b.d.)		
	N	**Antibiotics used**	***N***	**Antibiotics used**	**OR (95 CI)**
ITT, all	1102	196 (18%)	1133	151 (13%)	0.71 (0.56 to 0.90)
Influenza positive, all	765	139 (18%)	807	105 (13%)	0.82 (0.61 to 1.10)
Influenza positive, 'healthy'	**659**	**114 (17%)**	**718**	**92 (13%)**	**0.70 (0.52 to 0.96)**
Influenza positive, 'high-risk'	106	25 (24%)	89	13 (15%)	0.55 (0.24 to 1.23)

TABLE 34 *Complications requiring use of antibiotics*[500]

	Placebo		Zanamivir (10 mg inhaled b.d.)		
	N	**Antibiotics used**	***N***	**Antibiotics used**	**OR (95 CI)**
ITT, 'high-risk'	167	41 (25%)	154	24 (16%)	0.57 (0.31 to 1.03)
Influenza positive 'high-risk'	**122**	**29 (24%)**	**105**	**14 (13%)**	**0.49 (0.23 to 1.04)**

Hospitalisations

Very few data were obtained regarding hospitalisation rates within the trials from the published literature. In the 'high-risk' study NAI30008,[492] three out of 261 individuals in the treatment arm compared with two out of 263 in the placebo arm were hospitalised during the follow-up period of the trial.

GlaxoWellcome reported in their NICE submission in 2000[501] that although data on hospitalisations were not collected routinely as part of the patient case record form, they were noted in the serious adverse event forms reported by investigators. Twelve hospitalisations were identified in this way from trials NAIB2007, NAIB3001, NAIA3002, NAIB3002, NAI30009 and NAI30010 collectively,

TABLE 35 *Number of individuals developing pneumonia*[501]

	Placebo		Zanamivir (10 mg inhaled b.d.)		
	N	**Pneumonia**	***N***	**Pneumonia**	**OR (95% CI)**
ITT, all[a]	1507	22 (1%)	1520	11 (<1%)	0.49 (0.21 to 1.06)
ITT, 'high-risk[a]'	167	6 (4%)	154	5 (3%)	0.90 (0.21 to 3.62)
Influenza positive, all[a]	1028	16 (2%)	1047	7 (<1%)	0.43 (0.15 to 1.10)
Influenza positive, 'high-risk[a]'	122	5 (4%)	105	3 (3%)	0.69 (0.10 to 3.64)
Influenza positive, children	182	2 (<1%)	164	1 (<1%)	0.55 (0.01 to 10.72)

[a] Includes trials NAIB2007, NAIB3001, NAIA3002, NAIB3002, NAI30009 and NAI30010.

TABLE 36 *Median number of hours to the alleviation of symptoms for 'healthy' individuals in the oseltamivir treatment trials (ITT group)*

Trial	**Placebo**	**75 mg b.d.**	**150 mg b.d.**	**75 mg b.d. vs placebo**
	Median (SE)	**Median (SE)**	**Median (SE)**	**Median difference (95% CI)**
WV15670	[*N* = 235; *R* = 191] 116.1 (7.6)	[*N* = 240; *R* = 211] 97.6 (9.9)	[*N* = 241; *R* = 213] 89.4 (6.0)	–18.5 (–43.0 to 6.0)
WV15671	[*N* = 200; *R* = 178] 97.0 (5.3)	[*N* = 204;*R* = 182] 76.3 (6.4)	[*N* = 202; *R* = 179] 74.3 (4.0)	–20.7 (–37.0 to –4.4)
WV15730[a]	[*N* = 27; *R* = 21] 109.8 (31.2)	[*N* = 31; *R* = 27] 74.5 (7.2)		–35.3 (–98.5 to 27.8)
Above 3 studies combined	[*N* = 462; *R* = 390] 105.3 (5.0)	[*N* = 475; *R* = 420] 83.2 (4.3)	[*N* = 443;*R* = 392] 81.0 (4.5)	
Pooled meta-analysis result				–20.7 (–34.0 to –7.4)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished study.

which may have been linked to the influenza infection (i.e. excluding elective/planned admissions). Of these 12 hospitalisations, six influenza-related hospitalisations were reported in the zanamivir group and six in the placebo group. Six of the 12 hospitalisations occurred in the 'high-risk' population (four in the zanamivir group and two in the placebo group).

Note: hospitalisations incurred as a secondary complication of influenza are not easily separated from hospitalisations for other causes.

Adverse events

As discussed previously, the definition of adverse events varied between trials, and was often difficult to separate from certain complications. Therefore, adverse events data for the economic model were obtained from trials designed to evaluate the prophylactic use of NIs for the prevention of influenza (see Chapter 4).

Oseltamivir

For time to event outcomes the estimate of the median time allows for censored observations. For each subgroup, the difference between the placebo group and the dosage licensed (75 mg twice-daily group) is reported. Where other dosage levels were evaluated in a trial these data were also reported for completeness, although no formal comparisons were made. It is important to note that the times to outcome end-points are measured in hours. Since these are calculated from diary entries completed twice daily by study participants, they are always rounded upwards to the nearest hour.

Time to symptoms alleviated

'Healthy' individuals (aged 12–65 years) in the Oseltamivir treatment trials (ITT). *Table 36* reports the median time to symptoms alleviated in hours and the difference between the placebo group and 75 mg twice daily group. *Figure 20* displays the results from the random effects meta-analysis,

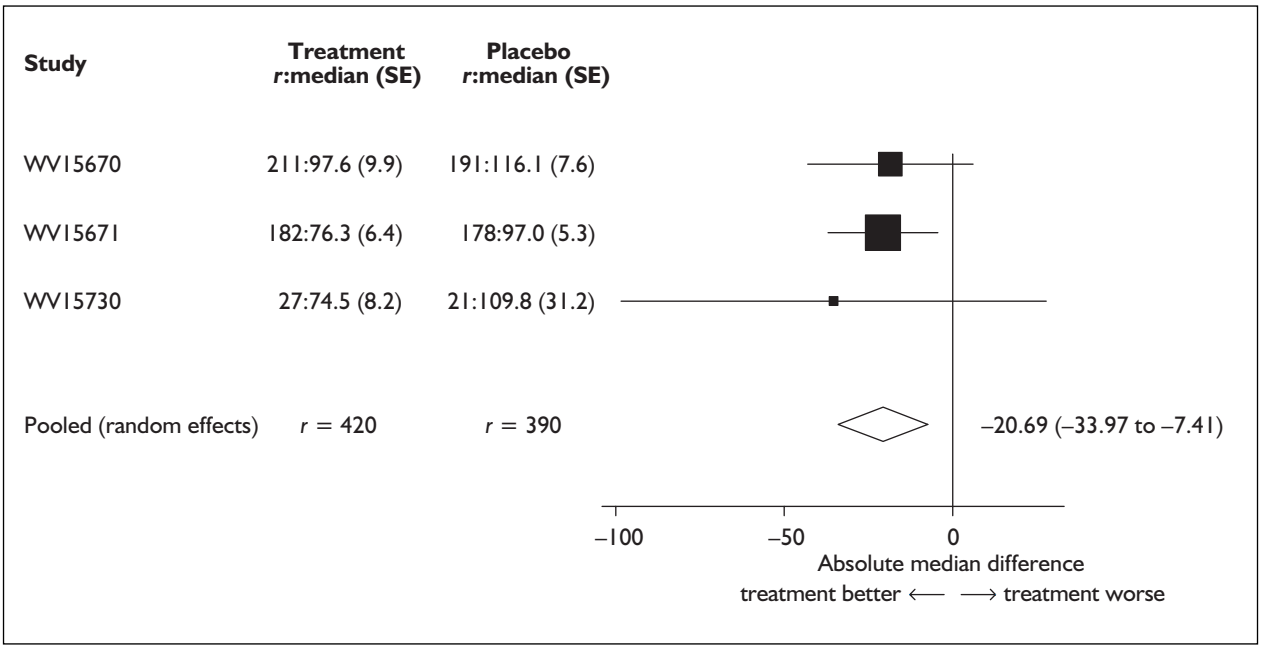

FIGURE 20 *Median time to symptoms alleviated in hours (random effects). ITT 'non-risk' 12–65 years-olds. Estimates with 95% CIs*

TABLE 37 *Median number of hours to the alleviation of symptoms for 'healthy' individuals in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	150 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
WV15670	[*N* = 161; *R* = 133] 116.5 (8.5)	[*N* = 157; *R* = 140] 87.4 (7.8)	[*N* = 155; *R* = 143] 81.8 (6.8)	–29.1 (–51.7 to –6.5)
WV15671	[*N* = 128; *R* = 113] 103.3 (7.9)	[*N* = 121; *R* = 112] 71.5 (5.6)	[*N* = 119; *R* = 107] 69.9 (6.2)	–31.8 (–50.7 to –12.8)
WV15730[a]	[*N* = 19; *R* = 15] 143.9 (24.8)	[*N* = 19; *R* = 17] 78.2 (10.6)		–65.8 (–118.7 to –12.8)
Above 3 studies combined	[*N* = 308; *R* = 261] 112.5 (4.9)	[*N* = 297; *R* = 269] 78.2 (3.9)	[*N* = 274; *R* = 250] 78.5 (5.3)	
Pooled meta-analysis result				–33.1 (–47.1 to –19.1)

N, no, of individuals in the study; *R* = no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished study.

which shows a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –20.69 hours (95% CI –33.97 to –7.41).

'Healthy' individuals (aged 12–65 years) in the oseltamivir treatment trials (influenza positive). *Table 37* reports the median time to symptoms alleviated in hours and the difference between the placebo group and 75 mg twice-daily group. *Figure 21* displays the results from the random effects meta-analysis, which shows a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –33.10 hours (95% CI –47.10 to –19.10).

'High-risk' individuals (aged ≥ 12 years) in the oseltamivir treatment trials (ITT). *Table 38* reports the median time to symptoms alleviated in hours and the difference between the placebo group and 75 mg twice-daily group. Owing to the design of the studies it was possible to sub-divide the 'high-

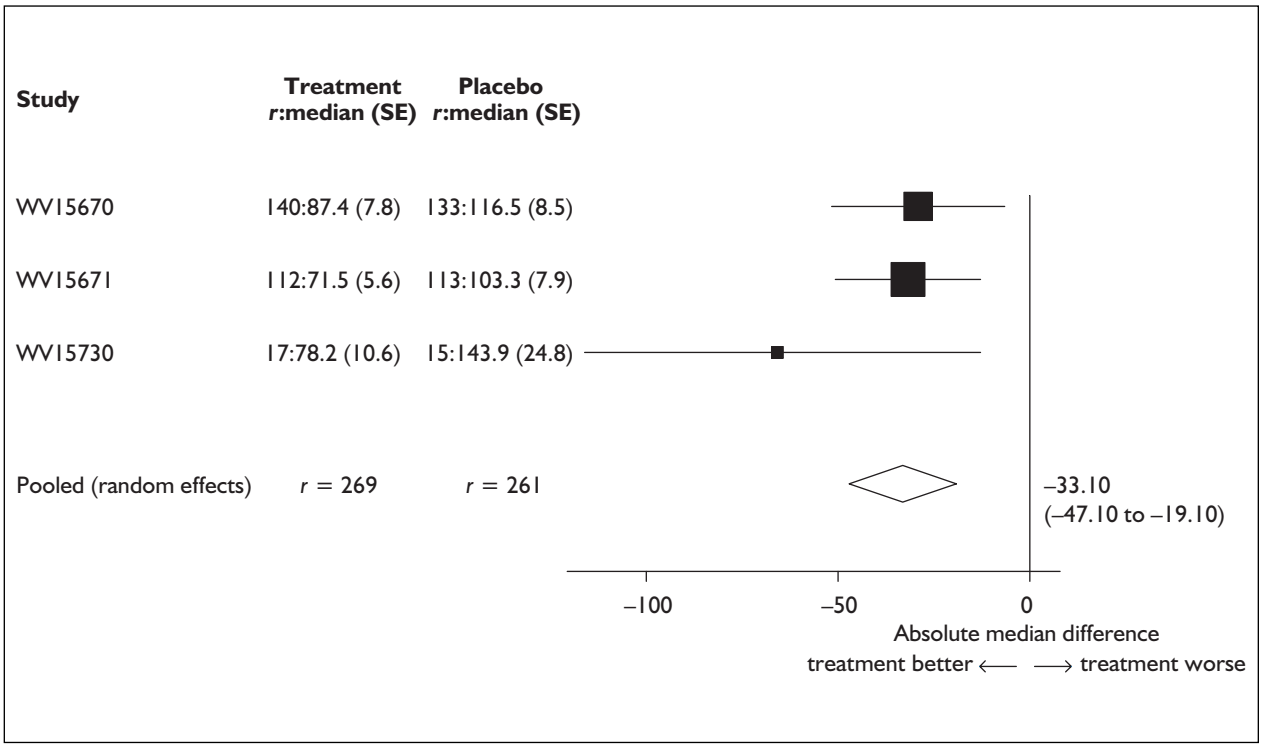

FIGURE 21 *Median time to symptoms alleviated in hours (random effects). Influenza positive 'non-risk' 12–65-year-olds. Estimates with 95% CIs.*

TABLE 38 *Median number of hours to the alleviation of symptoms for 'high-risk' individuals in the oseltamivir treatment trials (ITT group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median difference (95% CI)
WV15812[a]	[Omitted because commercial-in-confidence]		
WV15872[a]	[Omitted because commercial-in-confidence]		
Above 2 studies combined (chronic cardiac and/or respiratory)	[*N* = 202; *R* = 172] 163.0 (19.6)	[*N* = 199; *R* = 167] 143.0 (12.6)	
WV15819[a]	[Omitted because commercial-in-confidence]		
WV15876[a]	[Omitted because commercial-in-confidence]		
WV15978[a]	[Omitted because commercial-in-confidence]		
Above 3 studies combined (Otherwise healthy 65 years and older)	[*N* = 375; *R* = 331] 149.0 (13.2)	[*N* = 358; *R* = 312] 139.2 (12.2)	
Pooled meta-analysis result			–8.3 (–33.7 to 17.0)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished studies.

TABLE 39 *Median number of hours to the alleviation of symptoms for 'high-risk' individuals in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI)**
WV15812[a]	[Omitted because commercial-in-confidence]		
WV15872[a]	[Omitted because commercial-in-confidence]		
Above 2 studies combined (chronic cardiac and/or respiratory)	[*N* = 133; *R* = 113] 161.0 (24.2)	[*N* = 118; *R* = 97] 151.5 (22.6)	
WV15819[a]	[Omitted because commercial-in-confidence]		
WV15876[a]	[Omitted because commercial-in-confidence]		
WV15978[a]	[Omitted because commercial-in-confidence]		
Above 3 studies combined (Otherwise healthy 65 years and older)	[*N* = 254; *R* = 225] 174.9 (15.8)	[*N* = 223; *R* = 198] 150.0 (14.3)	
Pooled meta-analysis result			–10.9 (–45.0 to 23.2)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished studies.

FIGURE 22 *Omitted because forest plot of commercial-in-confidence data*

FIGURE 23 *Omitted because forest plot of commercial-in-confidence data*

risk' individuals further into those with chronic cardiac and/or respiratory conditions and those 65 years and older but otherwise 'healthy'. *Figure 22* displays the results from the random effects meta-analysis including the subgroups described above. It shows an overall difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –8.33 hours (95% CI –33.69 to 17.03) and hence not statistically significant at the 5% level.

'High-risk' individuals (aged ≥ 12 years) in the oseltamivir treatment trials (influenza positive). *Table 39* reports the median time to symptoms alleviated in hours and the difference between the placebo group and 75 mg twice-daily group. Owing to the design of the studies it was possible to sub-divide the 'high-risk' individuals further into those with chronic cardiac and/or respiratory conditions and those 65 years and older but otherwise 'healthy'. *Figure 23* displays the results from the random effects meta-analysis including the subgroups described above. It shows an overall difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –10.91 hours (95% CI –45.04 to 23.22) and hence not statistically significant at the 5% level.

Children aged 1–12 years (WV15758) (ITT). *Table 40* reports the median time to symptoms alleviated in hours and the difference between the placebo group and 75 mg twice-daily group for both the ITT and influenza positive populations. Note that there were no 'high-risk' individuals in this trial. The results show a difference in the time with symptoms alleviated in the treatment group compared with the placebo group of –20.9 hours (95% CI –35.7 to –6.1) for the ITT population and –35.8 hours (95% CI –53.3 to –18.2) for the influenza positive population.

All ('high-risk' and 'healthy') individuals in the oseltamivir treatment trials. For completeness, the median time to alleviation of symptoms in hours and the difference between the placebo group and

TABLE 40 *Median number of hours to the alleviation of symptoms for children in the oseltamivir treatment trials*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median difference (95% CI)
ITT	[*N* = 338; *R* = 319] 125.7 (5.1)	[*N* = 331; *R* = 310] 104.8 (5.6)	–20.9 (–35.7 to –6.1)
Influenza positive	[*N* = 225; *R* = 210] 137.0 (5.4)	[*N* = 209; *R* = 196] 101.3 (7.1)	–35.8 (–53.3 to –18.2)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

FIGURE 24 *Omitted because forest plot of commercial-in-confidence data*

FIGURE 25 *Omitted because forest plot of commercial-in-confidence data*

TABLE 41 *Median number of hours to return to normal activities for 'healthy' individuals in the oseltamivir treatment trials (ITT group)*

Trial	Placebo	75 mg b.d.	150 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
WV15670	[*N* = 234; *R* = 153] 173.0 (8.2)	[*N* = 240; *R* = 171] 132.4 (8.2)	[*N* = 241; *R* = 172] 150.0 (7.1)	–40.6 (–63.3 to –17.8)
WV15671	[*N* = 201; *R* = 135] 133.0 (7.8)	[*N* = 204; *R* = 164] 108.7 (7.0)	[*N* = 203; *R* = 148] 130.2 (7.7)	–24.3 (–44.8 to –3.7)
WV15730[a]	[*N* = 27; *R* = 14] 196.2 (36.3)	[*N* = 31; *R* = 18] 152.6 (24.8)		–43.6 (–129.8 to 42.6)
Above 3 studies combined	[*N* = 462; *R* = 302] 156.3 (5.4)	[*N* = 475; *R* = 353] 127.6 (5.1)	[*N* = 444; *R* = 320] 134.0 (5.2)	
Pooled meta-analysis result				–31.94 (–47.0 to –16.9)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished study.

75 mg twice-daily group for all individuals regardless of age and risk status are reported. No further tables are presented for this analysis since all the relevant information is provided in previous tables because no trial included more than one patient group type (e.g. 'healthy' and 'high-risk'). *Figures 24* and *25* display the results from the random effects meta-analysis, which show a difference in the time to symptoms alleviated in the treatment group compared with the placebo group of –19.15 hours (95% CI –28.36 to –9.94) for the ITT population and –31.98 hours (95% CI –42.40 to –21.56) for the influenza positive population.

Sensitivity analysis. Sensitivity analyses were performed to test the robustness of the meta-analyses results reported above to differential study quality (excluding studies with a Jadad score of <4) and publication status (excluding unpublished trials). For the 'healthy' group, both the magnitude and direction of the results remained consistent. None of the 'high-risk' studies had been published in peer-review journals and therefore no sensitivity analyses could be performed on publication status. As only two of the 'high-risk' studies were issued a Jadad quality rating of 4 or 5, the uncertainty around the pooled estimate increased but the overall conclusions remained the same (no statistically significant difference between treatment and no treatment)

Time to return to normal activities

'Healthy' individuals (aged 12–65 years) in the oseltamivir treatment trials (ITT). *Table 41* reports

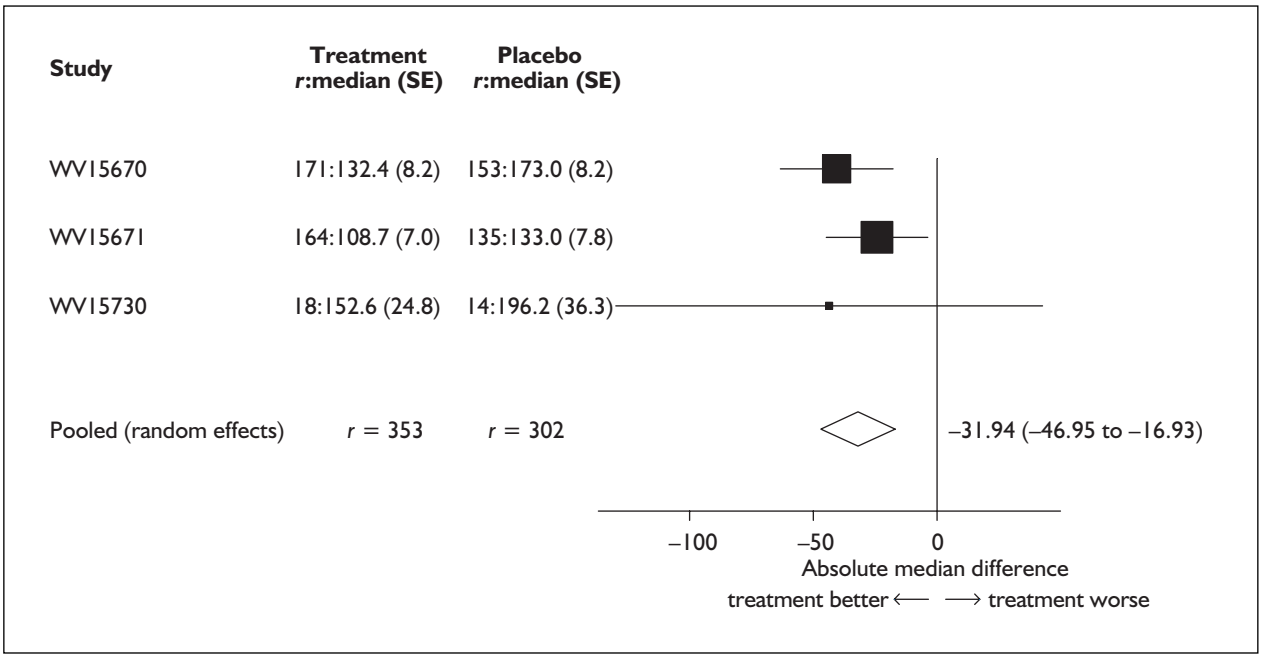

FIGURE 26 *Median time to return to normal in hours (random effects). ITT 'non-risk' 12–65-year-olds. Estimates with 95% CIs.*

TABLE 42 *Median number of hours to return to normal activities for 'healthy' individuals in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	150 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	Median (SE)	Median (SE)	Median difference (95% CI)
WV15670	[*N* = 161; *R* = 103] 174.2 (9.0)	[*N* = 157; *R* = 119] 127.1 (9.1)	[*N* = 155; *R* = 112] 133.5 (8.2)	–47.2 (–72.2 to –22.2)
WV15671	[*N* = 128; *R* = 90] 134.2 (8.8)	[*N* = 121; *R* = 106] 107.8 (1.5)	[*N* = 120; *R* = 89] 127.2 (10.0)	–26.3 (–43.9 to –8.8)
WV15730[a]	[*N* = 19; *R* = 9] 218.7 (36.1)	[*N* = 19; *R* = 13] 130.7 (17.4)		–88.0 (–166.5 to –9.5)
Above 3 studies combined	[*N* = 308; *R* = 202] 156.3 (6.6)	[*N* = 297; *R* = 238] 125.7 (5.4)	[*N* = 275; *R* = 201] 131.3 (3.3)	
Pooled meta-analysis result				–39.3 (–62.0 to –16.6)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished study.

the median time to return to normal activities in hours and the difference between the placebo group and 75 mg twice-daily group. *Figure 26* displays the results from the random effects meta-analysis, which shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –31.94 hours (95% CI –46.95 to –16.93).

'Healthy' individuals (aged 12–65 years) in the oseltamivir treatment trials (influenza positive).

Table 42 reports the median time to return to normal activities in hours and the difference between the placebo group and 75 mg twice-daily group. *Figure 27* displays the results from the random effects meta-analysis, which shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –39.28 hours (95% CI –61.97 to –16.59).

'High-risk' individuals (aged ≥ 12 years) in the oseltamivir treatment trials (ITT). *Table 43* reports

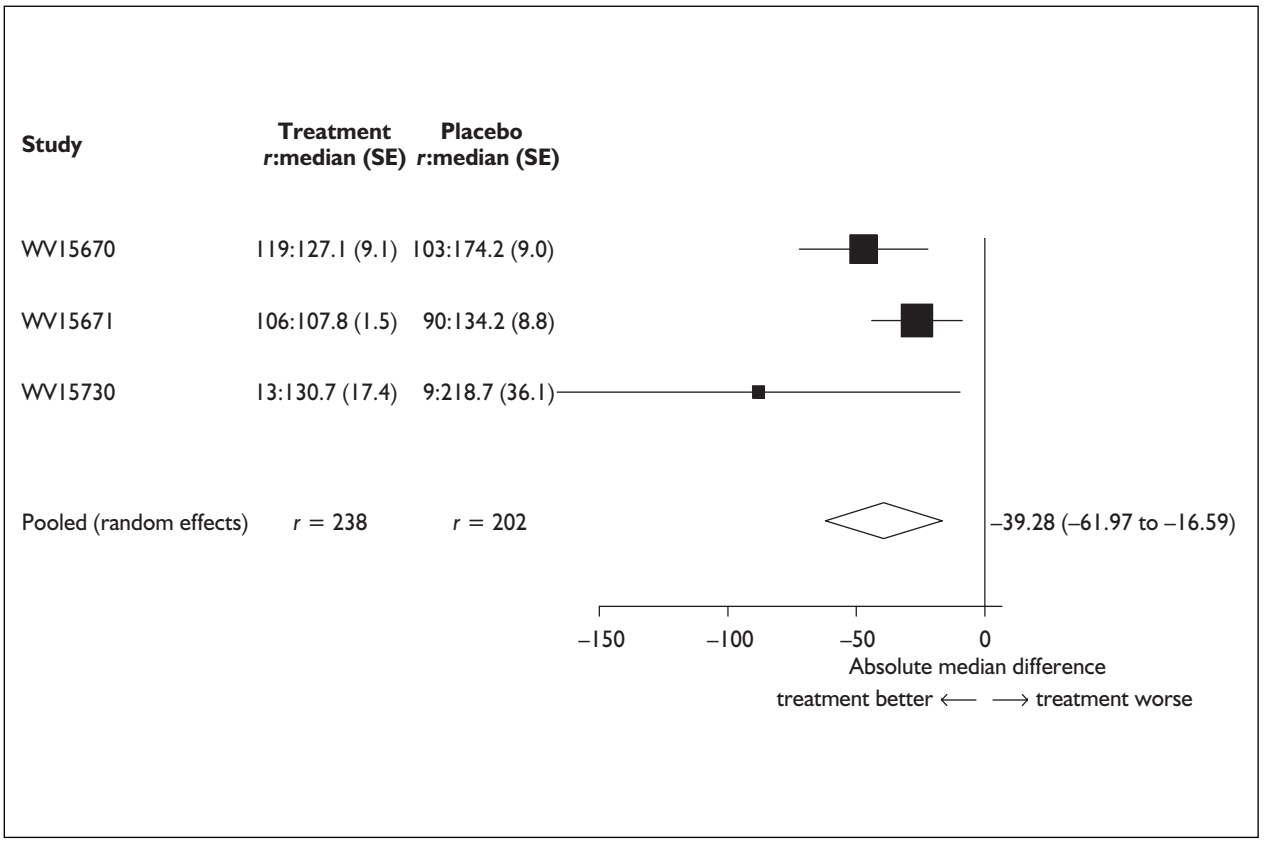

FIGURE 27 *Median time to return to normal in hours (random effects). Influenza positive 'non-risk' 12–65-year-olds. Estimates with 95% CIs.*

TABLE 43 *Median number of hours to return to normal activities for 'high-risk' individuals in the oseltamivir treatment trials (ITT group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI)**
WV15812[a]	[Omitted because commercial-in-confidence]		
WV15872[a]	[Omitted because commercial-in-confidence]		
Above 2 studies	[*N* = 201; *R* = 140]	[*N* = 199; *R* = 126]	
combined	293.2 (40.0)	299.0 (51.5)	
WV15819[a]	[Omitted because commercial-in-confidence]		
WV15876[a]	[Omitted because commercial-in-confidence]		
WV15978[a]	[Omitted because commercial-in-confidence]		
Above 3 studies combined	[*N* = 375; *R* = 236] 412.4 (18.7)	[*N* = 359; *R* = 243] 317.0 (27.9)	
Pooled meta-analysis result			–58.9 (–116.6 to –1.1)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished studies.

TABLE 44 *Median number of hours to to return to normal activities for 'high-risk' individuals in the oseltamivir treatment trials (influenza positive group)*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI)**
WV15812[a] WV15872[a]	[Omitted because [commercial-in-confidence]		
Above 2 studies combined	[*N* = 133; *R* = 89] 321.2 (41.9)	[*N* = 118; *R* = 77] 278.1 (41.0)	
WV15819[a]	[Omitted because commercial-in-confidence]		
WV15876[a]	[Omitted because commercial-in-confidence]		
WV15978[a]	[Omitted because commercial-in-confidence]		
Above 3 studies combined	[*N* = 223; *R* = 150] 397.0 (21.3)	[*N* = 254; *R* = 164] 388.1 (42.7)	
Pooled meta-analysis result			–72.0 (–141.0 to –3.0)

N, no, of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).
[a] Unpublished studies.

FIGURE 28 *Omitted because forest plot of commercial-in-confidence data*

FIGURE 29 *Omitted because forest plot of commercial-in-confidence data*

the median time to return to normal activities in hours and the difference between the placebo group and 75 mg twice–daily group. Owing to the design of the studies it was possible to sub-divide the 'high-risk' individuals further into those with chronic cardiac and/or respiratory conditions and those 65 years and older but otherwise 'healthy'. *Figure 28* displays the results from the random effects meta-analysis including the subgroups described above. It shows an overall difference in the time to return to normal activities in the treatment group compared with the placebo group of –58.85 hours (95% CI –116.59 to –1.11).

'High-risk' individuals (aged ≥ 12 years) in the oseltamivir treatment trials (influenza positive). *Table 44* reports the median time to return to normal activities in hours and the difference between the placebo group and 75 mg twice-daily group. Owing to the design of the studies it was possible to sub-divide the 'high-risk' individuals further into those with chronic cardiac and/or respiratory conditions and those 65 years and older but otherwise 'healthy'. *Figure 29* displays the results from the random effects meta-analysis including the subgroups described above. It shows an overall difference in the time to return to normal activities in the treatment group compared with the placebo group of –72.02 hours (95% CI –141.02 to –3.02).

Children aged 1–12 years (WV15758). *Table 45* reports the median time to return to normal health and activities in hours and the difference between the placebo group and 75 mg twice-daily group for both the ITT and influenza positive populations. The results shows a difference in the time to return to normal activities in the treatment group compared with the placebo group of –30.1 hours (95% CI –43.3 to –16.8) for the ITT population and –44.6 hours (95% CI –63.7 to –25.4) for the influenza positive population.

All ('high-risk' and 'healthy') individuals in the oseltamivir treatment trials. For completeness, the median time to return to normal activities in hours and the difference between the placebo group and 75 mg twice-daily group for all individuals regardless of age and risk status are reported. No further tables are presented for this analysis since all the relevant information is provided in previous tables because no trial

TABLE 45 *Median number of hours to return to normal health and activities for children in the oseltamivir treatment trials*

Trial	Placebo	75 mg b.d.	75 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI)**
ITT	[*N* = 338; *R* = 325] 100.1 (5.3)	[*N* = 331; *R* = 319] 70.0 (4.3)	–30.1 (–43.3 to –16.8)
Influenza positive	[*N* = 225; *R* = 204] 111.7 (7.5)	[*N* = 209; *R* = 204] 67.1 (6.3)	–44.6 (–63.7 to –25.4)

N, no. of individuals in the study; *R*, no. of events (i.e. no. of individuals whose symptoms are alleviated by the end of the study).

FIGURE 30 *Omitted because forest plot of commercial-in-confidence data*

FIGURE 31 *Omitted because forest plot of commercial-in-confidence data*

included more than one patient group type (e.g. 'healthy' and 'high-risk'). *Figures 30* and *31* display the results from the random effects meta-analysis, which show a difference in the time to return to normal activities in the treatment group compared to the placebo group of –31.70 hours (95% CI –41.50 to –21.91) for the ITT population and –39.31 hours (95% CI –50.53 to –28.09) for the influenza positive population.

Sensitivity analysis. Sensitivity analyses were performed to test the robustness of the meta-analyses results reported above to differential study quality (excluding studies with a Jadad score of <4) and publication status (excluding unpublished trials). For the 'healthy' group, both the magnitude and direction of the results remained consistent. As for symptoms alleviated, since none of the 'high-risk' studies had been published in peer-review journals, no sensitivity analyses were possible on publication status. Also, as only two of the 'high-risk' studies were issued a Jadad quality rating of 4 or 5, the uncertainty around the pooled estimate increased but the overall conclusions remained unchanged.

Complications of influenza

Some data were available from the individual studies regarding the use of antibiotics for complications in those treated with oseltamivir compared with those receiving placebo but this was limited. One previous pooled analysis of these data [although limited to the lower respiratory tract complications (LRTCs) only] was available[496] and is summarised below.

Hoffman La Roche Pharmaceuticals[496] performed a pooled/marginal analysis by combining the number of individuals requiring antibiotics for LRCTs from each of the following trials for each arm of the trial: WV15707, M76001, WV15872, WV15812, WV15819, WV15876 and WV15978. *Table 46* shows a statistically significant reduction in the RTCs requiring antibiotics in the oseltamivir group.

Data on the use of antibiotics for complications in general were obtained from the published literature and are summarised in *Table 47*.

Data used in the economic model are highlighted in bold in *Tables 46* and *47*. Note that since no

TABLE 46 Lower respiratory tract complications requiring use of antibiotics[496]

	Placebo		Oseltamivir (75 mg b.d.)		
	N	**Antibiotics used**	***N***	**Antibiotics used**	**OR (95 CI)**
Influenza positive, 'healthy'	662	35 (5%)	982	17 (2%)	0.32 (0.16 to 0.59)
Influenza positive, 'high-risk'	**401**	**74 (18%)**	**368**	**45 (12%)**	**0.62 (0.40 to 0.94)**

TABLE 47 *Complications requiring use of antibiotics*

	Placebo		Oseltamivir (75 mg b.d.)		
	N	**Antibiotics used**	***N***	**Antibiotics used**	**OR (95 CI)**
Influenza positive, 'healthy'[a]	**290**	**22 (8%)**	**282**	**9 (3%)**	**0.40 (0.16 to 0.93)**
Influenza positive, children[b]	**235**	**97 (41%)**	**217**	**68 (31%)**	**0.65 (0.43 to 0.97)**

[a] Includes trials: WV15670 and WV15671.
[b] Trial WV15758.[499]

TABLE 48 *Number of individuals developing pneumonia*[496]

	Placebo		Oseltamivir (75 mg b.d.)		
	N	**Antibiotics used**	***N***	**Antibiotics used**	**OR (95 CI)**
Influenza positive, all	1063	19 (2%)	1350	9 (<1%)	0.37 (0.15 to 0.86)
Influenza positive, 'healthy'	662	9 (1%)	982	2 (<1%)	0.15 (0.06 to 0.72)
Influenza positive, 'high-risk'	401	10 (2%)	368	7 (2%)	0.76 (0.24 to 2.23)

[a] Includes trials: WV15670, WV15671, WV15730, WV15707, M76001, WV15872, WV15812, WV15819, WV15876 and WV15978.

TABLE 49 *Number of hospitalisations (influenza positive group)*

	Overall		'healthy'		'high-risk'	
STUDY	**Control**	**Treatment**	**Control**	**Treatment**	**Control**	**Treatment**
Possibly ILI related	1.1% 12/1063	0.4% 6/1350	0.5% 3/662	0.1% 1/982	2.2% 9/401	1.4% 5/368
All causes	1.7% 18/1063	0.7% 9/1350	0.8% 5/662	0.3% 3/982	3.2% 13/401	1.6% 6/368

data were available for all complications requiring the use of antibiotics for the 'high-risk' group, it was necessary to rely on LRTC data for this variable.

Information on clinically diagnosed pneumonia was only available from the two published studies WV15670 and WV15671, but a marginal pooled analysis[496] made available to ourselves did report clinically confirmed pneumonia for a combined analysis of trials WV15670, WV15671, WV15730, WV15707, M76001, WV15872, WV15812, WV15819, WV15876 and WV15978 and these results are reported in *Table 48*.

The study in children reported the complication otitis media for the influenza positive populations. There were 26 out of 217 children (12%) in the oseltamivir group and 50 out of 235 children (21%) in the placebo group (OR = 0.50, 95% CI 0.29 to 0.87) with clinically diagnosed otitis media.

Hospitalisations

Very few data were obtained regarding hospitalisation rates for individual trials, although one previous unpublished pooled analysis was made available to us.[496] The results of this pooled/marginal analysis are reported in *Table 49* and include data from studies WV15670, WV15671, WV15730, WV15707, M76001, WV15872, WV15812, WV15819, WV15876 and WV15978.

Note: hospitalisations incurred as a result of a secondary complication of influenza are not easily separated from hospitalisations for other causes.

TABLE 50 *Median symptoms alleviated, ITT population (in days)*

	Difference (treatment – placebo)	
Group	**Zanamivir Pooled estimate (95% CI)**	**Oseltamivir Pooled estimate (95% CI)**
'High-risk'	–0.93 (–1.90 to +0.05)	–0.35 (–1.40 to +0.71)
'Healthy'	–0.78 (–1.31 to –0.26)	–0.86 (–1.41 to -0.31)

TABLE 51 *Median symptoms alleviated, influenza positive population (in days)*

	Difference (treatment – placebo)	
Group	**Zanamivir Pooled estimate (95% CI)**	**Oseltamivir Pooled estimate (95% CI)**
'High-risk'	–1.99 (–3.08 to –0.90)	–0.45 (–1.88 to +0.97)
'Healthy'	–1.26 (–1.93 to –0.59)	–1.38 (–1.96 to –0.80)

TABLE 52 *Median return to normal activities, ITT population (in days)*

	Difference (treatment – placebo)	
Group	**Zanamivir Pooled estimate (95% CI)**	**Oseltamivir Pooled estimate (95% CI)**
'High-risk'	–0.09 (–0.95 to +0.78)	–2.45 (–4.86 to –0.05)
'Healthy'	–0.51 (–1.04 to +0.02)	–1.33 (–1.96 to –0.71)

TABLE 53 *Median return to normal activities, influenza positive population (in days)*

	Difference (treatment – placebo)	
Group	**Zanamivir Pooled estimate (95% CI)**	**Oseltamivir Pooled estimate (95% CI)**
'High-risk'	–0.20 (–1.19 to +0.79)	–3.00 (–5.88 to –0.13)
'Healthy'	–0.46 (–0.90 to –0.02)	–1.64 (–2.58 to –0.69)

Adverse events

As previously discussed, the definition of adverse events varied between trials, and they were often difficult to separate from certain complications. Therefore, adverse events data for the economic model were obtained from trials designed to evaluate the prophylactic use of NIs for the prevention of influenza (see Chapter 4).

Summary results for time to event outcomes

Tables 50–53 are summary tables of the median time to event outcomes data (i.e. median time to symptoms alleviated and median time to return to normal activities) for both zanamivir and oseltamivir. Note that for comparison all times are presented in days (i.e. oseltamivir data have been converted from hours to days). It can be observed that the median time to symptoms alleviated is fairly similar across drugs (except for 'high-risk' influenza positive individuals where the difference between groups is less for oseltamivir) but very different for median time to return to normal activities for all subgroups and populations (i.e. the estimate of the difference ranges from –0.51 to –0.09 days for zanamivir and from –3.00 to –1.33 days for oseltamivir).

TABLE 54 *Median difference in time to symptoms alleviated in days: comparison of previous systematic reviews*

		Patient groups (Influenza positive) Median difference (95% CI)		
Treatment	**Study**	**All**	**Healthy**	**'High-risk'**
Zanamivir	Burls *et al*. (2000)[2]	–1.38 (–1.93 to –0.84) *based on 5 trials*	NDA	–1.92 (–4.33 to +0.49) *based on 4 trials*
	This review (2002)	–1.26 (–1.61 to –0.90) *based on 7 trials*	–1.26 (–1.93 to –0.59) *based on 5 trials*	–1.99 (–3.08 to –0.90) *based on 5 trials*
Oseltamivir[a]	Husereau *et al*. (2001)[7]	NDA	–1.27 (–1.80 to +0.75) *based on 4 trials*	–0.71 (–3.18 to +1.76) *based on 2 trials*
	This review (2002)	–1.33 (–1.77 to –0.90) *based on 9 trials*	–1.38 (–1.96 to –0.80) *based on 3 trials*	–0.45 (–1.88 to +0.96) *based on 5 trials*
NIs combined	Jefferson *et al*. (2000)[3]	NDA	–0.90 (–1.63 to –0.17) *based on 1 trial*	NDA
	This review (2002)	–0.53 (–0.96 to –0.10) *based on 16 trials*	–1.21 (–1.53 to –0.89) *based on 8 trials*	–1.51 (–2.37 to –0.64) *based on 10 trials*

NDA, no data available. [a] Converted into days.

Discussion

Overall, it would appear that both zanamivir and oseltamivir reduce the length of influenza illness and by similar durations, with many analyses reaching statistical significance at the customary 5% level. When comparing the results for zanamivir and oseltamivir, it should not be forgotten that different definitions of efficacy end-points have been used for both adults and children. It is difficult to predict what influence these discrepancies would have on the results. (It should be noted that the review of amantadine uses different end-point definitions again introducing further problems of comparability of treatments – see Chapter 5.)

Further, the issue of time to event outcomes being on different scales for the two compounds has already been mentioned. The decision was taken to work in days for the economic model. The cruder metric (i.e. half days rather than hours) used to evaluate zanamivir has the potential to exaggerate small differences in treatment effects since the primary end-point was very discrete, although no adjustment for this was possible.[2] Also, regarding technical aspects of the analysis, in this chapter results are mostly reported to two decimal places. More decimal places are actually used when such results are imputed into the economic decision model described later.

Table 54 compares the results from the above NI systematic review for the outcome time to symptoms alleviated with previously published meta-analyses. It can be observed by comparing the pooled results from the different meta-analyses that although the magnitude of the results may be different, the direction and therefore the conclusions drawn are consistent. Note that this report has identified and synthesised the greater number of trials.

Some critical comments on the methodology employed in this review are needed. Although the search strategy used to identify the NI treatment studies for this review may appear rather simplistic, it became apparent very early in the review process that contact was going to have to be made with the companies who manufacture the two drugs being reviewed. GlaxoSmithKline maintain a trial database (http://ctr.glaxowellcome.co.uk), which was used to cross-check the literature identified. Further, a

regular dialogue was maintained with representatives at both GlaxoSmithKline and Hoffman La Roche, both of whom supplied us with comprehensive lists of relevant references and information on unpublished studies. Also, we checked our evidence with that used in previous meta-analyses in the area[2,6,7,480] and with Hoffman La Roche and GlaxoSmithKline's submission to NICE. Therefore, we are confident that no relevant published data have been missed in this review. This does not mean that all existing randomised evidence is included; we know of unpublished trials for which data were not made available to us, and there may be further trials, currently confidential, of which we are unaware. Hence the possibility of publication bias,[485] and particularly time-lag publication bias[502] (i.e. the trials currently not published may show the drugs to be less favourable than those published), cannot be ruled out.

Although it is generally acknowledged that the assessment of study quality is an important aspect of any systematic review, less agreement exists regarding how any such assessment should be taken into account when performing meta-analyses based on the studies.[503] Owing to the heterogeneous nature of the information available to ourselves, the assessment of quality was hampered. Although the Jadad scale[484] was used to assess studies, these scores reflected the completeness of the trial report available rather than any true underlying quality score. For this reason, these quality scores were not considered further in the main analysis. However, a sensitivity analysis was carried out which excluded the unpublished studies from the analysis.

One of the objectives of this systematic review was to inform an economic decision model. Several methodological issues arose as a result of this. First, since different models were evaluating different patient groups, ideally separate meta-analyses should be carried out on those patient subgroups. Further data were obtained from Hoffman La Roche and GlaxoSmithKline that enabled separate meta-analyses of these groups to take place. Such classification was not attempted in previous meta-analyses of these trials.

A further problem that needed to be overcome was the conversion of medians to mean values for the time to event outcomes. The median values are reported in this chapter as these are more clinically meaningful; however selected converted mean values, required for the economic model, are presented in Appendix 3. It should be noted that in order to derive these, certain assumptions (outlined in Appendix 3) were required. This is a methodological issue that requires more attention as it will occur in the future in other areas of evaluation. Further, it should not be forgotten that carrying out meta-analyses on medians is also 'non-standard' practice and the standard error of the median is not well defined. Again, this is a methodological issue that requires further research.

As previously noted, evaluation of adverse events and complications was problematical. Owing to inconsistent and inadequate reporting, it was decided to assess adverse events using the prophylaxis trials (Chapter 4) where there was less chance of complications being misspecified as adverse events. Complications were not assessed using a meta-analysis of the individual treatment trials; instead, it was necessary to rely on pooled individual patient data analyses reported by the companies. The dangers of such marginal analyses have been documented elsewhere[486] and such analyses do not take into account any between trial heterogeneity; however, this approach was the only option available. Further, serious complications of influenza, such as complications requiring hospitalisation or death, are evidently rare (at least in otherwise healthy subjects), but potentially important in the evaluation of new therapies. There is very little evidence on the impact of the NIs on these outcomes since the trials were never powered for such analyses; however, it was necessary to use what evidence was available for the propagation of the economic model.

As was to be expected, the effectiveness of zanamivir is greater in those patients who have laboratory-confirmed influenza since zanamivir is not expected to have any impact on other ILIs. The issue of targeting the intervention to maximise the treatment of true influenza cases is very pertinent to the cost to the NHS and is discussed at length later in this report.

Addendum: recent zanamivir trials

At the time that the information was provided by the manufacturer (February 2002), the three trials described in *Table 55* and the data in *Tables 56–59* had not been published or accepted for academic publication. However, since then, two of the trials have been, or are about to be, published, and so are no longer commercial-in-confidence. The third trial (NAI30015) is still to be published, so its results remain commercial-in-confidence.

TABLE 55 *Characteristics of commercial-in-confidence zanamivir treatment trials*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Follow-up (days)	Data source + Extra information
NAI30011	≥ 18 years of age. Present within 48 hours after onset of symptoms. Some participants 'high-risk' (10% cardiovascular *N* = 47; 7% respiratory, *N* = 33) and 5 participants (1 treatment and 4 placebo) ≥ 65 years. 9% of individuals (21 in each arm) vaccinated for the present influenza season. US-based multicentre trial	237 placebo 229 10 mg inhaled twice daily	5	21	[Ref.: GlaxoSmithKline 2002 submission to NICE)
NAI30012	All subjects aged ≥ 65 years with or without underlying medical conditions. 20-country multicentre trial. Present within 48 hours after onset of symptoms. 44% and 47% vaccinated for the present influenza season in the placebo and treatment groups, respectively	167 placebo 191 10 mg inhaled twice daily	5	29	[Ref.: GlaxoSmithKline 2002 submission to NICE)
NAI30015	Males and females of Finnish Army living in residential units with or without underlying medical conditions. Age ranged from 17 to 29 years. Present within 48 hours after onset of symptoms. Only 3 subjects were vaccinated for the present influenza season (1 placebo, 2 treatment). 2% 'high-risk' (*N* = 13)	295 placebo 293 10 mg inhaled twice daily	5	29	[Ref.: GlaxoSmithKline 2002 submission to NICE)

TABLE 56 *Median number of days to the alleviation of symptoms for commercial-in-confidence zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI); *p*-value**
NAI30011 'High-risk + healthy'	[*N* = 237; *R* = NDA] 5.00 (NDA)	[*N* = 229; *R* = NDA] 4.50 (NDA)	–0.50 (NDA) *p* = 0.692
NAI30012 'High-risk'	[*N* = 167; *R* = NDA] 7.5 (NDA)	[*N* = 191; *R* = NDA] 6.5 (NDA)	–1.00 (–3.00 to 1.00) *p* = 0.159
NAI30015 'Mostly healthy'	[Commercial-in-confidence]		
NDA, no data available.			

TABLE 57 *Median number of days to the alleviation of symptoms for commercial-in-confidence zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI); *p*-value**
NAI30011 'High-risk + healthy'	[*N* = 107; *R* = NDA] 5.00 (NDA)	[*N* = 104; *R* = NDA] 4.50 (NDA)	–0.50 (NDA) *p* = 0.851
NAI30012 'High-risk'	[*N* = 114; *R* = NDA] 7.5 (NDA)	[*N* = 120; *R* = NDA] 7.25 (NDA)	–0.25 (–3.25 to 2.00) *p* = 0.609
NAI30015 'Mostly healthy'	[Commercial-in-confidence]		
NDA, no data available.			

TABLE 58 *Median number of days to return to normal activities for commercial-in-confidence zanamivir treatment trials (ITT group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI); *p*-value**
NAI30011 'High-risk + healthy'	NDA	NDA	NDA
NAI30012 'High-risk'	[*N* = 167; *R* = NDA] >26.5 (NDA)	[*N* = 191; *R* = NDA] >26.5 (NDA)	*p* = 0.892
NAI30015 'Mostly healthy'	No data collected	No data collected	NDA
NDA, no data available.			

Notes

1. There are no additional data provided by these studies on the **time to return to normal activities**. In the only study that did report the outcome (NAI30012), more than 50% of the patients had not returned to normal activities by the end of the follow-up period. Hence the median is undefined.
2. **Time to alleviation of symptoms** – none of the studies report the SE of the medians in the two groups making incorporation into the existing meta-analysis not possible.

TABLE 59 *Median number of days to return to normal activities for commercial-in-confidence zanamivir treatment trials (influenza positive group)*

Trial	Placebo	Inhaled 10 mg b.d.	Inhaled 10 mg b.d. vs placebo
	Median (SE)	**Median (SE)**	**Median difference (95% CI); *p*-value**
NAI30011 'High-risk + healthy'	NDA	NDA	NDA
NAI30012 'High-risk'	[*N* = 114; *R* = NDA] >26.5 (NDA)	[*N* = 120; *R* = NDA] >26.5 (NDA)	$p = 0.897$
NAI30015 'Mostly healthy'	No data collected	No data collected	NDA

NDA, no data available.

(a) The CIs around the median difference (where supplied) are not symmetrical, hence the standard error is difficult, if not impossible, to calculate. For the 'high-risk' population, the results of NAI30012 (–1.00, 95% CI –3.00 to 1.00) are consistent with the pooled result from the meta-analysis for the ITT population (–0.93, 95% CI –1.90 to 0.05). However, the results for the influenza positive population are not consistent [i.e. NAI30012 = –0.25 (–3.25 to 2.00) compared to pooled = –1.99 (–3.08 to –0.90)]. If this study were added to the meta-analysis it could reduce the treatment benefit and perhaps statistical inferences at the 5% level would change.

(b) Studies NAI30011 and NAI30015 contain predominantly 'healthy' individuals but some 'high-risk'. Data were not supplied for these subgroups individually. Assuming that the treatment effect reported for all patients is representative of that for the healthy persons in the trial NAI30011, including this study in the 'healthy' meta-analyses would reduce the treatment benefit but inferences at the 5% level will probably not change. [Comments on NAI30015 results commercial-in-confidence.]

Chapter 4

Systematic review and meta-analysis of the prophylaxis use of neuramindase inhibitors for prevention of influenza A and B

Introduction

This chapter describes the systematic review and meta-analyses of the prophylaxis use of NIs for the prevention of influenza. The first section describes the methods for reviewing the effectiveness of NIs for prevention of influenza. The results are presented in the second section, including the results of any meta-analyses performed. The chapter concludes with a discussion.

Methods for reviewing effectiveness

Search strategy

The overall search strategy for the systematic review of NIs (both treatment and prophylaxis) is described in the 'Search strategy' (p. 41)

Inclusion and exclusion criteria

All trials evaluating the prophylactic use of NIs for the prevention of influenza by zanamivir or ostletamivir were considered for inclusion in this systematic review. For selection in the systematic review, leading to further examination for inclusion in the meta-analyses, trials had to meet all the criteria outlined in *Table 60*.

Data extraction strategy

Data from the studies identified for inclusion in the systematic review were extracted using a data extraction form. Data were extracted on the patient groups considered by each trial and the summary statistics for the efficacy outcomes of interest (all described in detail below). Data were mainly obtained from the published literature.

TABLE 60 *Inclusion criteria*

- It had to be randomised (at individual or group level)
- At least one clinical outcome measure of relevance had to be reported. Those considered relevant are:
  - number of individuals with laboratory confirmed symptomatic influenza
  - adverse events due to intervention
  - withdrawals
- Data had to be available before 31 December 2001
- Necessary trial information had to be available in English

Patient groups

The patient groups of interest for the prophylaxis use of NIs for the prevention of influenza A and B were the same as those groups identified for the treatment systematic review in Chapter 3 ('healthy' and 'high-risk' adults and children) with the addition of 'elderly individuals in a residential home setting'.

Preventative strategies

Four different preventative strategies for administering NIs for the prevention of influenza have been evaluated by randomised controlled trial (RCT):

1. outbreak prophylaxis in the elderly in a residential home setting
2. seasonal prophylaxis in the elderly in a residential home setting
3. seasonal prophylaxis in a healthy population
4. post-exposure prophylaxis in the household setting.

Each of these strategies is treated separately with no pooling across them, with the exception of adverse event and withdrawals data.

Efficacy end-points

Laboratory-confirmed symptomatic influenza

The main outcome of interest was the number of individuals with laboratory-confirmed symptomatic influenza in each of the placebo and NI treatment groups at the end of the treatment duration of the trial. It is important to note that many of the individuals recruited into the trials, particularly the residential home trials, may have already been vaccinated against influenza.

Other efficacy end-points

Other end-points considered by this review are adverse events due to treatment and early withdrawals from the trials.

For all end-points, the statistical outcome of interest was the number of individuals with a particular event at the end of the treatment period (i.e. the number of individuals with laboratory-confirmed symptomatic influenza, adverse events due to treatment and withdrawals from the trial early).

Assessment of study validity

As for the treatment trials (see the section 'Assessment of study validity', p. 44), the Jadad trial quality scoring system was used to assess study validity (see Appendix 2).

Data analysis

Where sufficient information was available, results from different studies were combined using meta-analysis for each NI compound separately using the outcome measures defined in the section 'Data extraction strategy' (p. 42). Separate analyses were carried out on ITT populations for each patient subgroup and for all individuals and those confirmed influenza positive, where data were available. Separate analyses were also carried out for laboratory-confirmed influenza A and B, where the relevant data were available.

All meta-analyses were performed using the STATA software package (http://www.stata.com). As all the end-points of interest were binary, meta-analyses were performed on either the log odds or log OR scale.[485] Random effects models were used throughout to take into account any statistical heterogeneity that may exist. If possible, sensitivity analyses were performed to test the robustness of the meta-analysis results to differential study quality and publication status.

Results

Quantity and quality of research available

Below, each of the trials included in the NI prophylaxis systematic review are described; they are categorised by specific NI and the target population.

Zanamivir

Eleven zanamivir prevention trials were identified, of which five met all of the inclusion criteria outlined in *Table 60*. The six zanamivir prevention trials excluded from the review are reported in *Table 61* together with reasons for their exclusion. *Table 62* summarises the included studies together with a Jadad score of study quality. These are NAIA2010,[504] NAIA3005,[505] NAIA2009,[506] NAIB2009[506] and NAI30010.[332] Note that trials NAIA2009 and NAIB2009 are reported as a single trial in the literature and also in this report, thus reducing the number of trials to four.

TABLE 61 *Excluded zanamivir prophylaxis and related studies with reasons for exclusion*

Study ID	Reason for exclusion from systematic review
NAIB2002	Administered intranasally only (32 mg twice-daily dose) versus placebo – no publication or data supplied
NAIB2004	Administered intranasally only (32 mg twice-daily dose) versus placebo – no publication or data supplied.
NAIA2006	Pharmacokinetic analysis
NAIB2006	No data available
NAIA3003	Limited data – only ICAAC abstract available (September 2000) – nursing home
NAIA3004	Limited data – only American Geriatric Society abstract – nursing home

Table 63 indicates which studies provide data on the outcomes of interest.

Oseltamivir

Seven oseltamivir prophylaxis trials were identified, of which four RCTs met all of the inclusion criteria (*Table 60*). Three trials were excluded, two of which were Japanese trials with only an abstract available in English (*Table 64*). The included studies (WV15825,[507] WV15673,[297] WV15697,[297] WV15799[352]) are described in *Table 65* together with a Jadad score of study quality. Note that the pharmaceutical company reported trials WV15673 and WV15697 both individually and combined. In the analyses that follow, the trials are treated as separate studies, except for withdrawals where only combined data were available.

Table 66 indicates which studies provide data on the outcomes of interest.

Assessment of effectiveness

It is important to note that all of the studies identified were conducted on very different populations of individuals, preventative strategies and varying degrees of background levels of vaccination. This meant that combining the studies, even within the same NI compound, was often not appropriate.

TABLE 62 *Characteristics of zanamivir prophylaxis trials*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Jadad score	Data source + Extra information
NAIA2009 NAIB2009	Randomised double-blind, placebo-controlled multi-centre trial (Europe and North America) investigating the prophylactic effect of zanamivir after close contact with a person with ILI of no longer than 4 days' duration. Asymptomatic persons aged 13–65 years who had been exposed were eligible. None of the participants were vaccinated against influenza	(2 × 2 factorial study design) 146 inhaled (5 mg) twice daily + intranasal sprays (16 mg/ml) per nostril (0.1 ml per spray) 141 placebo inhaled + active spray 144 inhaled + placebo spray 144 placebo spray and inhalation	5	3	[Ref.: Kaiser *et al*., 2000[506]]
NAIA2010	Randomised unblinded study of chemoprophylaxis with zanamivir versus standard care in a 735-bed nursing home. Randomisation was at a ward (of which there were 14) and not an individual level. Once existence of an outbreak was established (treatment was given only in the ward where the outbreak had occurred). Persons who refused to take part in the study were given rimantadine automatically when influenza A was confirmed in their ward. Age group of participants and percentage vaccinated not reported	**Influenza A** 65 10 mg inhaled + 4.4 mg intranasal twice daily 23 100 mg rimantadine once daily **Influenza B** 35 10 mg inhaled + 4.4 mg intranasal twice daily 17 no drug	14	3	In the analysis no allowance was made for the clustering and hence there is a danger the results of the study are over precise [Ref.: Schilling *et al*., 1998[504]]
NAIA3005	Randomised double-blind, placebo-controlled trial of zanamivir for the prevention of influenza in healthy adults (two midwestern USA university communities). Persons aged 18–64 years (mean age 29 years) were eligible for participation as long as they did not have a chronic condition for which influenza vaccination was recommended (although other vaccinated persons were eligible for inclusion). 15% of participants vaccinated	553 10 mg inhaled once daily 554 placebo	28	4	[Ref.: Monto *et al*., 1999[505]]
NAI30010	Randomised double-blind, placebo-controlled study of the treatment and prevention of influenza in families. Families (2–5 members with one child 5 years of age or older) in which one member developed ILI were randomised. Note: the index case was randomised to inhaled zanamivir 10 mg twice daily for 5 days or placebo. The mean age of household contacts was 26 years (SD = 16). 16% of participants had been vaccinated	Contact cases: 414 10 mg inhaled once a day 423 placebo	10	4	Note that the results of treating the index cases are included in the treatment section of this systematic review. In the analysis no allowance was made for the clustering and hence there is a danger the results of the study are over precise [Ref.: Hayden *et al*., 2000[332]]

TABLE 63 *Relevant data extracted from different studies*

Trial	Laboratory-confirmed symptomatic influenza	Adverse events due to intervention	Withdrawals
NAIA/B2009	✓		
NAIA2010	✓		
NAIA3005	✓	✓	✓
NAI30010	✓	✓	✓

TABLE 64 *Excluded oseltamivir prophylaxis and related studies with reasons for exclusion*

Study ID	Reason for exclusion from systematic review
WV15708	Missed the local influenza outbreak and provided only safety data for regulatory purposes
Kashiwagi *et al.*, 2000[508]	Japanese study – only abstract available in English
Kashiwagi *et al.*, 2000[495]	Japanese study – only abstract available in English

Zanamivir

This review only considers inhaled zanamivir, hence trial arms considering intranasal administration of zanamivir are excluded from the analyses.

Efficacy end-points

Three different preventative strategies were investigated in the four RCTs. NAIA2010 is outbreak prophylaxis in the elderly in a residential home setting, NAIA3005 seasonal prophylaxis in a healthy population and NAIA/B2009 and NAI30010 previous household exposure prophylaxis in a healthy population. Clearly, pooling results from more than one strategy is not appropriate; hence, the only synthesis possible is for the two trials reporting post-exposure prophylaxis in households. The results of this synthesis, and the other individual studies, are presented below.

Outbreak prophylaxis in the elderly in a residential home setting. *Table 67* shows the results from study NAIA2010. This is a moderately sized study with only a small percentage of individuals experiencing the outcome of interest [i.e. three individuals (2%)]. Hence the results are inconclusive and not statistically significant, although no individual given zanamivir contracted laboratory-confirmed influenza.

Seasonal prophylaxis in a healthy population. *Table 68* shows the results from study NAIA3005. This is a large study that provides convincing evidence that prophylactic zanamivir reduces the chance of an individual contracting influenza. The study estimated a 69% (95% CI 36 to 86%) reduction in the incidence of influenza in the zanamivir group.

Post-exposure prophylaxis in households (ITT). *Table 69* shows the results from NAIA/B2009 and NAI30010. Both trials suggest considerable protective effects of prophylaxis with zanamivir, although only NAI30010 attains formal statistical significance at the 5% level. Note that although these trials are combined using meta-analysis, the duration zanamivir was given varied (NAIA/B2009 5 days, NAI30010 10 days). The meta-analysis estimates an OR of 0.19 (95% CI 0.09 to 0.38), suggesting a powerful preventative effect of zanamivir.

Post-exposure prophylaxis in households (laboratory-confirmed influenza). In addition to the results for all individuals enrolled into trial NAI30010 (i.e. ITT), results were reported separately for those individuals who had come into contact with a person with influenza. These results are summarised in *Table 70* and show a very similar result [OR = 0.18 (95% CI 0.07 to 0.43)] to the ITT population.

Sensitivity analysis. Owing to the limited number of prevention studies identified by the systematic review, no sensitivity analyses were performed.

Adverse events

As discussed in Chapter 3, the definition of adverse events varied between treatment trials, and was often difficult to separate from certain complications. Therefore, adverse events data for the economic model were obtained from trials

TABLE 65 *Characteristics of oseltamivir prophylaxis trials*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (weeks)	Jadad score	Data source + Extra information
WV15825	Randomised double-blind, placebo-controlled multicentre trial comparing the efficacy of oseltamivir prophylaxis in frail elderly subjects living in 31 residential homes across the USA and Europe. 548 persons who had a mean age of 81 years (range from 64 to 96 years) took part in the study, of whom 80% had been vaccinated against influenza	276 75 mg once daily 272 placebo	6	4	[Ref.: Peters *et al*., 2001[507]]
WV15673	Double-blind, randomised and placebo-controlled study conducted at 3 sites in Virginia, USA. Eligible subjects were healthy adults aged 18–65 years, and had not received influenza vaccine	268 75 mg once daily 267 75 mg twice daily 268 placebo	6	5	[Ref.: Hayden *et al*., 1999[297]]
WV15697	Same design as above. Double-blind, randomised and placebo-controlled study conducted at 2 sites in Texas, USA and 1 site in Kansas City. Eligible subjects were healthy adults aged 18–65 years, and had not received influenza vaccine	252 75 mg once daily 253 75 mg twice daily 251 placebo	6	5	[Ref.: Hayden *et al*., 1999[297]]
WV15799	Cluster-randomised, double-blind, placebo-controlled study conducted at 76 centres in N. America and Europe to investigate the efficacy of oseltamivir in preventing the spread of influenza to household contacts of influenza-infected index cases. Household contacts were randomly assigned by household cluster within 48 hours of symptom onset in the index case (the index case did not receive antiviral treatment). Acknowledgement was made of the need to take the cluster aspect of the design into account at the analysis stage. The age of contacts ranged from 12 to 85 years. 13% of contacts in each group had received influenza vaccination. About 40% of contacts had pre-existing diseases – the most common were asthma 3.0%, hypertension 5.7%, hypersensitivity 3.9% and depression 2.9%	493 75 mg once daily 462 placebo	1	4	[Ref.: Welliver *et al*., 2001[352]]

TABLE 66 *Relevant data extracted from different studies*

Trial	Laboratory-confirmed symptomatic influenza	Adverse events due to intervention	Withdrawals
WV15825	✓	[a]	
WV15673 WV15697	✓	[a]	✓
WV15799	✓	[a]	✓

[a] Some information available but not complete enough to include in the systematic review.

evaluating the prophylactic use of NIs for the prevention of influenza (i.e. it is assumed that reported adverse events are not due to influenza). The adverse events due to zanamivir were assumed to be the additional proportion in the active group compared to the placebo. Potential drug-related adverse events that have been reported in the trials are nasal symptoms, gastrointestinal symptoms, throat irritation, fever and cough.

The data was pooled for each arm of the trials separately on the log odds scale rather using the log OR as this was the most appropriate format for input into the model. *Table 71* shows the results of this meta-analysis converted to the percentage scale for ease of interpretation. It can be observed that the percentage of individuals with adverse events is very similar in the two groups.

Withdrawals

Data on the number of withdrawals in each arm of the trials were obtained from two of the four published studies. The data were pooled for each arm of the trials separately on the log odds scale rather using the log OR as this was the most appropriate format for input into the model. *Table 72* shows the results of this meta-analysis converted to the percentage scale for ease of interpretation. It can be seen that generally levels of withdrawal are low within the trials.

Oseltamivir

Efficacy end-points

Three different preventative strategies were investigated in the four RCTs included. Peters *et al*.[507] studied seasonal (long-term) prophylaxis in a mostly vaccinated frail elderly population in a residential home setting, Hayden *et al*.[297] reported two trials of seasonal prophylaxis in healthy adults and the trial described by Welliver *et al*.[352] involved post-exposure prophylaxis in households. As for the zanamivir trials, pooling across strategies is not appropriate hence the only synthesis possible is for the two trials reporting seasonal prophylaxis in healthy adults. The results of this synthesis and the other individual studies are presented below.

Seasonal (long-term) prophylaxis in a frail elderly population in a residential home setting. *Table 73* shows the results for WV15825. This study provides convincing evidence that oseltamivir prophylaxis reduces the chance of an individual contracting influenza. The ORs for all participants and those previously vaccinated are 0.08 (95% CI 0.01 to 0.61) and 0.09 (95% CI 0.001 to 0.67), respectively.

Seasonal prophylaxis in healthy adults. *Table 74* shows the results for WV15673 and WV15697. Note that the pooled results are different to those published in Hayden and colleagues[297] since their pooled result represents an analysis of the individual patient data. However, for consistency our pooled result is derived from a meta-analysis of the individual study results. The meta-analysis results show a statistically significant prevention benefit of oseltamivir [OR = 0.26 (95% CI 0.08 to 0.84]).

Post-exposure prophylaxis in households. *Table 75* shows the results from WV15799. Again, these studies show convincing evidence for the prophylactic use of oseltamivir with ORs of 0.10 (95% CI 0.04 to 0.29) and 0.10 (95% CI 0.03 to 0.34) for the ITT population and the influenza positive index case population, respectively.

Sensitivity analysis. Owing to the limited number of prevention studies identified by the systematic review, there was little scope for performing any sensitivity analyses.

Adverse events

As discussed in Chapter 3, the definition of adverse events varied between treatment trials, and was often difficult to separate from certain complications. Therefore, adverse events data for

TABLE 67 *Outbreak prophylaxis in the elderly in a residential home setting: NAIA2010*[a]

	Outcome	Total no. in rimantadine group	No. in rimantadine group with an event (%)	Total no. in zanamivir group	No. in zanamivir group with an event (%)	OR (95% CI)	*p*-Value for intervention effect
Prevention against influenza A (control arm received rimantadine)	Laboratory-confirmed influenza A	23	1 (4.3)	65	0 (0.0)	0.11 (0.005 to 2.91)	0.25 (exact)
	Influenza or ILI	23	1 (4.3)	65	1 (1.5)	0.34 (0.02 to 5.73)	0.46 (exact)
Prevention against influenza B (control arm received no drug)	Laboratory-confirmed influenza B	17	1 (5.9)	35	0 (0.0)	0.15 (0.006 to 4.01)	0.33 (exact)
	Influenza or ILI	17	1 (5.9)	35	0 (0.0)	0.15 (0.006 to 4.01)	0.33 (exact)

[a] None of the estimates take into account ICC clustering; however, it is so rare that is probably does not matter.

TABLE 68 *Seasonal prophylaxis in a healthy population (aged 18–64 years, 15% vaccinated): NAIA3005*

Outcome	Total no. in placebo group	No. in placebo group with an event (%)	Total no. in zanamivir group	No. in zanamivir group with an event (%)	OR (95% CI)	*p*-Value for intervention effect
Laboratory-confirmed clinical influenza	554	34 (6.1)	553	11 (2.0)	0.31 (0.14 to 0.64)	<0.001

TABLE 69 *Previous exposure prophylaxis in the general population (ITT group): NAI30010[a] and NAIA/B2009*

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 (%)	OR (95% CI)	*p*-Value for intervention effect
Symptomatic laboratory-confirmed influenza	NAI30010	423	40 (9.5)	414	7(1.7)	0.16 (0.07 to 0.37)	<0.001
	NAIA/B2009	144	9 (6.3)	144	3 (2.1)	0.27 (0.07 to 1.05)[b]	0.077[b]
	Pooled estimate					0.19 (0.09 to 0.38)	<0.001

[a] None of the above estimates take into account ICC clustering – however, it is so rare that is probably does not matter.
[b] OR estimate is stratified by centre but the given *p*-value is not.

TABLE 70 *Previous exposure prophylaxis in the general population (influenza positive index cases): NAI30010*

Outcome	Total no. in placebo group	No. in placebo group with an event (%)	Total no. in zanamivir group	No. in zanamivir group with an event (%)	OR (95% CI)	*p*-Value for intervention effect
Laboratory-confirmed influenza in contact	215	33 (15.3)	195	6 (3.1)	0.18 (0.07 to 0.43)	<0.001

TABLE 71 *Number of individuals with adverse events to treatment*

	Placebo		Zanamivir	
Trial	***N***	**Adverse events**	***N***	**Adverse events**
NAIA30010	581	27 (5%)	577	30 (5%)
NAIA2009	144	25 (17%)	144	27 (19%)
NAIA3005	554	27 (5%)	553	30 (5%)
Meta-analysis pooled results				
Percentage of adverse events	7.8% (95% CI 6.4 to 9.7%)		7.5% (95% CI 6.2 to 9.2%)	

TABLE 72 *Number of trial withdrawals*

	Placebo		Zanamivir	
Trial	***N***	**Withdrawals**	***N***	**Withdrawals**
NAIA30010	581	7 (1%)	577	6 (1%)
NAIA3005	554	17 (3%)	553	10 (2%)
Meta-analysis				
Percentage of withdrawals	2.4% (95% CI 1.7 to 3.8%)		1.3% (95% CI 0.9 to 2.0%)	

the economic model were obtained from trials evaluating the prophylactic use of NIs for the prevention of influenza. The adverse events due to oseltamivir treatment were assumed to be the additional proportion in the active treatment group compared with the placebo. Potential drug-related adverse events that have been reported in the trials were headache, upper gastrointestinal disturbances and vomiting. No overall number of individuals incurring at least one adverse event were reported in the published literature and therefore no results are presented here.

Withdrawals

Data on the number of withdrawals in each arm of the trials were obtained from three of the four published studies [WV15673 and WV15697 combined (no data available separately) and WV15799]. The data were pooled for each arm of the trials separately on the log odds scale rather using the log OR as this was the most appropriate format for input into the decision model. *Table 76* shows the results of this meta-analysis converted to the percentage scale for ease of interpretation. It can be seen that generally levels of withdrawal are low within the trials.

Discussion

Currently there is much less randomised evidence evaluating NIs for prevention compared with treatment. Since the evidence that is available is spread over four different preventative strategies, there is little evidence with which to undertake a formal meta-analysis (*Table 77*).

Most studies present promising results, suggesting that both NI compounds have considerable potential for the prevention of influenza, although there are considerable gaps in the knowledge base at present, including no isolated evidence in children. Owing to the paucity of evidence, it was decided not to request further information from the relevant companies to allow exact sub-grouping of evidence into the four population groups considered in the economic model, since this would have meant subdividing the evidence further. Only one previous systematic review was identified which considered NIs for preventing influenza in healthy adults.[3] This study combined all available trial data (i.e. NIs combined) for natural exposure influenza regardless of preventative strategy [pooled or of 0.22 (0.11 to

TABLE 73 *Seasonal prophylaxis in a mostly vaccinated elderly population in a residential home setting (aged 64–96 years, 80% vaccinated): WV15825*

Outcome: laboratory-confirmed clinical influenza	Total no. in placebo group	No. in placebo group with an event (%)	Total no. in oseltamivir group	No. in oseltamivir group with an event (%)	OR (95% CI)	*p*-Value for intervention effect
All participants	272	12 (4.4)	276	1 (0.4)	0.08 (0.01 to 0.61)	0.002
Vaccinated participants only	218	11 (5.0)	222	1 (0.5)	0.09 (0.001 to 0.67)	0.003

TABLE 74 *Seasonal prophylaxis in a healthy population (aged 18–65 years, none vaccinated): WV15673 and WV15697*

Outcome	Trial	Total no. in placebo group	No. in placebo group with an event (%)	Total no. in oseltamivir 75 mg/day group	No. in oseltamivir 75 mg/day group with an event (%)	Total no. in oseltamivir 150 mg/day group[a]	No. in oseltamivir 150 mg/day group with an event (%)[a]	OR (95% CI)	*p*-Value for intervention effect
Laboratory-confirmed clinical influenza	WV15673	268	19 (7.1)	268	3 (1.1)	267	4 (1.5)	0.15 (0.04 to 0.51)	<0.001
	WV15697	251	6 (2.4)	252	3 (1.2)	253	3 (1.2)	0.49 (0.12 to 1.99)	0.34
	Pooled (Random effect)							0.26 (0.08 to 0.84)	0.025

[a] 150 mg/day arm included here for completeness.

TABLE 75 *Previous exposure prophylaxis in the general population (aged 12–85 years, 13% vaccinated): WV15799*

Outcome: symptomatic laboratory-confirmed clinical influenza	Total no. in placebo group	No. in placebo group with an event (%)	Total no. in oseltamivir group	No. in oseltamivir group with an event (%)	OR (95% CI)	*p*-Value for intervention effect
ITT analysis	462	34 (7.4)	493	4 (0.8)	0.10 (0.04 to 0.29)	<0.001
Influenza-positive index case	206	26 (12.6)	209	3 (1.4)	0.10 (0.03 to 0.34)	<0.001

TABLE 76 *Number of trial withdrawals*

	Placebo		Oseltamivir	
Trial	***N***	**Withdrawals**	***N***	**Withdrawals**
WV15673/WV15697	519	21 (4%)	520	17 (3%)
WV15799	461	2 (<1%)	494	5 (1%)
Meta-analysis pooled results				
Percentage of withdrawals	3.2% (95% CI 2.2% to 4.9%)		2.5% (95% CI 1.7% to 3.8%)	

TABLE 77 *Summary of meta-analyses results for laboratory-confirmed influenza*

	OR (95% CI)	
Strategy	**Zanamivir**	**Oseltamivir**
Outbreak prophylaxis – elderly	Influenza A: 0.11 (0.00 to 2.91) *based on 1 trial*	NDA
	Influenza B: 0.15 (0.00 to 4.01) *based on 1 trial*	NDA
Seasonal prophylaxis – elderly	NDA	Influenza A and B: 0.08 (0.01 to 0.61) *based on 1 trial*
Seasonal prophylaxis – healthy	Influenza A and B: 0.31 (0.14 to 0.64) *based on 1 trial*	Influenza A and B: 0.26 (0.08 to 0.84) *based on 2 trial*
Post-exposure prophylaxis in households	Influenza A and B: 0.19 (0.09 to 0.38) *based on 2 trials*	Influenza A and B: 0.10 (0.04 to 0.29) *based on 1 trial*
NDA, no trial data available.		

0.44) from three studies (WV15673, WV15697 and NAIA3005)] and therefore is not directly comparable to the results obtained above. As discussed previously, evidence on adverse events (required for the economic decision model) and withdrawals were also meta-analysed. All adverse events reported appear to be relatively minor and the withdrawal rates low. A description of how the results reported in this chapter are applied to the economic decision model is given in Chapter 6.

The comments made regarding potential publication bias and data quality in Chapter 3 are equally pertinent here. In addition, it should be noted that, owing to the lack of evidence, the inclusion criteria were relaxed in this systematic review to allow the inclusion of an unblinded study.[504]

Chapter 5

Systematic review of the treatment and prophylaxis of influenza A by amantadine hydrochloride in children and the elderly

Introduction

This chapter describes a systematic review of the effectiveness of amantadine in treating and preventing influenza A in children and the elderly. This review was considered necessary in order to inform the economic decision model since no previous systematic reviews in the area were identified (although reviews in the area have been registered, but not completed, in the Cochrane Database of Systematic Reviews[9]). A systematic review of the use of amantadine for the treatment and prophylaxis of influenza in an otherwise healthy adult population (18–65 years)[4,509] has been published in the Cochrane Database of Systematic Reviews and is used, where necessary, to inform the economic model and hence this population is not considered in the systematic review reported below.

The next section describes the methods used for reviewing the effectiveness of amantadine for treatment and prevention for children (aged <18 years) and elderly (>65 years). The results of the review are presented in the subsequent section and the chapter concludes with a discussion.

Methods for reviewing effectiveness

Search strategy

Online electronic databases were searched to ensure as complete an ascertainment of published reports as possible: MEDLINE (1966 to December 2001) and EMBASE (1980 to December 2001). Furthermore, amantadine studies were identified in an initial search of all databases outlined in *Table 6* (Chapter 3). Also searched was a database compiled by the study team of references used in the project. The main subject terms used for the literature searches are given in *Table 78* and were used to search title, abstract and keyword section of the citations (with the exception of the RCT filter).

TABLE 78 *Main subject terms for searching databases for amantadine articles*

- Amantadine (both MeSH and keyword) OR amantadine hydrochloride OR adamantine OR symmetrel
- Search terms for elderly
- Search terms for children

In addition to the above sources of information, a review of published amantadine or amantadine and rimantadine reviews (not necessarily systematic) was conducted. Nineteen articles were identified (see *Table 79*) and their citations searched for relevant articles.

A final source of information on amantadine evidence that was searched was the industry submission to NICE produced by Alliance Pharmaceutical (Alliance, 2001).

Inclusion and exclusion criteria

All trials evaluating either the treatment or prophylactic use of amantadine in either the elderly or children were considered for inclusion in this review. For selection in the review, trials also had to meet all of the criteria outlined in *Table 80*.

Data extraction strategy

Data from the studies identified for inclusion in the systematic review were extracted using a standardised form. Data were extracted on the relevant patient groups considered by each trial and the summary statistics for the efficacy outcomes of interest (all described in detail below). Data were solely obtained from the published literature.

Assessment of study validity

The Jadad trial quality scoring system[484] was used to assess study validity (see Appendix 2).

TABLE 79 *Previous reviews of amantadine or amantadine and rimantadine used to assist with the identification of relevant primary studies*

Reference
Arden NH. Control of influenza in the long-term-care facility: a review of established approaches and newer options. *Infect Control Hosp Epidemiol* 2000;**21**:59–64[510]
Betts RF. Amantadine and rimantadine for the prevention of influenza A [Review]. *Semin Respir Infect* 1989;**4**:304–10[511]
Brady MT. Influenza virus infections in children. *Semin in Pediatr Infect Dis* 1998;**9**:92–102[512]
Douglas RG Jr. Drug therapy: prophylaxis and treatment of influenza. *N Engl J Med* 1990;**322**:443–50[513]
Galbraith AW. Influenza – recent developments in prophylaxis and treatment. *Br Med Bull* 1985;**41**:381–5[514]
Guay DR. Amantadine and rimantadine prophylaxis of influenza A in nursing homes. A tolerability perspective [Review]. *Drugs Aging* 1994;**5**:8–19[515]
Hayden FG. Antivirals for pandemic influenza [Review]. *J Infect Dis* 1997;**176** Suppl 1:S56–S61[516]
Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine [Review]. *Curr Top in Microbiol Immunol* 1992;**176**:119–30[261]
Hirsch MS, Swartz MN. Drug therapy: antiviral agents (first of two parts) [Review]. *N Engl J Med* 1980;**302**:903–7[517]
McGeer A., Sitar DS, Tamblyn SE, Kolbe F, Orr P, Aoki FY. Use of antiviral prophylaxis in influenza outbreaks in long term care facilities. *Can J Infect Dis* 2000;**11**:187–92[518]
Monto AS. Using antiviral agents to control outbreaks of influenza A infection [Review]. *Geriatrics* 1994; **49**:30–4[519]
Monto AS, Arden NH. Implications of viral resistance to amantadine in control of influenza A [Review]. *Clin Infect Dis* 1992; **15**:362–7[520]
Nicholson KG. Use of antivirals in influenza in the elderly: prophylaxis and therapy. *Gerontology* 1996;**42**:280–9[521]
Shigeta S. Recent progress in anti-influenza chemotherapy. *Drugs R & D* 1999;**2**:153–64[522]
Sperber SJ, Gross PA. Influenza: manifestations, treatment, and prevention. *Infect Med* 1994;**11**:675–83[523]
Tominack RL, Hayden FG. Rimantadine hydrochloride and amantadine hydrochloride use in influenza A virus infections [Review]. *Infect Dis Clin North Am* 1987;**1**:459–78[524]
Treanor J, Falsey A. Respiratory viral infections in the elderly. *Antiviral Res* 1999;**44**:79–102[525]
Van Voris LP, Newell PM. Antivirals for the chemoprophylaxis and treatment of influenza. *Sem Respir Infect* 1992;**7**:61–70[526]
Wiselka M. Influenza: diagnosis, management, and prophylaxis. *BMJ* 1994;**308**:1341–5[527]

TABLE 80 *Inclusion criteria*

- It had to be randomised (at individual or group level)
- At least one clinical outcome measure of relevance had to be reported. Those considered relevant were: occurrence of influenza or ILI in prophylaxis trials and symptom days, fever days, adverse events and withdrawals in treatment trials
- Data had to be available before 31 December 2001
- Necessary trial information had to be available in English
- Study must include results on subjects exclusively under 18 years or over 65 years [i.e. if study included more than one age category (children, adult or elderly) then analysis of each age subgroup must be presented]
- Studies had to have at least an abstract published

Data analysis

If studies identified were considered to be too diverse and/or had unrepresentative study populations, then formal meta-analysis was not carried out.

Results

Quantity and quality of research available

Each of the trials included in the review of amantadine for both children and elderly are described below. They are categorised by the target population and whether for treatment or prophylaxis.

Children

Eight amantadine prevention trials were identified of which three met all of the inclusion criteria outlined in *Table 80*. The five excluded prevention trials[70,251,252,528,529] are reported in *Table 81* together with reasons for their exclusion. The studies included in the review are Finklea and colleagues,[530] Quilligan and colleagues[531] and Leung *et al*.[532] These are summarised in *Table 82* together with a Jadad score of study quality.

Four studies were identified that examined amantadine treatment in children. Two were included in the review[533,534] and are summarised in *Table 83* together with a Jadad score of study quality. Two studies by Galbraith were excluded

TABLE 81 *Excluded amantadine prophylaxis and related children studies with reasons for exclusion*

Study ID	Reason for exclusion from systematic review
Children's prophylaxis studies	
Galbraith, 1969[251]	Included a study population ranging from 2 to >80 without publishing a breakdown of analysis by age groups
Galbraith, 1969[252]	Included a study population ranging from 2 to >80 without publishing a breakdown of analysis by age groups
Schapira, 1971[529]	Data were not presented as a children's subgroup
Nafka, 1970[528]	Study population were 3–50 years of age but did not give results for children-only group
Wright, 1976[70]	Study population of 153 included 20 people over the age of 18 years. No subgroup analysis was performed on those under 18
Children's treatment studies	
Galbraith, 1971	Data were not presented on a children's subgroup
Galbraith, 1973	Data were not presented on a children's subgroup

from the review as the data were not presented for individuals aged under 18 years as a distinct group[251,252] (*Table 81*).

A reference list relating to all the excluded and included trials is provided in Appendix 5.

Elderly

Seven amantadine prophylaxis trials were identified. Two RCTs met all of the inclusion criteria (*Table 80*). These trials are Pettersson and colleagues[71] and Leeming[537] and are summarised in *Table 85* together with a Jadad score of study quality. The excluded studies, together with reasons for their exclusion, are presented in *Table 84*.

A reference list relating to all the excluded and included trials is provided in Appendix 5.

There were no studies identified that met the inclusion criteria and addressed amantadine treatment in the elderly. Excluded trials are summarised in *Table 84* and a reference list is provided in Appendix 5.

Assessment of effectiveness

It is important to note that all of the studies identified were conducted using different populations, dosages, preventative strategies and varying degrees of background levels of vaccination. This meant that combining the studies, even within the same treatment and age group, was considered inappropriate.

Amantadine prophylaxis in children

All children in the three studies identified were from residential populations. The dose level ranged from 35 to 200 mg per day and the duration of prophylaxis ranged from 4 weeks to 5 months. Study quality was also variable. Trials by Finklea and colleagues[530] and Leung and colleagues[532] stated that they were randomised double-blind studies. For Quilligan and colleagues,[531] although a placebo was given, the study was not explicitly stated to be either randomised or blinded, hence the Jadad score of zero. Indeed, it was impossible to be sure that this study was indeed randomised.

All studies gave the number of cases of laboratory-confirmed influenza in the study arms. The number of clinically defined cases were given for Quilligan and colleagues[531] and Finklea and colleagues,[530] but not for Leung and colleagues.[532] The degree to which adverse events were cited varied. Leung and colleagues[532] merely stated that "no significant toxicity occurred". In the trial by Quilligan and colleagues,[531] there were originally 50 patients in each arm but final results were given for 43 placebo patients and 126 treatment patients. The paper mentions that some children left the home but gives no breakdown of why some participants did not complete the trial. For Finklea and colleagues[530] the authors stated that there were seven minor adverse events that could be drug related in each arm of the study. Withdrawals were described as "small" and were stated to occur evenly in the two study groups. The reason given for withdrawals was discharge from the school itself.

For Quilligan and colleagues,[531] data were presented on 43 control participants and 126 treatment participants. During the first period, laboratory-confirmed influenza occurred in five of 43 (11.6%) controls and two of 126 (1.6%) recipients of amantadine. During the second period, when no prophylaxis was given, six cases of influenza occurred in the controls and 10 in the experimental group (attack rates 14% and 7.9%, respectively). During the third period, two cases occurred in the control group and none occurred in the experimental group, (attack rates 4.7% and 0%, respectively). Overall, 13 cases occurred in the controls and 12 in the experimental group, representing attack rates of

TABLE 82 *Characteristics of amantadine prophylaxis trials in children included in the review*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration	Jadad score	Data source + Extra information
Quilligan, 1966	Placebo-controlled trial of amantadine prophylaxis in a home for children with learning difficulties (the term mentally retarded is used in the paper). Prophylaxis was used in two time periods with a period of no prophylaxis separating them. Outcomes were cases of naturally occurring influenza prevented and influenza was laboratory confirmed. The mean age of participants was 8.6 years	There were four study arms. There was one placebo arm (43 patients). There were three treatment arms. The first received 70 mg of amantadine in both periods. The second received 105 mg of amantadine in both periods. The third received 35 mg in the first period and 140 mg of amantadine in the second period	Duration of treatment was from 9 January to the 12 March in the first period and from 10 March to the 15 July in the second period	0	[Ref.: Quilligan *et al*., 1966[531]]
Finklea, 1967	Randomised placebo-controlled trial of amantadine prophylaxis in a home for children with learning difficulties (mentally retarded is used in the study paper). Outcomes were clinically defined respiratory illness and laboratory-confirmed influenza. Participants were 8–19 years of age	Prepubescent children received 60 mg of amantadine and postpubescent received 100 mg. There were 154 patients in treatment group, of whom 104 had laboratory confirmation. There were 139 in the control group, of whom 133 had laboratory confirmation	Duration of treatment was from 10 February to 10 June 1985	3	[Ref.: Finklea *et al*., 1967[530]]
Leung, 1979	Randomised double-blind study of amantadine prophylaxis in residential asthmatic children. Laboratory-confirmed influenza A/USSR infections were quoted as an outcome measure. Participants were between 9 and 16 years of age	Participants received either 100 mg of amantadine twice a day (20 participants) or placebo twice a day (20 participants). However, there were paired sera obtained in 35 cases, the numbers for controls and experimental group were not given	Duration of prophylaxis was 4 weeks	2	[Ref,: Leung *et al*., 1979[532]] Note. Abstract only was obtained, so information given was very limited

TABLE 83 *Characteristics of amantadine treatment studies in children included in the review*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration (days)	Jadad score	Data source + Extra information
Kitamoto, 1968	Randomised double-blind, placebo-controlled trial conducted during the 1967–68 influenza season. Study included children and adults but only the children are discussed here. There were 54 participants who were defined as children in the study	There were two arms: a placebo arm (33 participants) and a treatment arm (21 participants). Participants who were 1–2 years old received 50 mg per day. Those 3–5 years old received 100 mg per day. Those 6–10 years old received 150 mg per day. Those 11 years and older received 200 mg per day	7	2	[Ref.: Kitamoto, 1968[534]]
Kitamoto, 1970	Randomised double-blind, placebo-controlled trial conducted during the 1968–69 influenza season. Study included children and adults but only the children are discussed here. There were 50 participants who were defined as children in the study	There were two arms: a placebo arm (20 participants) and a treatment arm (30 participants). Participants who were 1–2 years old received 50 mg per day. Those 3–5 years old received 100 mg per day. Those 6–10 years old received 150 mg per day. Those 11 years and older received 200 mg per day	7	2	[Ref.: Kitamoto, 1970[533]]

TABLE 84 *Excluded amantadine elderly studies with reasons for exclusion*

Study ID	Reason for exclusion from systematic review
Elderly prophylaxis studies	
Galbraith, 1969a	Data were not presented as an elderly subgroup
Galbraith, 1969b	Data were not presented as an elderly subgroup
Drinka, 1998	Study population were randomised to two different length periods of antiviral prophylaxis. There was no placebo control group
Schapira, 1971	Data were not presented as an elderly subgroup
Galbraith	Cranage Hall Hospital. Study was not published but was referred to in Alliance Pharmaceutical's submission to NICE
Treatment in the elderly	
Galbraith, 1971	Data were not presented as an elderly subgroup
Galbraith, 1973	Data were not presented as an elderly subgroup

30.2% and 9.5%, respectively. The results during the first period and overall were described as statistically significant at the 0.01 level.

Finklea and colleagues[530] presented data on 133 of 139 control group patients who had laboratory confirmation. There were also data on 104 out of 154 experimental group patients who had laboratory-confirmation. In the control group there were 11 cases of influenza A and one case of influenza B. This gives an attack rate of 9%. In the experimental group, there was a single case of influenza A and two cases of influenza B. This gave an attack rate of 2.9% for all influenza. The *p*-value for the difference in influenza A was given as <0.01.

Only an abstract is available for the study carried out by Leung and colleagues.[532] There were 20 individuals in each group. There were eight laboratory-confirmed influenza cases in the control group and seven in the experimental group. However, laboratory confirmation was obtained in only 35 out of 40 subjects in the study and the numbers who had laboratory confirmation in each group were not given.

Amantadine treatment in children

Information was obtained from two studies from Japan.[534,533] The subjects discussed here were healthy community-dwelling children. Analysis was presented only for children with laboratory-confirmed influenza, and hence did not present an ITT analysis.

Kitamoto[534] studied 54 children who had clinical influenza with serological confirmation in whom medication was started within the second day of illness. There were 21 children in the amantadine group and 33 children in the placebo group. The mean duration of fever was 1.48 days (SD = 1.36) in the amantadine group and 2.64 days (SD = 2.07) in the placebo group. Numbers of symptoms were presented for the two groups but no difference was detected.

Kitamoto[533] studied 50 children with symptomatic serologically confirmed influenza. Medication was started within the second day of treatment. Thirty children received amantadine and 20 children were given placebo. The mean duration of fever was 0.63 days (SD = 1.00) in the amantadine group and 1.10 day (SD = 1.02) in the placebo group. Rates of adverse events were given. The authors stated that no difference could be found in adverse events and that no patients withdrew from treatment.

Amantadine prophylaxis in the elderly

The results of amantadine prophylaxis in the elderly were given for two randomised trials of prophylaxis in institutions. The results were complicated by the fact that influenza did not occur in one study and occurred in only one of a number of settings in the second. Adverse events were not noted by Leeming.[537] Pettersson and colleagues[71] reported treatment withdrawal by five of 94 (5%) amantadine recipients and two of 101 (2%) controls. These withdrawals were not included in the final analysis.

For Leeming,[537] results were published for only one study setting (the only one with an influenza outbreak). On this ward, 29 subjects received placebo and 25 received amantadine 200 mg daily. Laboratory-confirmed clinical influenza occurred in six of 25 (24%) patients who received amantadine and in 11 of 29 (38%) controls. Two patients in the amantadine arm had sub-clinical, serologically confirmed influenza. For clinical influenza there were seven cases (28%) in the experimental group and 11 (38%) in the control group.

For Pettersson and colleagues[71] prophylaxis was given to 89 individuals for 9 weeks. There were 89 participants in the control group. There were

TABLE 85 *Characteristics of amantadine prophylaxis trials in the elderly included in the review*

Trial	Patient characteristics	Trial design arms (no. of patients in each arm)	Treatment duration	Jadad score	Data source + Extra information
Pettersson, 1980	Participants were elderly people in a home for the aged in the winter of 1978. The mean age was 77 years in the treatment group and 79 years in the control group. There were 188 participants in total	There were 99 participants in the control group and 89 in the treatment group. Treatment was 100 mg per day	Duration was 9 weeks	5	[Ref.: Pettersson *et al*., 1980[71]]
Leeming, 1969	Participants were elderly patients in an acute rehabilitation ward and three long-stay wards. Results were reported for rehabilitation ward as this was the only one to have an influenza outbreak. There were 54 study participants on this ward. Laboratory confirmed influenza was a quoted outcome	There were 29 placebo patients and 25 treatment patients. Patients were given 2 × 100 mg tablets per day	Mean duration of prophylaxis was 25 days	2	[Ref.: Leeming, 1969[537]]

no outbreaks of influenza so effectiveness results were not given.

Amantadine treatment in the elderly

There were no studies identified that met the inclusion criteria and addressed amantadine treatment in the elderly.

Discussion

As can be seen from this review, there is a paucity of quality randomised evidence relating to the use of amantadine in either the elderly or children. The lack of controlled evidence in adults would be related to the difficulty in carrying out randomised trials if amantadine prophylaxis is considered a standard or recommended treatment. It is also apparent that the evidence relating to the use of amantadine in children is both old and of questionable quality. Two of the prophylaxis studies identified related to institutionalised children with learning difficulties[530,531] and the other concerns institutionalised children with severe asthma.[532] The treatment studies of children that were identified were conducted in a Japanese population during the late 1960s[533,534] Both studies of elderly people concerned subjects living in either hospital or residential care.[71,537] The studies of elderly people were also affected by a low occurrence of influenza in the institutions being evaluated.

Because of these issues with heterogeneity and generalisability and also with the varied nature and quality of these studies, no formal quantitative synthesis was carried out.

Chapter 6

Analysis of cost-effectiveness

Introduction

This chapter includes both a review of existing evidence of the cost-effectiveness of NIs and a new analysis of cost-effectiveness of their use for both prophylactic and treatment strategies for the control of influenza.

In the first section an overview of existing evidence is presented. The second section presents the economic models used in this analysis. The values used in these models, and the evidence supporting our estimates, are presented in three subsections on valuation of health outcomes, costs and probabilities. The third section contains the results including an analysis of uncertainty. The final section summarises the findings of this chapter.

Existing economic evidence

We identified seven published studies that examined the cost-effectiveness of one or both of oseltamivir or zanamivir. These studies are listed in *Table 86*. Few of these are directly comparable since they assess different interventions for different patient groups. Comparisons are further complicated by the range of international settings.

Burls and colleagues[2,538]

Burls and colleagues[2] examined the cost-effectiveness of zanamivir versus 'standard treatment', where standard treatment consists of symptomatic treatment only, in a UK context on behalf of NICE. An NHS perspective was used and results were presented as cost per illness day avoided (IDA) and cost per QALY generated in high-risk and healthy adult patient groups.

High-risk groups were defined as >65 years of age, or with any of chronic respiratory disease, heart disease, renal disease, diabetes mellitus or immunosuppression. QALYs were estimated by assuming each day of influenza to be equal to health state 22222 on the EQ-5D instrument [standardised assessment method for quality of life (QoL) (EuroQol)] which equates to a valuation of 0.516. The valuation of normal health was assumed to be 0.8. The incremental cost per symptom day avoided whilst influenza is known to be circulating in the high-risk group was estimated as £36. The incremental cost per QALY was estimated as £47,000 in the base case analysis, which employed a diagnostic accuracy level of 34%. This result was found to be extremely sensitive to the effect of treatment on hospitalisations. The base case analysis assumes no difference in hospitalisations between treatment and control groups, but zanamivir is found to be cost-saving if the rates quoted by Mauskopf and colleagues,[5] 2.7% and 5.1%, respectively, are used. However, these figures for hospitalisations are based on extremely small numbers of patients (n = 2 and 1, respectively).

Other elements addressed in the sensitivity analysis that have a substantial impact on the incremental cost-effectiveness ratios (ICERs) were the number of follow-up GP visits, prevalence of true influenza, effectiveness in the ITT population, days to alleviation of symptoms, QALY scores and price of zanamivir. GP visits were assumed equal in the base case scenario and were varied in the sensitivity analysis to 0.46 for zanamivir patients and 0.72 for standard therapy patients, using figures from Mauskopf and colleagues.[5] The sensitivity analysis showed that variations in these parameters can cause the ICER to range from –£37,000 to £184,000 per QALY gained.

Overall, the study showed that given existing evidence regarding the effectiveness of zanamivir in high-risk groups, the technology is unlikely to be cost-effective. However, there is a substantial degree of uncertainty in model parameters. Given that these results were based on subgroups of five trials totalling less than 300 influenza positive persons (Ref. 2, p. 37, Table 12), this is not surprising.

A supplement to the above report that was based on new evidence from GlaxoSmithKline study NAI30008 (see *Table 13* for details) prompted revisions to the high-risk cost-effectiveness analysis (CEA).[538] The report describes how the new data made little difference to the existing estimate of cost per QALY in the high-risk model, actually increasing this ratio from £27,000 (see footnote to *Table 86*) to £31,500. However, in the light of the additional evidence on reductions of antibiotic use

TABLE 86 *Summary of existing economic studies*

Study details	Drug	Patient group	Base case result (Converted to £s)	Potential conflicts of interests
Mauskopf *et al.*[5]	Zanamivir	High-risk adults	5674 per QALY gain	Two of the authors employed by Glaxo Wellcome
Burls *et al.*[2]	Zanamivir	All adults when influenza circulating	65,000 per QALY gain	On behalf of NICE
		High-risk adults when influenza circulating	47,000 per QALY gain[a]	
Burls *et al.*[538]	Zanamivir	High-risk adults when influenza circulating	31,500 per QALY gain (original model) 21,000 per QALY gain (modified model)	On behalf of NICE
Brady *et al.*[6]	Zanamivir	All adults when influenza circulating	50,740 per QALY gain	On behalf of CCOHTA
		High-risk adults when influenza circulating	42,000 per QALY gain	
Husereau *et al.*[7]	Oseltamivir	Healthy adults when influenza circulating	64,095 per QALY gain	On behalf of CCOHTA
		High-risk adults when influenza circulating	91,557 per QALY gain	
Scuffham and West[8]	Zanamivir and oseltamivir	Elderly, prophylaxis and treatment	121,324 per LYG (prophylaxis)	Grants received from Solvay Pharmaceuticals, Aventis Pasteur, Chiron Therapeutics, Berna and Medeva
O'Brien *et al.*[11]	Oseltamivir	Healthy adults	31,035 per QALY gain	Study funded by Hoffman La Roche
Armstrong *et al.*[1]	Zanamivir and oseltamivir	Healthy adults and high-risk	10.53 incremental cost per symptom-free day gained 24.99 with oseltamivir	Authors employed by GlaxoSmithKline Wellcome

[a] This is the figure quoted in Table 9, p. 44. and again in Table 10, p. 45 in the original report. In the text and in the supplement to this study, it is reported that the base case was £27,000.

for patients treated with zanamivir, the authors extrapolated these results to hospital admission rates and mortality. This resulted in a cost per QALY estimate of £21,000.

For healthy adults, ICERs were estimated at £158,000 per QALY gained over the duration of the influenza season, dropping to £65,000 if restricting treatment to periods when influenza is known to be circulating. The sensitivity analysis did not examine the potential impact on hospitalisations.

Brady and colleagues[6]

The authors present an economic evaluation on behalf of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), which drew heavily on the report by Burls and colleagues.[2] Consequently, the results are broadly similar. QALY values used in this study were generated from HUI3 scores (a quality of well-being scale) from 11 patients that yielded a mean QALY score of 0.636. Non-influenza health was assumed equal to 1. Hospitalisations were assumed to generate QALY scores of 0.35 based on assumed HUI3 scores and rates varied between zanamivir and no treatment based on the RR reduction for antibiotic use. Mortality reductions were included in the high-risk model sensitivity analysis in the same proportion as reductions in physician visits and hospitalisations. Results were calculated on the basis of the mean prevalence of

influenza throughout the season (14%) and when influenza is known to be circulating (35%). Converting results using purchasing power parities, Brady and colleagues estimate a cost per QALY of approximately £42,000 for high-risk adults when influenza is known to be circulating. A number of one-way and multi-way sensitivity analyses reflect significant uncertainties associated with this estimate. These range from £161 to £185,045 and are particularly sensitive to the assumption regarding mortality reductions for zanamivir. In the healthy adult model base case, results were £126,000 and £50,740 at levels of diagnostic accuracy of 14% and 35%, respectively.

Mauskopf and colleagues[5]

Mauskopf and colleagues[5] estimated a base-case incremental cost-effectiveness ratio of £5674 in a study of high-risk adults receiving zanamivir. The study was based on analysis of the MIST trial (GlaxoSmithKline NAIB3001), although only 76 patients in total were considered high risk (39 control, 37 treatment) (see Chapter 3 for details of this trial). The authors assumed that zanamivir was only administered to those presenting prior to 36 hours of onset of illness and that the prevalence of influenza was 70% based on the rate observed in the trial. Furthermore, influenza complications in this trial were assumed to be 46% in the control group and only 14% for zanamivir patients. Utility weights in this study were derived from assumptions relating to the Quality of Well-being scale. Each day of influenza was assumed equal to 0.5579 of a QALY. Sensitivity analysis was undertaken on this base case but most scenarios maintained optimistic assumptions relating to the cost-effectiveness of zanamivir.

O'Brien and colleagues[11]

This study estimated the cost-effectiveness of oseltamivir for influenza treatment in healthy Canadian adults (aged 16–64 years). The base case analysis estimated a cost per QALY of £31,035 with 95% CIs of £26,238 to £37,625 based on Monte Carlo simulation. The base case used a probability of influenza infection of 0.69. Two-way sensitivity analysis on the probability of influenza infection and the percentage of patients getting treated beyond 48 hours, two key variables, indicated that ICERs could lie outside these CIs dependent on these values. O'Brien and colleagues argue that their base-case value of 69% diagnostic certainty from the trials of oseltamivir and zanamivir is justified by evidence from a Canadian study.[58] They also use a value of 50% as the base-case probability of a patient with ILI presenting to their physician within 48 hours of symptom onset. This was based on an assumption. The model also allows for differential hospitalisation rates between oseltamivir and no treatment patients based on the probability of pneumonia.

The QALY values used in this study were derived from Likert scale (ordinal scale) data from trial patients. The raw scores from this 10-point scale, anchored at 0 (labelled 'worst possible health') and 10 (labelled 'normal health for someone your age'), were normalised to 0–1 and used as QALYs. The mean value for influenza positive control patients using this method is 0.01162 QALYS [4.24 quality-adjusted life-days (QALDs)] and for those treated with oseltamivir is 0.01258 (4.59 QALDs), a difference of 0.00096 (0.35 QALDs). O'Brien and colleagues[11] actually apply a slightly higher QALY score for those treated with oseltamivir since the trial data reveal a higher value in those who are influenza negative (0.01214 versus 0.01195, 4.43 versus 4.36 QALDs). Although this is cited as a key difference between the study and the NICE/CCOHTA appraisals of zanamivir, in fact this score is very similar. The gain from zanamivir treatment in the NICE base-case healthy adult model is $[(0.8–0.516)/365] \times 1.384 = 0.001077$[a] (0.39 QALDs) (0.8 = assumed value of non-influenza health, 0.516 = assumed QALY score of each day with influenza, 1.384 = median reduction in length of influenza illness).

Husereau and colleagues[7]

This study examined the cost-effectiveness of oseltamivir in healthy adults and high-risk populations. The report was based on similar methods to the previous CCOHTA report on zanamivir.[6] The base-case analysis for healthy adults, using a rate of diagnostic accuracy of 35%, estimated an incremental cost per QALY of £64,095. A number of one-way and multi-way sensitivity analyses indicate that this result is highly sensitive to a range of values used in the model, particularly diagnostic accuracy and the likelihood of late presenters receiving the drug. They conclude that oseltamivir is likely to be cost-effective "only under very favourable assumptions" (p. 43).

In at-risk groups, the cost per QALY was estimated at £91,557 in the base case analysis when the prevalence of influenza was 35%. Uncertainty was addressed using one-way and multi-way sensitivity analyses. At this rate of diagnostic certainty most scenarios were over £54,000 (Canadian $100,000)

per QALY gained. Health utilities were equivalent to the CCOHTA report on zanamivir.

Armstrong and colleagues[1]

In a comparison of the cost-effectiveness in healthy adults of zanamivir and oseltamivir with standard care, Armstrong and colleagues[1] estimate an incremental cost per symptom-free day gained of £10.53 with zanamivir treatment and £24.99 with oseltamivir. The viewpoint for this analysis was an American managed care organisation and made several assumptions that could be considered optimistic. Particularly important is the assumption of 100% diagnostic accuracy. Hoffman La Roche disputed the findings in a reply,[539] and some changes were subsequently made to the analysis which revised the estimate for oseltamivir to £45.43 per symptom-free day gained.

Scuffham and West[8]

This study focuses mainly on the prophylactic use of NIs as a class of drug compared with adamantanes and vaccination strategies, although they also consider the cost-effectiveness of NIs and adamantanes for the treatment of influenza. The study takes the healthcare provider perspective in three European countries (England and Wales, France and Germany) and is restricted to the elderly. For England and Wales they estimate that both opportunistic and active vaccination strategies are cost-saving. Incremental costs per life-year gained are £121,324 for NI prophylaxis and £22,329 for adamantane prophylaxis (assuming a Euro conversion rate of 0.613 current at time of review), but are dominated by vaccination. They also estimate that drug treatment strategies generate an incremental cost per morbidity day avoided of £348 (NIs) and £263 (adamantanes).

These results arise partly because vaccination averts a substantial proportion of hospitalisations and deaths. Prophylactic drug use was assumed to impact on hospitalisations and deaths in proportion to the number of cases averted relative to vaccine. Treatment strategies are assumed to have no impact on either hospitalisations or deaths.

The sensitivity analysis identified that results for vaccine strategies were most sensitive to vaccine price and discount rate. Drug prophylactic strategies were sensitive to the timing of the programme and price.

Summary

Although few treatment studies are directly comparable and only one study was identified that considered the prophylactic use of NIs, several common themes are evident:

- The majority of good-quality studies indicate that it is not possible to conclude whether either oseltamivir or zanamivir is cost-effective either as treatment or prophylactic influenza strategies in **any** patient group given current knowledge. There is a vast amount of uncertainty leading to broad ICERs. This is particularly true in at-risk populations, where cost-effectiveness is highly dependent on the assumptions used to model the effects of treatment on mortality, hospitalisations and other severe complications of influenza.
- Little or no evidence exists regarding the effectiveness of NIs in reducing complications from influenza, hospitalisations and deaths. Such events are rare, particularly in otherwise healthy adult populations. Clinical trials are inevitably underpowered to evaluate such outcomes. In the main, studies have assumed no difference between NI treatment and 'no treatment' groups. Consequently, estimates of QoL for complications from influenza such as pneumonia have not been required.
- The rate of diagnostic certainty is a key quantity in the evaluation of cost-effectiveness of NI treatment strategies.
- The proportion of patients who present within the 48-hour treatment window and the proportion of those presenting after 48 hours who receive treatment are also key variables.
- QoL data are scarce in relation to uncomplicated influenza illness. Most studies have assumed (a) the value of each day with influenza and (b) that influenza days are homogeneous. O'Brien and colleagues[11] were able to take a more sophisticated approach using mean values from QoL data obtained from Hoffman La Roche trials.

Methods for analysis of cost-effectiveness

Alternative options for the treatment and prophylaxis of influenza were assessed in terms of cost-effectiveness using decision analytic models for four separate patient groups: healthy adults, high-risk adults, children and residential care elderly [see the section 'Patient groups' (p. 42) for definitions]. Main results are reported in terms of incremental cost per QALY gained and we also report the cost per influenza illness day avoided. All incremental values are compared with standard care.

Probabilistic sensitivity analysis using second-order Monte Carlo simulation was used to analyse uncertainty in the data. This approach assigns a distribution to model parameters. Random values from those distributions are taken for each sample of the Monte Carlo simulation and a cost-effectiveness result generated based on these values. A large number of samples (10,000) were run for these simulations owing to the degree of uncertainty associated with certain model parameters and the existence of several very small probabilities. This probabilistic sensitivity analysis allowed us to generate CIs around costs and effects. We also present the results of these analyses in CEACs which track the changing percentage of the simulation samples as a function of willingness-to-pay for additional health benefits. In addition, a series of one-way and two-way sensitivity analyses were performed and the effect of alternative model specifications was examined.

Treatment models compare four alternative strategies for each of the patient groups; standard treatment, amantadine treatment, zanamivir treatment and oseltamivir treatment. The form of the model is outlined in *Figure 32*.

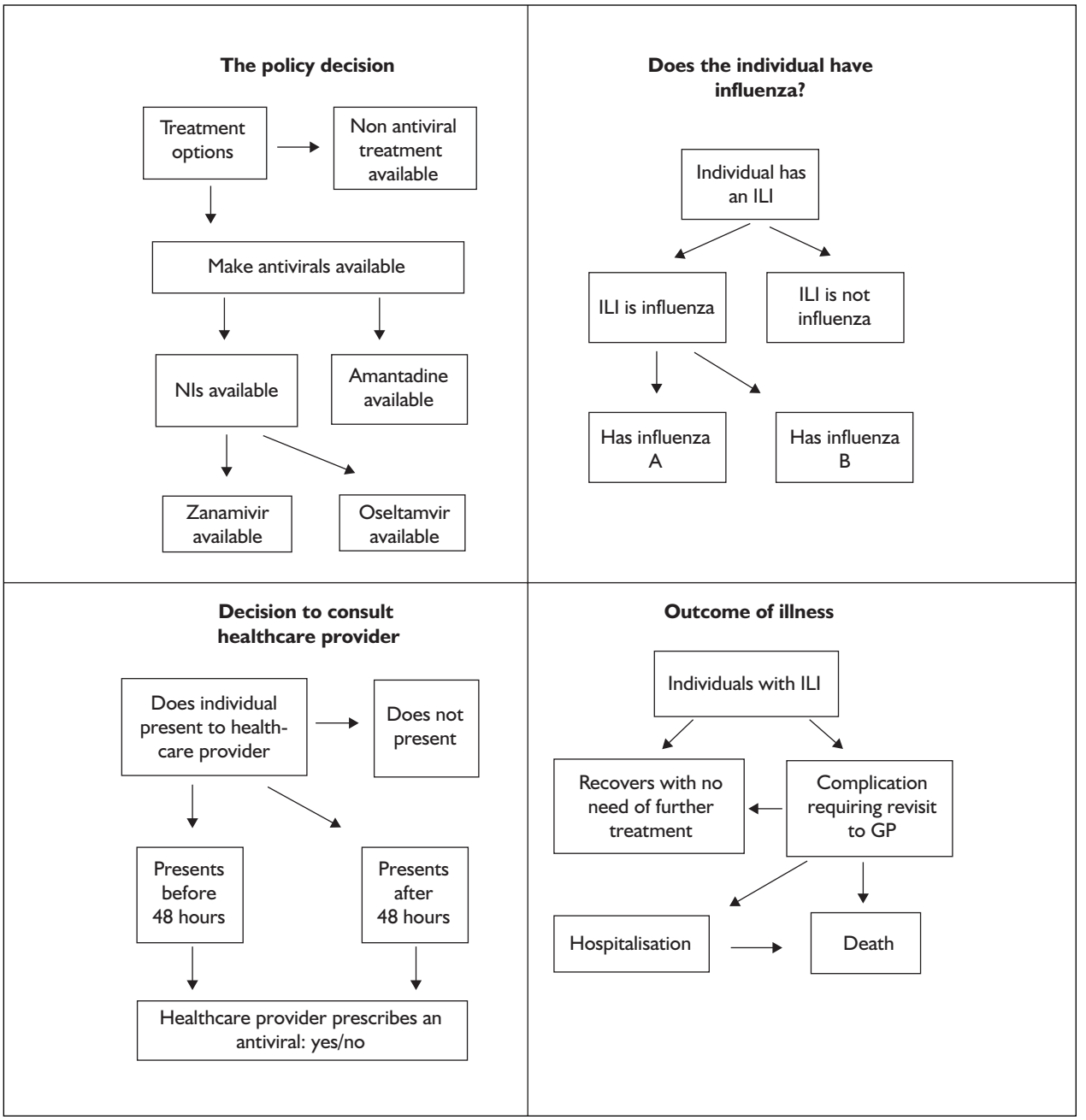

FIGURE 32 *Treatment options*

Subsequent progression through the model is dependent on:

1. the probability that the patient actually has influenza. We assume that no treatment benefits can accrue to non-influenza positive patients. In the case of amantadine the patient must have influenza A to accrue treatment benefits. This is shown in the upper right quadrant of *Figure 32*.
2. The probability that the patient presents to the GP and that they do so within 48 hours of the onset of symptoms, beyond which drug treatments are assumed to generate no benefits. Patients who present have a probability of receiving antivirals. These events are shown in the lower left quadrant of *Figure 32*.
3. The probability that a patient re-visits their GP because of influenza complications. Patients can also experience severe complications and hospitalisations. Of those who experience complications, there is a probability of death. These possible outcomes are shown in the lower right quadrant of *Figure 32*.

Prophylaxis models compare eight strategies: no prophylaxis, vaccination, amantadine, oseltamivir, zanamivir, vaccination combined with amantadine, vaccination combined with oseltamivir and vaccination combined with zanamivir. The decision model is illustrated in *Figure 33*, and shows that the outcome for an individual following any prophylactic strategy is that they may or may not develop an ILI. The structure of the model is only shown for the no prophylaxis strategy. This structure is denoted clone 1 and is the same for all prophylaxis strategies. The costs and benefits associated with each ILI are derived from the 'no treatment' arm of the treatment model described above. These costs and benefits are modified in the case of all strategies that include vaccination on the basis of evidence that vaccination may reduce the severity of influenza. Prophylaxis is assumed to occur during periods when community surveillance by the RCGP report consultation rates for influenza/ILI exceed 50 per 100,000 of the population. In cases where two prophylaxis strategies are used, for example vaccination combined with antiviral prophylaxis, an ICER is presented. This shows the extra costs and benefits of the strategy compared with vaccination on its own.

The analysis is primarily undertaken from the perspective of the NHS although the impact of reduced time away from work is addressed in the sensitivity analysis of healthy adults.

In the following three sections, a brief outline of the values used as benefits, costs and probabilities is given. These values are summarised in *Tables 87–92*. Appendices are used throughout to provide more detailed descriptions of these values and their derivation.

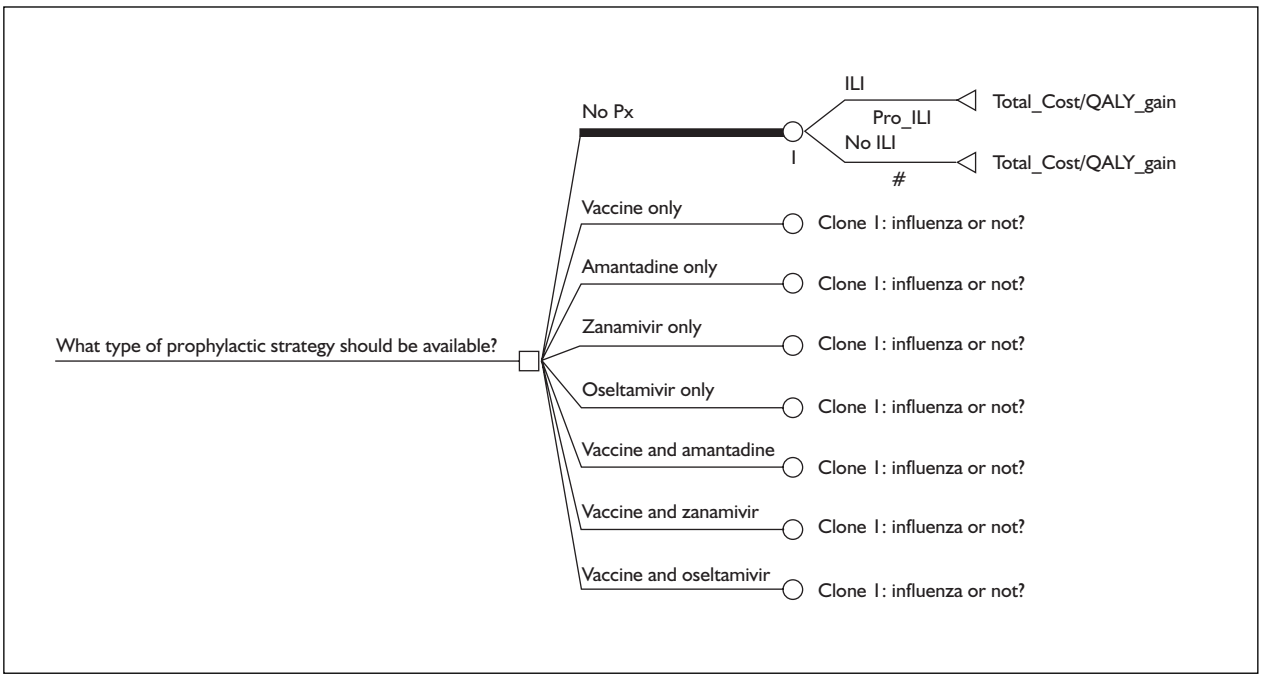

FIGURE 33 *Prophylaxis model*

TABLE 87 *Parameters in healthy adult treatment model*

Description	Mean value	Type of distribution	Distribution parameters
Probabilities			
ILI is influenza	0.460	Normal on log of odds	Mean (–0.162), SD (0.713)
Attack rate	0.066	Normal on log of odds	Mean (–2.657), SD (0.297)
Influenza is influenza A	0.684	β	α (13.51), β (6.251)
Patient presents to GP	0.282	Derived from excess influenza consultations (log normal) and attack rate (normal on log of odds)	μ (13.325), σ (0.190), mean (–2.657), SD (0.297)
Patient presents to GP before 48 hours	0.178	Derived from present on first day (normal on log of odds) and present on second day (normal on log of odds) and rapid onset (normal on log of odds)	Mean (–2.098), sd (0.124), Mean (–2.28), sd (0.133), Mean (0.46), sd (0.443)
Receives treatment if presenting before 48 hours	0.952	β	α (10), β (0.5)
Receives treatment if presenting after 48 hours	0.028	Derived from previous values	
Complication if receiving no treatment	0.371	Normal on log of odds	Mean (–0.528), SD (0.0188)
Complication if zanamivir	0.275	Derived from relative risk of antibiotics (normal on log of RR)	Mean (–0.300), SD (0.129)
Complication if oseltamivir	0.157	Derived from RR of antibiotics (normal on log of RR)	Mean (–0.859), SD (0.383)
Complication if amantadine	0.371	As no treatment	
Pneumonia if no treatment	0.013	Normal on log of odds	Mean (–4.349), SD (0.225)
Pneumonia if zanamivir	0.004	Derived from RR (normal on log of RR)	Mean (–1.051), SD (0.582)
Pneumonia if oseltamivir	0.002	Derived from RR (normal on log of RR)	Mean (–1.898), SD (0.780)
Pneumonia if amantadine	0.013	As no treatment	
Death if no treatment	0.00039	Normal on log of odds	Mean (–7.856), SD (0.174)
Death if zanamivir	0.00014	Derived from pneumonia if zanamivir	
Death if oseltamivir	0.0001	Derived from pneumonia if oseltamivir	
Death if amantadine	0.00039	As no treatment	
Antibiotics at first visit if no treatment	0.420	Normal on log of odds	Mean (–0.323), SD (0.007)
Antibiotics at first visit if given other treatment	0.048	β	α (0.5), β (10)
Adverse event amantadine	0.0164	Derived from OR (normal on log of odds)	Mean (1.18), SD (0.159)
Hospitalisation if no treatment	0.00025	Derived from number of low-risk who are hospitalised (normal on log of odds)	Mean (–8.286), SD (0.0457)
Hospitalisation if zanamivir	0.00009	Derived from number of low-risk who are hospitalised and RR of pneumonia	
Hospitalisation if oseltamivir	0.00004	Derived from number of low-risk who are hospitalised and RR of pneumonia	
Hospitalisation if amantadine	0.00025	As no treatment	
Costs			
GP visit	21.380	No distribution	
Hospital episode	3503	Log normal	μ (8.127), σ (0.262)
Zanamivir	24.98	No distribution	
Oseltamivir	19.16	No distribution	
Amantadine	3.38	No distribution	

continued

TABLE 87 *Parameters in healthy adult treatment model (cont'd)*

Description	Mean value	Type of distribution	Distribution parameters
Antibiotics	4.05	No distribution	
Cost of day off work	39.48	No distribution	
Outcomes			
Length of illness no treatment	7.69	Log normal	μ (2.0382), σ (0.0577)
Length of illness zanamivir	6.01	Derived from difference between treatment and control in zanamivir trials (normal)	Mean (1.683), SD (0.439)
Length of illness oseltamivir	5.77	Derived from difference between treatment and control in oseltamivir trials (normal)	Mean (1.919), SD (0.506)
Length of illness amantadine	6.35	Derived from length of fever amantadine (log normal) and length of fever amantadine control (log normal)	μ (0.758), σ (0.14), μ (1.147), σ (0.1088)
7-day QALY no treatment	0.009	β	α (12.502), β (1408.98)
7-day QALY zanamivir	0.010	Derived from length of illness zanamivir	
7-day QALY oseltamivir	0.010	β	α (17.447), β (1672.03)
7-day QALY amantadine	0.010	Derived from length of illness amantadine	
21-day QALY no treatment	0.043	β	α (110.941), β (2476.02)
21-day QALY zanamivir	0.045	Derived from length of illness zanamivir	
21-day QALY oseltamivir	0.045	β	α (129.078), β (2755.29)
21-day QALY amantadine	0.044	Derived from length of illness amantadine	
QALY death	18.987	None	
QALY pneumonia	0.724	None	
Length of illness amantadine adverse events	5.000	None	
QALY per day amantadine adverse events	0.810	None	
Reduction in time to return to normal activities zanamivir (days)	0.460	Varied in sensitivity analysis within 95% CIs	Low (0.02), high (0.9)
Reduction in time to return to normal activities oseltamivir (days)	1.637	Varied in sensitivity analysis within 95% CIs	Low (0.691), high (2.582)

TABLE 88 *Parameters in high-risk and residential care elderly treatment models*

Description	Mean value	Type of distribution	Distribution parameters
Probabilities			
ILI is influenza	0.460	Normal on log of odds	Mean (–0.162), SD (0.713)
Attack rate	0.062	Normal on log of odds	Mean (–2.722), SD (0.400)
Influenza is influenza A	0.799	β	α (19.068), β (4.807)
Patient presents to GP	0.325	Derived from excess influenza consultations (Log normal) and attack rate (normal on log of odds)	μ (12.004), σ (0.165), mean (–2.722), SD (0.400)

continued

TABLE 88 *Parameters in high-risk and residential care elderly treatment models (cont'd)*

Description	Mean value	Type of distribution	Distribution parameters
Patient presents to GP before 48 hours	0.122	Derived from present on first day (normal on log of odds) and present on second day (normal on log of odds) and rapid onset (normal on log of odds)	Mean (–2.633), SD (0.312), mean (–2.296), SD (0.271), mean (1.335), SD (0.355)
Receives treatment if presenting before 48 hours	0.952	β	α (10), β (0.5)
Receives treatment if presenting after 48 hours	0.011	Derived from previous values	
Complication if receiving no treatment	0.394	Normal on log of odds	Mean (–0.432), SD (0.0439)
Complication if zanamivir	0.221	Derived from RR of antibiotics (normal on log of RR)	Mean (–0.578), SD (0.297)
Complication if oseltamivir	0.261	Derived from RR of antibiotics (normal on log of RR)	Mean (–0.412), SD (0.175)
Complication if amantadine	0.394	As no treatment	
Pneumonia if no treatment	0.0287	Normal on log of odds	Mean (–3.522), SD (0.262)
Pneumonia if zanamivir	0.02	Derived from RR (normal on log of RR)	Mean (–0.361), SD (0.718)
Pneumonia if oseltamivir	0.0219	Derived from RR (normal on log of RR)	Mean (–0.271), SD (0.488)
Pneumonia if amantadine	0.0287	As no treatment	
Death if no treatment	0.007	Derived from probability of death (normal on log of odds)	Mean (–4.934), SD (0.063)
Death if zanamivir	0.005	Derived from pneumonia if zanamivir	
Death if oseltamivir	0.005	Derived from pneumonia if oseltamivir	
Death if amantadine	0.007	As no treatment	
Antibiotics at first visit if no treatment	0.547	Normal on log of odds	Mean (0.189), SD (0.016)
Antibiotics at first visit if given other treatment	0.048	β	α (0.5), β (10)
Adverse event amantadine	0.049	Derived from OR (normal on log of odds)	Mean (0.438), SD (0.508)
Hospitalisation if no treatment	0.012	Derived from number of high-risk who are hospitalised (normal on log of odds)	Mean (–4.405), SD (0.01)
Hospitalisation if zanamivir	0.008	Derived from number of high-risk who are hospitalised and RR of pneumonia	
Hospitalisation if oseltamivir	0.009	Derived from number of high-risk who are hospitalised and RR of pneumonia	
Hospitalisation if amantadine	0.012	As no treatment	
Costs			
GP visit	27.427	No distribution	
Hospital episode	3714.890	Log normal	μ (8.127), σ (0.262)
Zanamivir	24.978	No distribution	
Oseltamivir	19.158	No distribution	
Amantadine	3.378	No distribution	
Antibiotics	4.048	No distribution	

continued

TABLE 88 *Parameters in high-risk and residential care elderly treatment models (cont'd)*

Description	Mean value	Type of distribution	Distribution parameters
Outcomes			
Length of illness no treatment	9.985	Log normal	μ (2.3), σ (0.048)
Length of illness zanamivir	7.305	Derived from difference between treatment and control in zanamivir trials (normal)	Mean (2.68), SD (0.880)
Length of illness oseltamivir	8.48	Derived from difference between treatment and control in oseltamivir trials (normal)	Mean (1.5), SD (1.0907)
Length of illness amantadine	8.64	Derived from length of fever amantadine (log normal) and length of fever amantadine control (log normal)	Mean (0.76), σ (0.14), μ (1.15), σ (0.11)
7-day QALY no treatment	0.006	β	α (11.234), β (1829.28)
7-day QALY zanamivir	0.007	Derived from length of illness zanamivir	
7-day QALY oseltamivir	0.007	β	α (14.525), β (2192.45)
7-day QALY amantadine	0.007	Derived from length of illness amantadine	
21-day QALY no treatment	0.028	β	α (88.09), β (3036.36)
21-day QALY zanamivir	0.031	Derived from length of illness zanamivir	
21-day QALY oseltamivir	0.030	β	α (112.25),β (3657.95)
22 day QALY amantadine	0.030	Derived from length of illness amantadine	
QALY death	4.100	None	
QALY pneumonia	0.720	None	
Length of illness amantadine adverse events	5.000	None	
QALY per day amantadine adverse events	0.740	None	
Length of illness pneumonia	23.000	None	
Residential care[a]			
Probabilities			
ILI is influenza	0.46	Normal on log of odds	
Attack rate	0.0485	Normal on log of odds	Mean (–2.976), SD (0.286)
Patient presents to GP	0.413	Derived from excess influenza consultations (log normal) and attack rate (normal on log of odds)	μ (12.004), σ (0.165), Mean (–2.976), SD (0.286)
Hospitalisation if no treatment	0.148	Derived from number of high-risk who are hospitalised (normal on log of odds)	Mean (–1.753), SD (0.167)
Hospitalisation if zanamivir	0.103	Derived from number of high-risk who are hospitalised and RR of pneumonia	
Hospitalisation if oseltamivir	0.113	Derived from number of high-risk who are hospitalised and RR of pneumonia	
Hospitalisation if amantadine	0.148	As no treatment	
Death if no treatment	0.094	Derived from probability of death (normal on log of odds)	Mean (–2.265), SD (0.204)
Death if zanamivir	0.066	Derived from pneumonia if zanamivir	
Death if oseltamivir	0.072	Derived from pneumonia if oseltamivir	
Death if amantadine	0.094	As no treatment	
Costs			
GP visit	36.000	No distribution	

[a] Variables as for high-risk except for those below.

TABLE 89 *Parameters in children's treatment model*

Description	Mean value	Type of distribution	Distribution parameters
Probabilities			
ILI is influenza	0.475	Normal on log of odds	Mean (–0.1019), SD (0.096)
Attack rate	0.192	Normal on log of odds	Mean (–1.436), SD (0.157)
Influenza is influenza A	0.705	β	α (12.82), β (5.359)
Patient presents to GP	0.155	Derived from excess influenza consultations (log normal) and attack rate (normal on log of odds)	μ (12.578), σ (0.236), mean (–1.436), SD (0.157)
Patient presents to GP before 48 hours	0.572	Derived from present on first day (normal on log of odds) and present on second day (normal on log of odds) and rapid onset (normal on log of odds)	Mean (–0.336), SD (0.239), Mean (–1.253), SD (0.283), Mean (0.432), SD (0.213)
Receives treatment if presenting before 48 hours	0.952	β	α (10), β (0.5)
Receives treatment if presenting after 48 hours	0.121	Derived from previous cells	
Complication if receiving no treatment	0.226	Normal on log of odds	Mean (–1.231), SD (0.0522)
Complication if zanamivir	0.180	Derived from RR (normal on log of RR)	Mean (–0.228), SD (0.278)
Complication if oseltamivir	0.172	Derived from RR (normal on log of RR)	Mean (–0.276), SD (0.383)
Complication if amantadine	0.226	As no treatment	
Pneumonia if no treatment	0.013	Normal on log of odds	Mean (–4.349), SD (0.225)
Pneumonia if zanamivir	0.004	Derived from RR (normal on log of RR)	Mean (–1.051), SD (0.582)
Pneumonia if oseltamivir	0.002	Derived from RR (normal on log of RR)	Mean (–1.898), SD (0.780)
Pneumonia if amantadine	0.013	As no treatment	
Otitis media if no treatment	0.213		
Otitis media if zanamivir	0.213		
Otitis media if oseltamivir	0.120	Normal on log of RR	Mean (–0.574), SD (0.225)
Otitis media if amantadine	0.213		
Death if no treatment	0.000048	Normal on log of odds	Mean (–9.947), SD (1)
Death if zanamivir	0.000017	Derived from pneumonia if zanamivir (log of odds of RR)	
Death if oseltamivir	0.000007	Derived from pneumonia if oseltamivir	
Death if amantadine	0.000048	As no treatment	
Antibiotics at first visit if no treatment	0.279	Normal on log of odds	Mean (–0.949), SD (0.017)
Antibiotics at first visit if given other treatment	0.048	β	α (0.5), β (10)
Adverse event amantadine	0.082	Derived from OR (normal on log of odds)	Mean (0.507), SD (0.0997)
Hospitalisation if no treatment	0.00029	Derived from number of low-risk who are hospitalised (normal on log odds)	Mean (–8.146), SD (0.046)
Hospitalisation if zanamivir	0.0001	Derived from number of low-risk who are hospitalised and RR of pneumonia	
Hospitalisation if oseltamivir	0.00004	Derived from number of low-risk who are hospitalised and RR of pneumonia	
Hospitalisation if amantadine	0.00029	As no treatment	

continued

TABLE 89 *Parameters in children's treatment model (cont'd)*

Description	Mean value	Type of distribution	Distribution parameters
Costs			
GP visit	21.380	No distribution	
Hospital episode	711.500	Log normal	μ (6.52), σ (0.318)
Zanamivir	24.978	No distribution	
Oseltamivir	19.158	No distribution	
Amantadine	3.378	No distribution	
Antibiotics	4.048	No distribution	
Outcomes			
Length of illness no treatment	6.590	Log normal	μ (1.882), σ (0.085)
Length of illness zanamivir	5.190	Derived from difference between treatment and control in zanamivir trials (normal)	Mean (1.4), SD (0.740)
Length of illness oseltamivir	4.957	Derived from difference between treatment and control in oseltamivir trials (normal)	Mean (1.633), SD (0.49)
Length of illness amantadine	5.245	Derived from length of fever amantadine (log normal) and length of fever amantadine control (log normal)	μ (0.6989), σ (0.1087), μ (1.1089), σ (0.0746)
7-day QALY no treatment	0.009	β	α (12.502), β (1408.98)
7-day QALY zanamivir	0.010	Derived from length of illness zanamivir	
7-day QALY oseltamivir	0.010	β	α (17.447), β (1672.03)
7-day QALY amantadine	0.010	Derived from length of illness amantadine	
21-day QALY no treatment	0.043	β	α (110.94), β (2476.02)
21-day QALY zanamivir	0.044	Derived from length of illness zanamivir	
21-day QALY oseltamivir	0.045	β	α (129.08), β (2755.29)
21-day QALY amantadine	0.044	Derived from length of illness amantadine	
QALY death	41.659	None	
QALY pneumonia	0.720	None	
QALY otitis media	0.977		
Length of illness amantadine adverse events	5.000	None	
QALY per day amantadine adverse events	0.810	None	
Length of illness pneumonia	23.000	None	

TABLE 90 *Parameters in healthy adult prophylaxis model*

Description	Mean value	Type of distribution	Distribution parameters
Probabilities			
OR for vaccine	0.268	Normal on log of OR	Mean (–1.316), SD (0.177)
OR for amantadine	0.320	Normal on log of OR	Mean (–1.139), SD (0.126)
OR for zanamivir	0.310	Normal on log of OR	Mean (–1.171), SD (0.387)
OR for oseltamivir	0.258	Normal on log of OR	Mean (–1.355), SD (0.603)
Period of prophylaxis for NIs (weeks)	6	Constant	

continued

TABLE 90 *Parameters in healthy adult prophylaxis model (cont'd)*

Description	Mean value	Type of distribution	Distribution parameters
Mean length of influenza epidemic (weeks)	9.66	Constant	
Probability of exit zanamivir	0.013	Normal on log of OR	Mean (–4.343), SD (0.004)
Probability of exit oseltamivir	0.020	Normal on log of OR	Mean (–3.912), SD (0.015)
Probability of exit amantadine	0.057	Derived from OR of amantadine withdrawals (normal on log of RR)	Mean (0.900), SD (0.213)
Probability of influenza after no prophylaxis	0.066	Derived from attack rate (as in treatment model), and probability that ILI is influenza across influenza season (normal on log of odds)	Mean (–0.847), SD (0.059)
Probability of influenza after zanamivir	0.041	Derived from information described above	
Probability of influenza after oseltamivir	0.039	Derived from information described above	
Probability of influenza after amantadine	0.05	Derived from information described above	
Probability of influenza after vaccination	0.018	Derived from information described above	
Probability of influenza after amantadine and vaccination	0.014	Derived from information described above	
Probability of influenza after zanamivir and vaccination	0.012	Derived from information described above	
Probability of influenza after oseltamivir and vaccination	0.011	Derived from information described above	
OR for reductions in hospitalisations after vaccination	0.500	Normal on log of OR	Mean (–0.693), SD (0.165)
OR for reductions in pneumonias after vaccination	0.470	Normal on log of OR	Mean (–0.755), SD (0.165)
OR for reductions in deaths after vaccination	0.320	Normal on log of OR	Mean (–1.140), SD (0.155)
Probability of adverse event with amantadine prophylaxis	0.039	Sensitivity analysis only	Mean (–0.507), SD (1.000)
Costs			
Cost of course of zanamivir	105.888	Constant	
Cost of oseltamivir	81.444	Constant	
Cost of vaccination	8.395	Constant	
Cost of amantadine	15.378	Constant	
Outcomes			
QALY loss associated with adverse events of amantadine	0.003	Constant	

TABLE 91 *Parameters in high-risk adult prophylaxis model*

Description	Mean value	Type of distribution	Distribution parameters
Probabilities			
OR for vaccine	0.480	Normal on log of OR	Mean (–0.734), SD (0.196)
OR for amantadine	0.320	Normal on log of OR	Mean (–1.139), SD (0.126)
OR for zanamivir	0.310	Normal on log of OR	Mean (–1.171), SD (0.387)
OR for oseltamivir	0.258	Normal on log of OR	Mean (–1.355), SD (0.603)
Period of prophylaxis for NIs (weeks)	6	Constant	
Mean length of influenza epidemic (weeks)	9.66	Constant	
Probability of exit zanamivir	0.013	Normal on log of OR	Mean (–4.343), SD (0.004)
Probability of exit oseltamivir	0.02	Normal on log of OR	Mean (–3.912), SD (0.015)
Probability of exit amantadine	0.128	Normal on log of odds	Mean (–1.917), SD (0.188)
Probability of influenza after no prophylaxis	0.062	Derived from attack rate (as in treatment model), and probability that ILI is influenza across influenza season (normal on log of odds)	Mean (–0.847), SD (0.059)
Probability of influenza after zanamivir prophylaxis	0.039	Derived from information described above	
Probability of influenza after oseltamivir prophylaxis	0.037	Derived from information described above	
Probability of influenza after amantadine prophylaxis	0.046	Derived from information described above	
Probability of influenza after vaccination	0.031	Derived from information described above	
Probability of influenza after amantadine and vaccination	0.023	Derived from information described above	
Probability of influenza after zanamivir and vaccination	0.019	Derived from information described above	
Probability of influenza after oseltamivir and vaccination	0.018	Derived from information described above	
OR for reductions in hospitalisations after vaccination	0.5	Normal on log of OR	Mean (–0.693), SD (0.165)
OR for reductions in pneumonias after vaccination	0.47	Normal on log of OR	Mean (–0.755), SD (0.165)
Odds ratio for reductions in deaths after vaccination	0.32	Normal on log of OR	Mean (–1.140), SD (0.155)
Probability of adverse event with amantadine prophylaxis	0.317	Sensitivity analysis only	
Costs			
Cost of course of zanamivir for prophylaxis	105.888	Constant	
Cost of oseltamivir for prophylaxis	81.444	Constant	
Cost of vaccination	8.395	Constant	
Cost of amantadine	15.378	Constant	

continued

TABLE 91 *Parameters in high-risk adult prophylaxis model (cont'd)*

Description	Mean value	Type of distribution	Distribution parameters
Outcomes			
QALY loss associated with adverse events of amantadine	0.003562	Constant	
Residential care[a]			
Probabilities			
Probability of influenza after no prophylaxis	0.0485	Derived from attack rate (as in treatment model), and probability that ILI is influenza across influenza season (normal on log of odds)	Mean (–0.847), SD (0.059)
Probability of influenza after zanamivir prophylaxis	0.03	Derived from information described above	
Probability of influenza after oseltamivir prophylaxis	0.029	Derived from information described above	
Probability of influenza after amantadine prophylaxis	0.035	Derived from information described above	
Probability of influenza after vaccination	0.024	Derived from information described above	
Probability of influenza after amantadine and vaccination	0.017	Derived from information described above	
Probability of influenza after zanamivir and vaccination	0.015	Derived from information described above	
Probability of influenza after oseltamivir and vaccination	0.014	Derived from information described above	

[a] Variables as for high-risk except for those below.

Estimation of benefits

Length of influenza illness

In the treatment models, the mean length of influenza illness for persons receiving standard treatment was derived from the control arms of relevant zanamivir and oseltamivir trials. The length of influenza illness for individuals given zanamivir and oseltamivir was derived from the treatment arms of the relevant trials. The mean length of illness for persons receiving amantadine was based on the observed length of fever in the Cochrane Review of amantadine.[4] This evidence was modified to include only trials using doses of 100 mg of amantadine per day. This was extrapolated to length of influenza illness using meta-regression based on the observed relationship between length of fever and length of influenza illness observed in oseltamivir trials. Full details are given in Appendix 6.

Quality of life weights for influenza

In the treatment models, QALYs were estimated for each of the four treatment options based on influenza positive patient health state valuations conducted alongside a number of randomised trials of oseltamivir [WV15670, WV15671 and WV15730 in healthy adults (n = 309 placebo, 301 treatment) and WV15819, WV15876, WV15978, WV15812, WV15872 for elderly and high-risk (n =387 control, 339 treatment)]. An 10-point Likert scale (see *Figure 34*) was completed daily over a 21-day period. In order to generate QALY values from this instrument, the following procedure was undertaken:

1. The top end of the Hoffman La Roche Likert scale was recalibrated to mean visual analogue scale (VAS) scores from the Measurement and valuation of health (MVH) study.[540] This was done in order to identify the expected valuation of 'normal health for someone your age' which was used in the Hoffman La Roche Likert scale.
2. VAS equivalent scores were converted to Time Trade Off (TTO) (a method deriving the utilities of individuals' states of health) equivalent scores based on the following equation:[541]

$$\text{QALY} = -0.445 + (2.112 \times \text{VAS}) + (-0.58 \times \text{VAS}^2)$$

TABLE 92 *Parameters in children's prophylaxis model*

Description	Mean value	Type of distribution	Distribution parameters
OR for vaccine	0.199	Normal on log of OR	Mean (–1.615), SD (0.287)
OR for amantadine	0.320	Normal on log of OR	Mean (–1.139), SD (0.126)
OR for zanamivir	0.310	Normal on log of OR	Mean (–1.171), SD (0.387)
OR for oseltamivir	0.258	Normal on log of OR	Mean (–1.355), SD (0.603)
Period of prophylaxis for NIs (weeks)	6	Constant	
Mean length of influenza epidemic (weeks)	9.66	Constant	
Probability of exit zanamivir	0.013	Normal on log of OR	Mean (–4.343), SD (0.004)
Probability of exit oseltamivir	0.020	Normal on log of OR	Mean (–3.912), SD (0.015)
Probability of exit amantadine	0.057	Derived from OR of amantadine withdrawals (normal on log of RR)	Mean (0.900), SD (0.213)
Probability of influenza after no prophylaxis	0.192	Derived from attack rate (as in treatment model), and probability that ILI is influenza across influenza season (normal on log of odds)	Mean (–0.594), SD (0.078)
Probability of influenza after zanamivir prophylaxis	0.131	Derived from information described above	
Probability of influenza after oseltamivir prophylaxis	0.126	Derived from information described above	
Probability of influenza after amantadine prophylaxis	0.152	Derived from information described above	
Probability of influenza after vaccination	0.045	Derived from information described above	
Probability of influenza after amantadine and vaccination	0.036	Derived from information described above	
Probability of influenza after zanamivir and vaccination	0.031	Derived from information described above	
Probability of influenza after oseltamivir and vaccination	0.03	Derived from information described above	
OR for reductions in hospitalisations after vaccination	1.000	Constant	
OR for reductions in pneumonias after vaccination	1.000	Constant	
OR for reductions in deaths after vaccination	1.000	Constant	
Probability of adverse event with amantadine prophylaxis	0.082	Only in sensitivity analysis	
Costs			
Cost of course of NIs for prophylaxis	105.888	Constant	
Cost of oseltamivir for prophylaxis	81.444	Constant	
Cost of vaccination	8.395	Constant	
Cost of amantadine for prophylaxis	15.378	Constant	
Outcomes			
QALY loss associated with adverse events of amantadine	0.001	Constant	

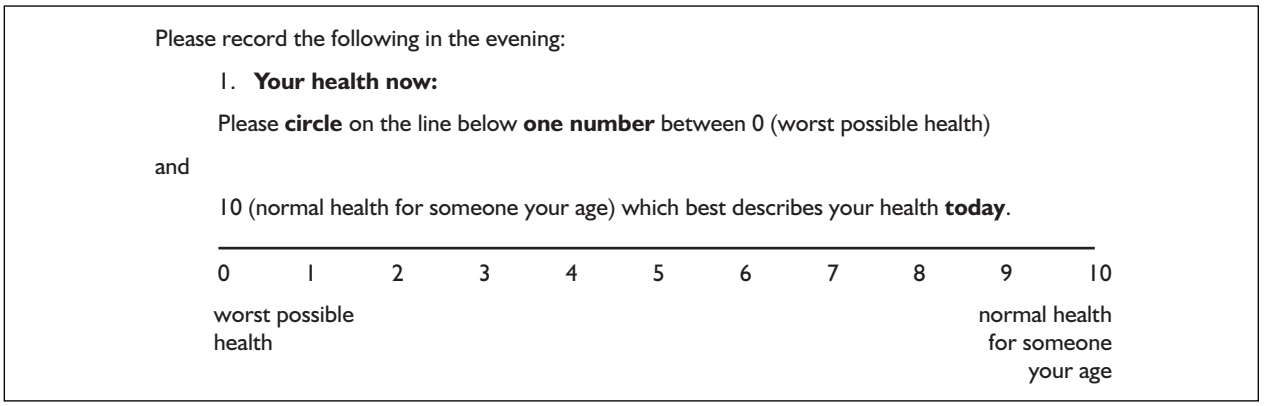

FIGURE 34 *Hoffman La Roche Likert scale*

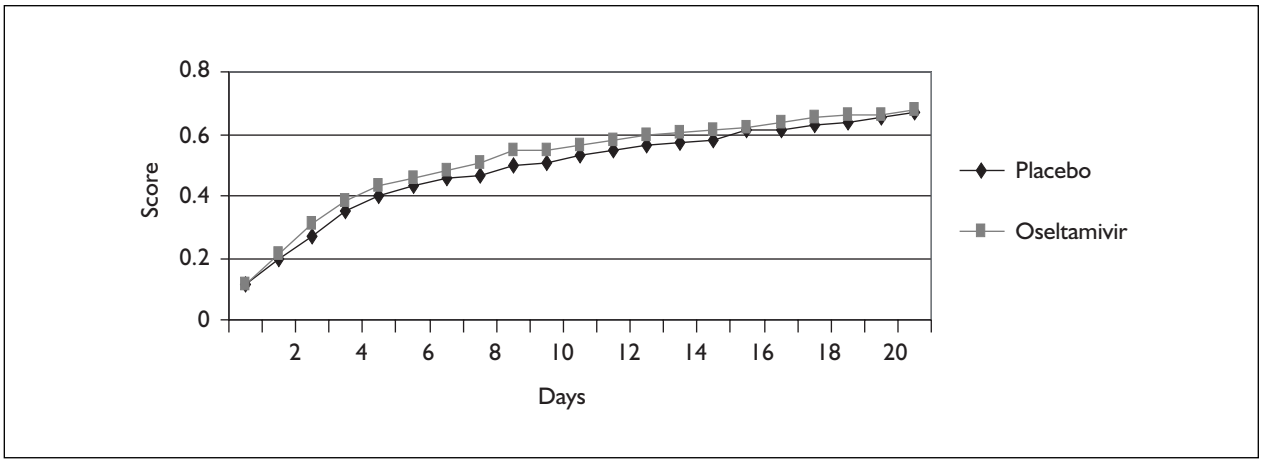

FIGURE 35 *QALDs for elderly and high-risk groups combined*

3. Values for those receiving placebo or oseltamivir were used directly in the model as the QoL values for the 'no treatment' and oseltamivir arms, respectively. These scores were adjusted according to length of influenza illness for zanamivir and amantadine treatments.

The QoL scores for subjects in the 21 days for which the VAS scores were completed are shown in *Figure 35* and *Table 93*.

In trials of healthy adults, patients continued to complete the instrument after 7 days only if they had not recovered. We therefore assigned normal health valuations to missing observations beyond the 7-day period in this patient group, that is, we assumed patients scored 10 on the Hoffman La Roche scale. Results are shown in *Figure 36* and *Table 94*. No information specific to children was available. The adult 'no treatment' and oseltamivir values were therefore used and adjusted for zanamivir and amantadine according to the children-specific length of influenza illness. The sensitivity analysis also examines the impact of using values from the first 7 days alone. The probabilistic analysis of uncertainty did not include that which exists in relation to the transformation steps but was based entirely on the variability in the raw data.

Lives saved

Lives saved were valued according to quality-adjusted life expectancy for each of the three patient groups based on estimation of mean age of influenza deaths, life expectancy, discount rate and quality adjustment according to age. Full details of this process are given in Appendix 7. *Table 95* shows the values used in the models.

Valuation of serious adverse events due to treatment

The treatment models include only the effect of serious adverse events from amantadine since adverse events associated with oseltamivir and zanamivir were considered sufficiently minor not to impact the model (see Appendix 8). The valuation of these events was based on an assumed EQ-5D status.

TABLE 93 *QALDs for elderly and high-risk groups combined*

Day	Placebo QALD	Oseltamivir QALD	Difference
1	0.117313	0.111745	–0.00557
2	0.197075	0.213862	0.016787
3	0.270045	0.311437	0.041392
4	0.348902	0.384854	0.035952
5	0.401373	0.436523	0.03515
6	0.432902	0.460356	0.027454
7	0.460299	0.483436	0.023137
8	0.4639	0.509715	0.045815
9	0.494421	0.543382	0.048961
10	0.502314	0.547231	0.044917
11	0.532226	0.565495	0.033269
12	0.543382	0.576452	0.03307
13	0.561641	0.594872	0.033231
14	0.572611	0.601892	0.029281
15	0.576452	0.615933	0.039481
16	0.612671	0.619619	0.006948
17	0.616314	0.637228	0.020914
18	0.626906	0.651299	0.024393
19	0.640805	0.658247	0.017441
20	0.651299	0.665139	0.01384
21	0.668569	0.678469	0.0099
Total	10.29142	10.86719	0.575766009
Total QALY	0.028196	0.029773	0.001577441

TABLE 94 *QALDs for healthy adults*

Day	Placebo QALD	Oseltamivir QALD	Difference
1	0.067543	0.082757	0.015213
2	0.244658	0.369697	0.125039
3	0.396576	0.513446	0.11687
4	0.526019	0.61172	0.085701
5	0.61172	0.693377	0.081657
6	0.658876	0.738223	0.079347
7	0.704713	0.760151	0.055439
8	0.757784	0.784536	0.020897
9	0.778053	0.792279	0.011224
10	0.787365	0.804462	0.013595
11	0.795763	0.812164	0.013119
12	0.797749	0.817108	0.015525
13	0.798634	0.817179	0.014878
14	0.802947	0.817715	0.01187
15	0.807632	0.820322	0.010227
16	0.80953	0.821819	0.009917
17	0.809846	0.824986	0.012233
18	0.811355	0.823955	0.010183
19	0.811705	0.824773	0.010565
20	0.813527	0.824702	0.009041
21	0.86484	0.86484	0
Total	14.45684	15.22021	0.722538672
Total QALY	0.039608	0.041699	0.001979558

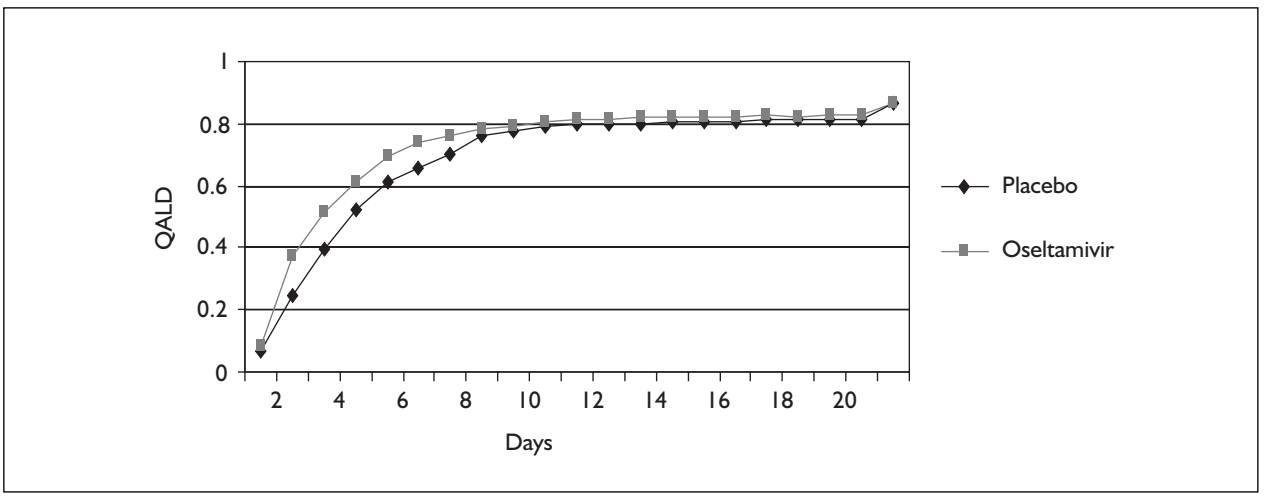

FIGURE 36 *QALDs for healthy adults*

TABLE 95 *Quality-adjusted life expectancy*

Patient group	Discount rate (%) 0	1.50	6
Healthy adults	23.2	19	11.6
High-risk	4.3	4.1	3.5
Paediatric	67.1	41.7	16.8

Valuation of influenza complications

We assume that the self-reported QoL instrument administered in trials of oseltamivir and used to calculate QoL impact for all four treatment options includes patient valuations of commonly reported minor influenza complications.

Valuation of severe complications was based on WHO disability weights for lower respiratory

conditions[542] and applied to the rates of pneumonia observed in the trials. The value used was 0.724 in the healthy adult model and 0.72 in the high-risk and children's models. This approach was taken since the data to which we had access did not identify cases where patients suffered from more than one complication. Pneumonia tended to be the most frequent severe complication and other severe influenza complications such as bronchitis have associated disability weights that are minor (for example, 0.99 for bronchitis). In the children's model we also included otitis media, which was valued at 0.977 from the same source.

Time to return to normal activities

This was applied only to the sensitivity analysis of the healthy adult models in order to value the reduction in productivity costs. Values from *Tables 126* and *127* in Appendix 3 were used to estimate the reduction for oseltamivir and zanamivir. In the absence of equivalent data relating to amantadine, no impact was included.

Estimation of costs

Cost estimates used are for the year 2001.

GP visits

Unit costs for GP visits in the surgery and at home are provided by Netten and Curtis.[543] We estimated a mean cost per GP visit based on the proportions of patients receiving home visits. This proportion was taken from Nicholson and colleagues[544] for the elderly model (25%) and from Ross and colleagues[545] for the healthy adult model (7%). We applied the latter rate to the paediatric model.

Drug costs

For the treatment models, the cost of zanamivir was taken from a published source of drug prices.[546] The expected cost of oseltamivir was obtained from Hoffman La Roche pharmaceuticals. The cost of amantadine was taken from the 2001 industry submission to NICE from Alliance Pharmaceuticals. The cost of antibiotics was derived from a study by Davey and colleagues[547] and the mix of antibiotics used in this study was costed using current prices.[546] The cost of prophylaxis with NIs was based on a 6-week course at 50% of the treatment dose. The prophylaxis costs of amantadine were based on 100 mg per day for 6 weeks. Each drug cost has been increased to take into account pharmacy prescribing fees and container allowances. The cost of vaccination was taken from payments to GPs for vaccination, see Appendix 9. This includes the cost of administration of the vaccination and therefore no GP visit is assumed for patients receiving vaccination. Sensitivity analysis was included which examined the effect of increasing vaccination costs by £10.

Inpatient stays

Costs were based on estimates of mean duration of stay and mean cost per day. For more information, see Appendix 10. For healthy adults we used Healthcare Resource Groups (HRG) code D13 (Lobar, Atypical or Viral Pneumonia <70 without complications or comorbidities) to estimate the mean cost per day. For high-risk groups code D14 (Lobar, Atypical or Viral Pneumonia >69 or with complications or comorbidities) was used. For children we used HRG code PO4 (Lower Respiratory Tract Disorders) to estimate the mean cost per day of hospitalisation. The mean duration of stay was relatively low (2.3 days) for children and it was therefore considered appropriate to use this HRG code which has a relatively low mean duration of episode.

Productivity costs

In the healthy adult model sensitivity analysis, an additional cost was applied to represent the value of lost days of work due to influenza illness. Each day of work was valued according to the proportion of the population in employment[548] and the mean average weekly wage for the UK weighted for full- and part-time employment rates.[549]

Probabilities

Probability of presenting to GP

The probability of presenting to the GP for a patient who develops ILI is derived from estimates of the size of the population,[550] excess influenza consultations[551,552] and attack rates (various sources, see Appendix 11) for the four patient groups.

The estimate of the attack rate for symptomatic influenza was multiplied by the relevant national population estimate to obtain an estimate for the expected numbers of cases of influenza seen each season. The estimate of excess GP consultations due to influenza was divided by the estimate of influenza cases to give an estimate of the proportion of influenza cases who consult their GP. This value does not vary between treatment options in the base-case analysis but the impact of increasing this probability for zanamivir and oseltamivir treatment options is explored in the sensitivity analysis.

Probability of presenting within 48 hours

Data were used to estimate the proportion of those who visit their GP within 48 hours of onset of

illness.[545] This value was adjusted according to the proportion of persons experiencing abrupt onset of influenza using data from a meta-analysis. See Appendix 12 for full details of these data.

Probability of receiving drug treatment

The base case treatment models assume that patients presenting within 48 hours of onset of illness would be likely to receive antiviral treatment (either amantadine, oseltamivir or zanamivir depending on which strategy is under consideration). The probability that those presenting after 48 hours receive antivirals treatment is derived from the numbers of patients where onset of symptoms may not correspond with first exposure. The data obtained from Ross and colleagues[545] and described in Appendix 12 were used to estimate this probability. Subjects who presented in the last 12 hours of the 48-hour period who had insidious onset of influenza symptoms were assumed to be outside the 48-hour period.

Probability of antibiotics

The base case treatment models assume that patients receiving antiviral treatment would be unlikely to receive antibiotics at the initial GP consultation. The rate of antibiotic use was taken from the literature for those receiving standard treatment.[552] Appendix 13 describes these data in more detail. This assumption is tested in the sensitivity analysis.

Probability of complications requiring additional GP visits

For the no treatment strategy, the estimate of complications was taken from an annual report of the Weekly Returns Service, which presented data on first and new consultations and follow-up consultations with GPs for influenza.[553,554] For oseltamivir and zanamivir treatment options we adjusted the standard treatment strategy rate by the relative risk of having antibiotics at a follow-up GP visit; see *Tables 33*, *34*, and *46* and *47*. This was used as a proxy for complications as those in the trials would automatically have follow-up visits to the GP as part of trial protocol. No adjustment was made to the amantadine treatment option as there were considered to be insufficient data to show any reduction in complications with amantadine. See Appendix 14 for more details.

Probability of hospitalisation

Hospitalisations are not considered in the base case models but are included in the sensitivity analysis extrapolated models. In these extrapolated models, for the no treatment strategy we used UK-based data from Ahmed and colleagues[215] and Fleming[551] to estimate the probability of hospitalisation in healthy adult and high-risk populations. Full details are provided in Appendix 15. For paediatric populations the number of hospitalisations for healthy adults was divided by the rate of expected numbers of influenza cases for children. These values were adjusted according to the relative risk of pneumonia referred to above since few data exist on hospitalisations for oseltamivir or zanamivir. In the sensitivity analysis, the hospitalisation rate for oseltamivir was adjusted according to the reduction observed in a clinical trial setting; see *Table 49*.

For the effect of vaccination in reducing hospitalisations in individuals with influenza, the rates used in the base case model for adults, high-risk individuals and residential elderly persons were adjusted according to ORs obtained from a published meta-analysis of the effectiveness of vaccination in the elderly.[555] No effect was assumed in the paediatric model or for antiviral prophylaxis since there was no evidence on which such adjustments could be made.

Probability that ILI is influenza

We assume that NIs and amantadine are effective only in influenza positive patients. Estimates of the proportion of all ILIs which are influenza were obtained from the RCGP (Fleming D, Royal College of General Practitioners, Birmingham Research Unit: personal communication) and were given for both epidemic (defined as greater than 50 reports per 100,000 people per week) and non-epidemic periods. Appendix 16 gives full details.

Amantadine is effective only for the treatment of influenza A. Data from the PHLS[556] recording influenza A and B reports for a 9-year period from 1992 to 2001 were used to estimate the probability that influenza was influenza A; See Appendix 17.

Probability of adverse events

The probability of adverse events from vaccination is estimated at 2% based on the observation of a 2-day work absence per 100 healthy adults from influenza vaccination;[382] see Appendix 18. We assumed that each day of work absence was equivalent to a single day with influenza symptoms.

The probability of adverse events associated with amantadine were taken from studies using dose level of 100 mg only. Appendix 8 provides full details.

Adverse events from oseltamivir and zanamivir are not included in the model since they are both minor and rare. In three oseltamivir prophylaxis trials in healthy adults (WV15673/WV15697,[352] 23/980 control (2.3%) and 22/1014 treatment (2.2%) patients withdrew. Withdrawals in prophylaxis trials of zanamivir in healthy adults trials NAIA30010 and NAIA3005 were lower in the treatment group than the control group. These studies are reported in Chapter 4.

Probability of pneumonia

The probability of pneumonia with standard treatment is based on the pooled control arms of the zanamivir and oseltamivir trials. Reductions in the zanamivir and oseltamivir treatment groups were also drawn from these sources as shown in *Tables 35* and *48*. No data relating to children were available for oseltamivir and were limited for zanamivir. Therefore, the rates observed in the healthy adult population were used. The effectiveness of vaccine in reducing pneumonia was estimated using ORs from a published meta-analysis of vaccines in the elderly.[555] This was applied to the adult model, the high-risk model and the elderly residential model. No effect was assumed in the paediatric model or for antiviral prophylaxis.

Probability of otitis media

Otitis media complications were included in the children's models since this is a relatively frequent event in this age group. Reductions were applied only to the oseltamivir treatment arm based on the results reported in Chapter 3.

Mortality

The probability of influenza-related death without antiviral treatment was based on a study[552] which used information from practices contributing to the General Practice Research Database (GPRD); see Appendix 19. No reference was made to subjects living in residential care – we assume that the probability of death from influenza in the >65-year-old group includes community-dwelling subjects and people living in residential care.

We are not aware of any evidence regarding the impact of drug interventions on mortality. In the base-case analysis no reduction in mortality is assumed for any treatment strategy. In the sensitivity analysis we have assumed that observed reductions in pneumonia, which are observed only in the two NIs, also reduce mortality.

Evidence from the literature suggested that vaccination conferred a benefit in terms of reduced mortality rates even if the individual contracted influenza.[555] Evidence from this source was used to estimate the effect that vaccination has in reducing mortality in the adult, high-risk and residential care settings. No effect was assumed in the paediatric model or for antiviral prophylaxis.

Probability of developing influenza after prophylaxis

The effectiveness of prophylaxis strategies was built on a number of pieces of information. The numbers of influenza cases expected in the 'no prophylaxis' arms of models were estimated according to a review of attack rates in placebo groups of trials. The effectiveness of NIs in reducing influenza was taken from our review of the effectiveness of these agents. The value for zanamivir was taken from trial NAIA3005; see Chapter 4, *Table 68*. this value was used for all models. The effectiveness of oseltamivir prophylaxis was taken from a pooled analysis of trials WV15673 and WV15697; see Chapter 4, *Table 74*. The effectiveness of vaccine prophylaxis was taken from a review of vaccination evidence; see Appendix 20. The effectiveness of amantadine prophylaxis was taken from the Cochrane review of amantadine and rimantadine for the treatment and prevention of influenza in healthy adults.[4] For high-risk and children's models there was more limited information on the effectiveness of prophylaxis. For the high-risk and elderly residential care models the benefit of vaccination was taken from a single study.[557] For the children's model a review of existing literature was carried out. A random-effects meta-analysis was then used to estimate a value for the effectiveness of vaccination in children; see Appendix 20. For vaccine prophylaxis we considered that individuals were protected throughout the whole influenza season. For antiviral prophylaxis individuals were assumed to be protected only during the period when they were taking the antiviral. The length of prophylaxis was taken to be 6 weeks in the model. Data for 3 years from the RCGP was used to derive an average number of weeks where influenza was considered to be epidemic. (Fleming D, Royal College of General Practitioner, Birmingham Research Unit, Zambon M, PHLS Central Public Health Laboratory, London: personal communication). The proportion of all influenza cases that occurred in the epidemic period was also calculated from these data. The 6-week prophylactic period was assumed to occur during the epidemic period. The probability that an individual is taking the antiviral during the

epidemic period was the length of prophylaxis divided by the average length of the epidemic period. This value was then multiplied by the proportion of all influenza cases that occurred in the epidemic period. The following calculation was used:

> probability of protection = (total proportion of influenza cases in epidemic period) × (length of prophylaxis/average length of epidemic period)

Three combined strategies were also modelled. The first of these was vaccination and amantadine combined. The second combined strategy was oseltamivir and vaccination combined. The third combined strategy was zanamivir and vaccination. For the combined strategies the effectiveness was assumed to be cumulative, that is, the effectiveness of the antiviral would be applied to any influenza cases not estimated to be prevented by vaccines.

It is also the case with antiviral prophylaxis that if an individual stops taking the agent, protection will also cease soon after this point. The degree to which people withdrew from prophylaxis was taken from the rate of withdrawals cited in the meta-analyses used. For withdrawals from amantadine prophylaxis in elderly residential care it is likely that adverse events and hence withdrawals would be higher than in prophylaxis for healthy adults. For this reason, evidence from a review of mainly observation studies in residential homes was used; see Appendix 8. It is likely that the rate of withdrawal from amantadine prophylaxis in community-dwelling elderly people would lie somewhere between these values. However, in our base-case model the lower value from the healthy adult populations was used as there was limited evidence to justify a different value from this. If an individual withdrew from antiviral prophylaxis they were assumed to do so quickly so no protective benefit was assumed for those who withdrew.

Results of cost-effectiveness models

Base case results are shown in *Tables 96–103*. We present results of the probabilistic model for incremental costs and incremental QALYs for each drug treatment compared with standard treatment. Also presented are 95% CIs around these mean values generated from the probabilistic model. In addition, the mean incremental cost per QALY from the probabilistic model, the deterministic mean cost per QALY and the mean cost per IDA are reported.

Treatment models

Healthy adult treatment model

Table 96 shows that all three drug treatments are more costly and more effective than the standard treatment strategy. The incremental cost per IDA is £5.05, £20.01 and £33.24 for amantadine, oseltamivir and zanamivir, respectively. ICERs are £6190 £19,015 and £31,529 for amantadine, oseltamivir and zanamivir, respectively. Amantadine has the lowest cost per QALY ratio. This is due to the low incremental cost although it generates the lowest incremental benefits. Oseltamivir dominates zanamivir as it produces greater incremental benefits and lower incremental costs.

The data from the probabilistic sensitivity analysis were used to generate the CEACs curves shown in *Figure 37*. The *x*-axis shows the willingness to pay (WTP) for additional QALYs and the *y*-axis shows the proportion of the 10,000 samples from the probabilistic sensitivity analysis that are acceptable given the level of WTP. The three curves show that

TABLE 96 *Treatment 21-day model results for healthy adult population compared with usual care (either antibiotics or no treatment)*

	Stochastic model			Deterministic model	
Strategy	**Incremental cost (95% CI) (£)**	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**	**Mean cost per QALY (£)**	**Mean cost per IDA (£)**
Amantadine	0.107 (0.049 to 0.208)	0.0000173 (–0.00012 to 0.000162)	6190	6132	5.05
Oseltamivir	0.895 (0.416 to 1.701)	0.0000474 (–0.0001482 to 0.0002617)	19015	18690	20.01
Zanamivir	1.290 (0.606 to 2.45)	0.0000409 (–0.0001557 to 0.0002536)	31529	30750	33.24

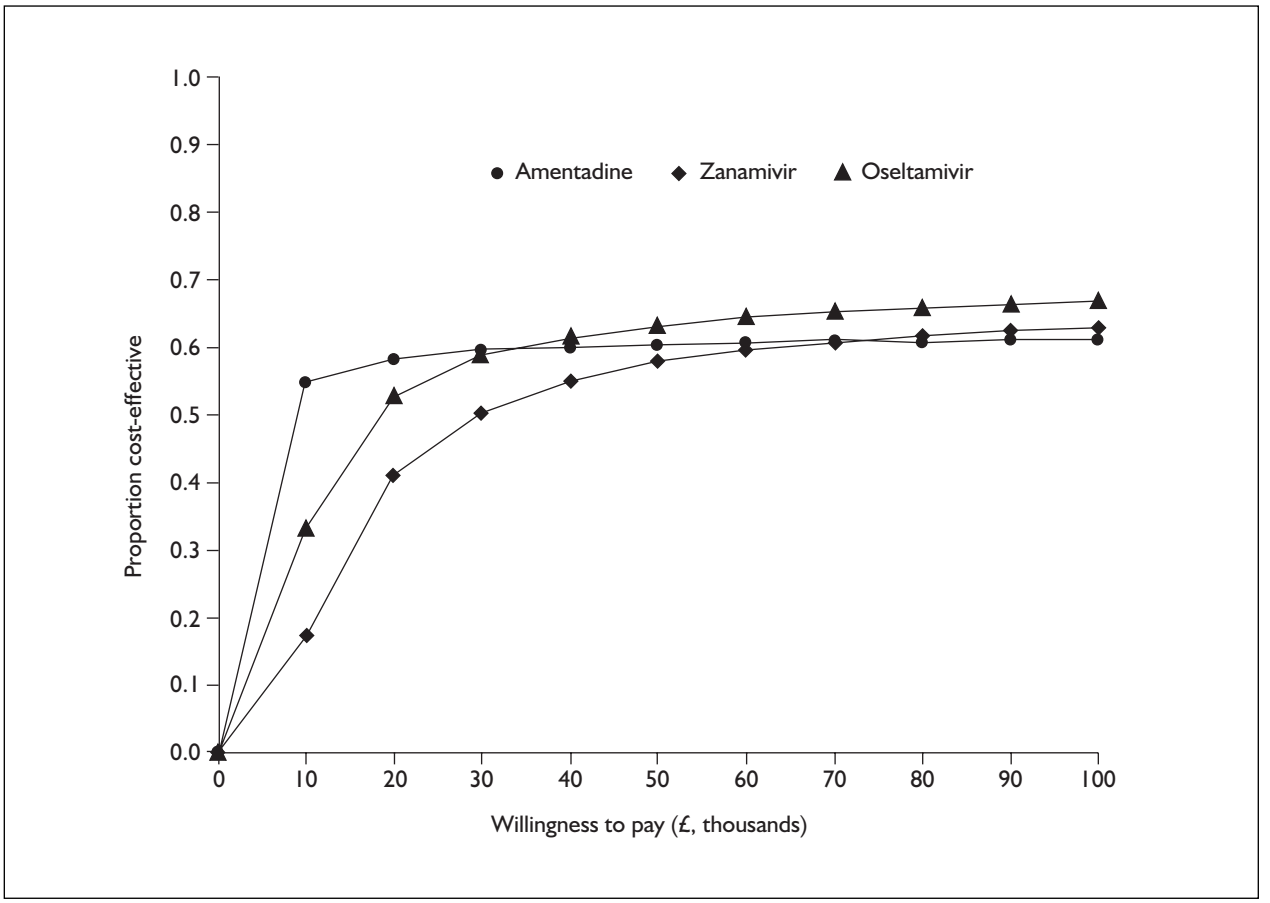

FIGURE 37 *Acceptability curves for healthy adult base-case treatment model*

for each of the three treatments the probability that they are cost-effective rises rapidly at low levels of WTP but begins to plateau beyond £20,000 per QALY. Even at a WTP of £100,000 per additional QALY none of the three drug treatments is more than 70% likely to be cost-effective.

High-risk treatment model

Base case results are shown in *Table 97*. The cost per IDA is £2.99, £24.25 and £18.25 for amantadine, oseltamivir and zanamivir, respectively. ICERs are £4535, £22,502 and £17,289 for amantadine, oseltamivir and zanamivir, respectively.

The CEACs are shown in *Figure 38*. The probability that amantadine is cost-effective is approximately 0.6 at a WTP of £100,000 per QALY.

TABLE 97 *Treatment 21-day model results for high-risk population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model			Deterministic model	
	Incremental cost (95% CI) (£)	Incremental utility (95% CI)	Mean cost per QALY (£)	Mean cost per QALY (£)	Mean cost per IDA (£)
Amantadine	0.063 (0.022 to 0.146)	0.000014 (–0.000098 to 0.000129)	4535	4471	2.99
Oseltamivir	0.712 (0.260 to 1.599)	0.0000317 (–0.0001001 to 0.0001872)	22502	21441	24.25
Zanamivir	0.960 (0.353 to 2.148)	0.0000555 (–0.0000667 to 0.0002207)	17289	16468	18.25

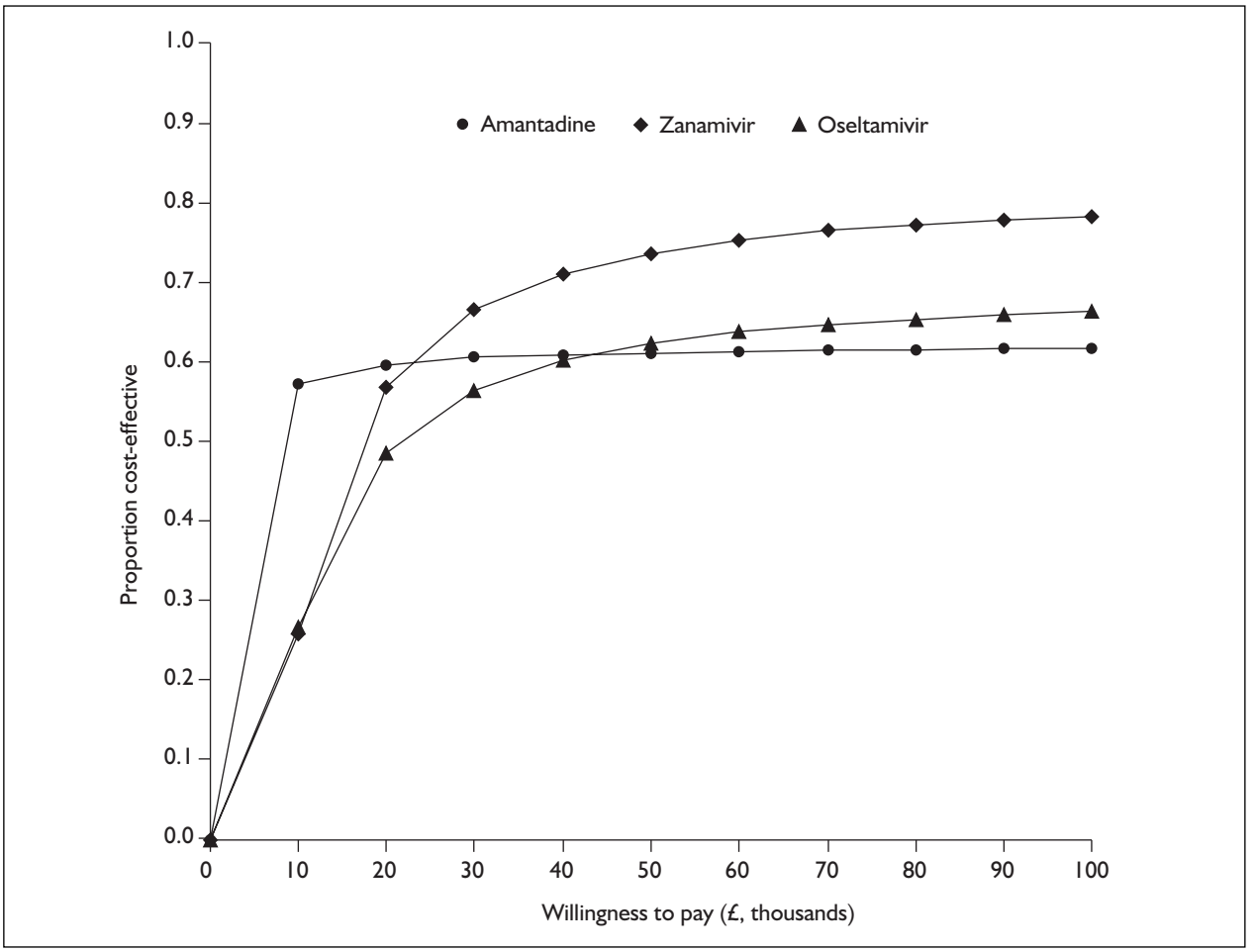

FIGURE 38 *Acceptability curves for high-risk base case treatment model*

The probability that zanamivir is cost-effective is clearly higher than that for oseltamivir beyond a WTP of £20,000 per QALY. At a WTP of £20,000 per QALY zanamivir is approximately 60% likely to be cost-effective and oseltamivir approximately 50% likely to be cost-effective.

Residential care elderly treatment model

Table 98 shows base-case results for the residential care model. The cost per IDA is £2.99, £23.49 and £17.7 for amantadine, oseltamivir and zanamivir, respectively. The ICERs are £5057, £21,781 and £16,819 for amantadine, oseltamivir and zanamivir, respectively.

Figure 39 shows the CEACs for the residential elderly population. In a similar manner to the high-risk population, the acceptability curve for amantadine fails to exceed 60% probability owing to the magnitude of adverse events. Zanamivir is probably more cost-effective than oseltamivir at levels of WTP in excess of £20,000, according to these data.

Children's treatment model

Table 99 shows the base-case results for the children's model. The cost per IDA is £5.96, £24.94 and £38.86 for amantadine, oseltamivir and zanamivir, respectively. ICERs are £6117, £19,461 and £30,825 for amantadine, oseltamivir and zanamivir, respectively. Zanamivir is dominated by oseltamivir.

Figure 40 shows the CEACs generated from the probabilistic sensitivity analysis. These curves are extremely similar to those generated for the adult model. It can be seen that for all three drug treatments the probability of cost-effectiveness never exceeds levels of around 65%.

Prophylaxis models

Healthy adult prophylaxis model

Table 100 shows that the only prophylactic strategy that is cost-effective in healthy adults is vaccination (assuming a threshold value of £30,000 per QALY). Vaccination dominates all independent antiviral strategies. It can be seen

TABLE 98 *Treatment 21-day model results for residential care elderly population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model			Deterministic model	
	Incremental cost (95% CI) (£)	**Incremental QALY (95% CI)**	**Mean cost per QALY (£)**	**Mean cost per QALY (£)**	**Mean cost per IDA (£)**
Amantadine	0.077 (0.031 to 0.16)	0.000015 (–0.00011 to 0.00015)	5057	4471	2.99
Oseltamivir	0.85 (0.37 to 1.64)	0.000039 (–0.00012 to 0.00021)	21781	22350	23.49
Zanamivir	1.14 (0.49 to 2.23)	0.000068 (–0.000082 to 0.000255)	16819	16838	17.7

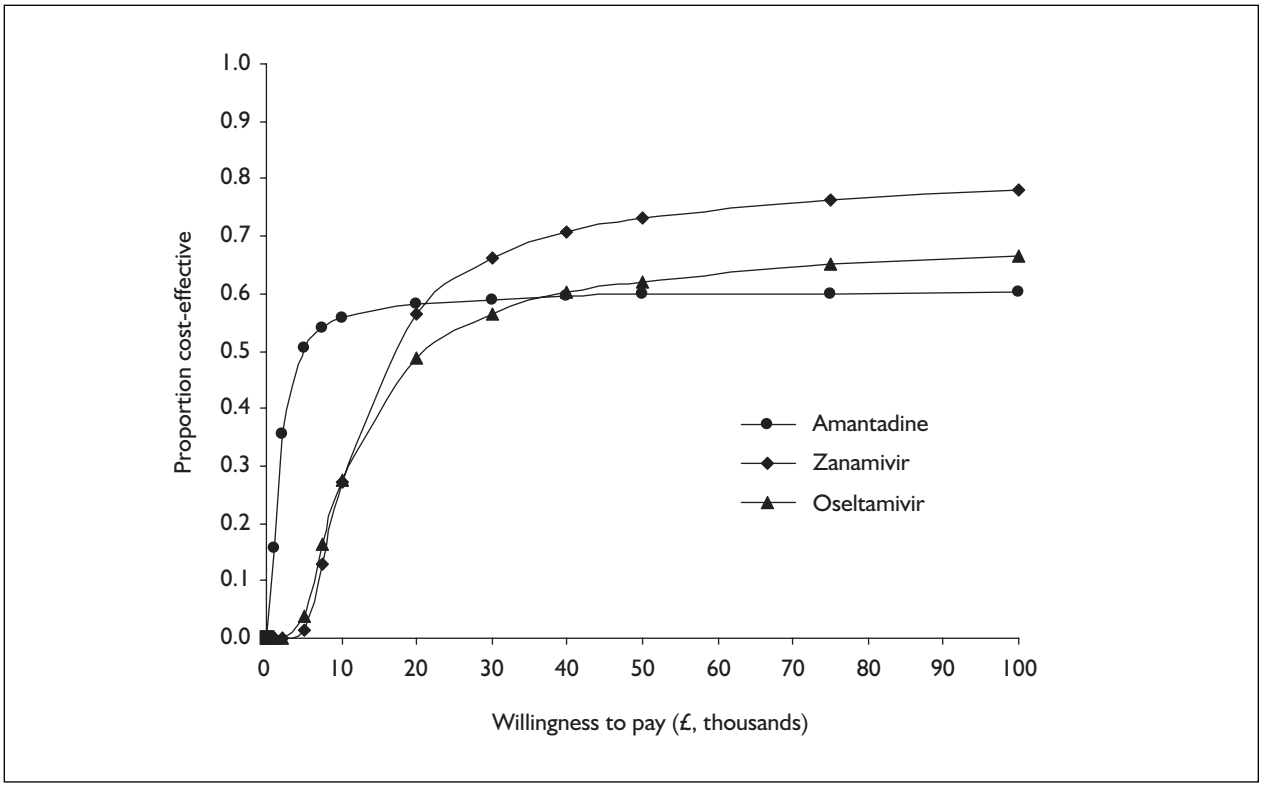

FIGURE 39 *Acceptability curves for residential care base-case treatment model*

TABLE 99 *Treatment 21-day model results for children population compared with usual care (either antibiotics or no treatment)*

Strategy	Stochastic model			Deterministic model	
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**	**Mean cost per QALY (£)**	**Mean cost per IDA (£)**
Amantadine	0.229 (0.119 to 0.405)	0.0000375 (–0.00021 to 0.00029)	6117	5911	5.96
Oseltamivir	1.661 (0.874 to 2.856)	0.0000854 (–0.0002535 to 0.0004391)	19461	19739	24.94
Zanamivir	2.222 (1.165 to 3.838)	0.0000721 (–0.0002691 to 0.0004239)	30825	31142	38.86

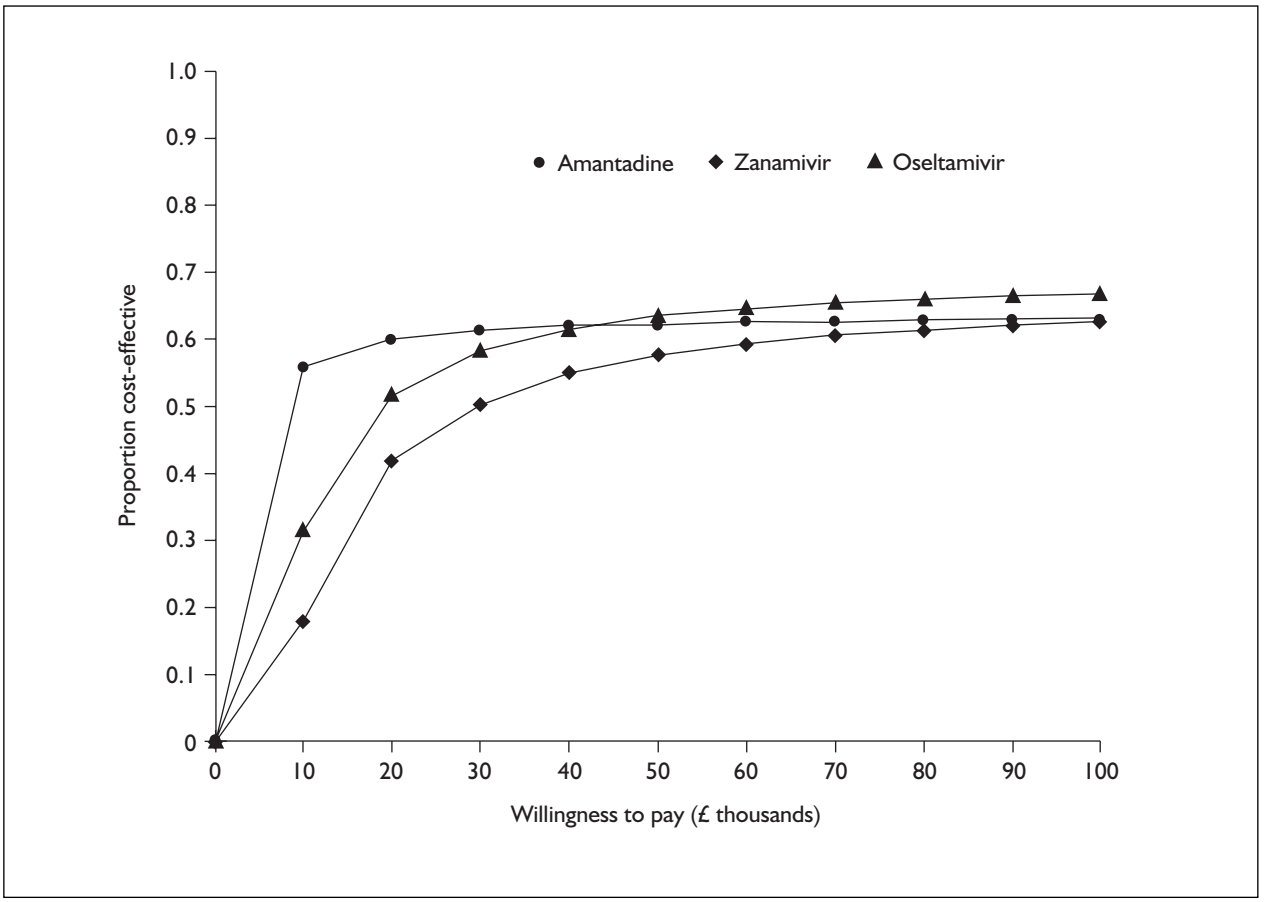

FIGURE 40 *Acceptability curves for children's base-case treatment model*

TABLE 100 *Prophylaxis 21-day model results for healthy adult population compared with no intervention*

Strategy	Stochastic model			Deterministic model	
	Incremental cost (95% CI) (£)	Incremental QALY (95% CI)	Mean cost per QALY (£)	Mean cost per QALY (£)	Mean cost per IDA (£)
Compared with no intervention					
Vaccine prophylaxis	7.60 (7.26 to 7.86)	0.00075 (0.00011 to 0.0016)	10184	10627	21
Amantadine prophylaxis	34.12 (33.97 to 34.23)	0.00021 (0.00001 to 0.0005)	158691	164343	282
Zanamivir prophylaxis	124.49 (124.26 to 124.7)	0.00033 (0.00001 to 0.00077)	382920	385579	662
Oseltamivir prophylaxis	100.03 (99.76 to 100.36)	0.00034 (–0.00002 to 0.00083)	296002	287030	493
Compared with vaccine only					
Vaccine and amantadine	34.3 (34.25 to 34.34)	0.00004 (–0.00002 to 0.00011)	909210	956709	1007
Vaccine and zanamivir	124.77 (124.69 to 124.84)	0.000063 (–0.00003 to 0.00017)	2188039	2237582	2356
Vaccine and oseltamivir	100.33 (100.23 to 100.42)	0.00006 (–0.00003 to 0.00018)	1693168	1667016	1755

that antivirals combined with vaccination produce very high cost per QALY ratios. The cost per QALY ratios for amantadine, zanamivir and oseltamivir, in addition to vaccination, are £909,210, £2,188,039 and £1,693,168 respectively.

High-risk Prophylaxis model

Table 101 shows the results for the high-risk prophylaxis model. Again, vaccination generates a low mean ICER (£2333) and dominates all other independent strategies. Adding antiviral prophylactic strategies to vaccination generates extremely high ICERs: £124,854, £324,414 and £251,004 for amantadine, zanamivir and oseltamivir, respectively.

Residential care elderly prophylaxis model

Table 102 shows the results of the residential care elderly prophylaxis model. In this patient group, vaccination is a cost-saving strategy and dominates the three alternative single prophylactic strategies. ICERs are £28,920, £84,682 and £64,841 for amantadine, zanamivir and oseltamivir, respectively.

Children's prophylaxis model

The results for this model are shown in *Table 103* and are similar to those previously described. Again, the only prophylactic strategy that generates a low ICER is vaccination alone.

Sensitivity analysis

Treatment

For all treatment models, three alternative probabilistic models were run, referred to as 21-day extrapolated, 7-day standard and 7-day extrapolated models. These analyses were undertaken to identify the impact of changing certain key parameters. First, the extrapolated models include valuations for avoided deaths and reduced hospitalisations for the NIs. We found no evidence to support changing these parameters from their no treatment rates for patients receiving amantadine. Second, the valuations for length of influenza illness were recalculated on the basis of patient reported QoL for the first 7 days, as opposed to the 21 days used in the base case. In each case the same probabilistic sensitivity analysis was undertaken as reported previously for the base-case models.

A series of one- and two-way sensitivity analyses were performed on the base-case models. The purpose of these analyses was to identify the variables which are the key drivers of the cost-effectiveness results. Additional one-way sensitivity analyses were performed on variables that were relevant only in the extrapolated models.

The key points from these analyses are highlighted below.

TABLE 101 *Prophylaxis 21-day model results for high-risk adult population compared with no intervention*

Strategy	Stochastic model			Deterministic model	
	Incremental cost (95% CI) (£)	Incremental QALY (95% CI)	Mean cost per QALY (£)	Mean cost per QALY (£)	Mean cost per IDA (£)
Compared with no intervention					
Vaccine prophylaxis	5.53 (2.62 to 7.14)	0.0024 (0.001 to 0.0046)	2333	2501	18
Amantadine prophylaxis	33.27 (32.24 to 33.87)	0.00088 (0.00037 to 0.0017)	37710	39578	209
Zanamivir prophylaxis	123.34 (121.72 to 124.31)	0.0012 (0.00043 to 0.0026)	99941	101801	536
Oseltamivir prophylaxis	98.84 (97.03 to 100.15)	0.0013 (0.00022 to 0.0027)	77156	75561	398
Compared with vaccine only					
Vaccine and amantadine	33.97 (33.58 to 34.19)	0.00028 (0.0001 to 0.00059)	124854	132432	429
Vaccine and zanamivir	124.34 (123.74 to 124.67)	0.000385 (0.00012 to 0.00086)	324414	336526	1090
Vaccine and oseltamivir	99.93 (99.29 to 100.38)	0.0004 (0.000061 to 0.00092)	251004	250603	812

TABLE 102 *Prophylaxis 21-day model results for residential population compared with no intervention*

Strategy	Stochastic model			Deterministic model	
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**	**Mean cost per QALY (£)**	**Mean cost per IDA (£)**
Compared with no intervention					
Vaccine prophylaxis	–13.04 (–34.45 to –0.74)	0.017 (0.0084 to 0.030)	Cost saving	Cost saving	Cost saving
Amantadine prophylaxis	26.22 (18.21 to 30.90)	0.0058 (0.0028 to 0.01)	4511	4732	194
Zanamivir prophylaxis	114.32 (102.96 to 121.22)	0.0075 (0.0029 to 0.014)	15178	15369	629
Oseltamivir prophylaxis	89.44 (76.92 to 98.38)	0.0078 (0.0016 to 0.016)	11397	11104	454
Compared with vaccine only					
Vaccine and amantadine	32.19 (29.57 to 33.55)	0.0011 (0.00046 to 0.0023)	28920	31021	109
Vaccine and zanamivir	122.02 (118.37 to 124.01)	0.0014 (0.00045 to 0.0023)	84682	88095	383
Vaccine and oseltamivir	97.48 (93.43 to 99.95)	0.0015 (0.00028 to 0.0033)	64841	65,212	299

TABLE 103 *Prophylaxis 21-day model results for children's population compared with no intervention*

Strategy	Stochastic model			Deterministic model	
	Incremental cost (95% CI) (£)	**Incremental utility (95% CI)**	**Mean cost per QALY (£)**	**Mean cost per QALY (£)**	**Mean cost per IDA (£)**
Compared with no intervention					
Vaccine prophylaxis	7.05 (6.64 to 7.42)	0.0014 (–0.00057 to 0.004)	5024	6053	7
Amantadine prophylaxis	34.01 (33.85 to 34.15)	0.00037 (–0.00016 to 0.001	92716	107477	309
Zanamivir prophylaxis	124.34 (124.09 to 124.63)	0.00054 (–0.00023 to 0.0015)	229935	259105	40
Oseltamivir prophylaxis	99.87 (99.56 to 100.32)	0.00057 (–0.00026 to 0.0017)	174749	191250	100.6
Compared with vaccine only					
Vaccine and amantadine	34.29 (34.21 to 34.34)	0.000076 (0.000042 to 0.00022)	450240	470878	550
Vaccine and zanamivir	124.76 (124.64 to 124.84)	0.00011 (–0.000062 to 0.00034)	1110263	1129674	1319
Vaccine and oseltamivir	100.31 (100.17 to 100.42)	0.00012 (–0.000073 to 0.00037)	845452	834854	975

Healthy adult treatment models
Appendix 22 shows the results of the sensitivity analyses for the healthy adult treatment models. The additional probabilistic results on alternative model specifications to the base case model show that the extrapolation of base-case results to impacts on hospitalisations and deaths significantly improves the mean ICERs for oseltamivir and zanamivir to £4729 and £8884 in *Table 160*. This improvement in cost-effectiveness is also evident in the acceptability curves shown in *Figure 54*. Models based on 7-day QALY differences rather than the 21 days used in the base case return higher cost-effectiveness ratios for all three drug treatments.

The series of one-way sensitivity analyses on the base-case model (*Table 163*) and those run on the extrapolated model (*Table 164*) indicate that the cost-effectiveness of all alternatives to no treatment is particularly sensitive to the probability that patients presenting with ILI are influenza positive and the probability that patients presenting after 48 hours receive drug treatment. *Figure 55(a)–(c)* is drawn to reinforce the importance of these values. Two-way sensitivity analysis is shown in *Table 165*. This demonstrates the effect of varying both the probability that a person presents to their GP if NIs are available and also the probability that ILI is influenza. It can be seen that the cost per QALY rises rapidly if both the probability of presenting to the GP rises and the probability that any ILI is influenza falls.

The relative risk of pneumonia has a greater impact on model results in the extrapolated model since in this specification the value informs QALYs generated both directly from pneumonia and mortality and informs hospitalisation costs. The impact is greater for zanamivir owing to the relatively wide CIs associated with this treatment for this patient group. In fact, the upper 95% CI in this situation exceeds unity, accounting for the incremental cost effectiveness ratio of £60,500.

The inclusion of productivity gains is based on the mean reported time to return to normal activities in *Tables 126* and *127* in Appendix 3 and their associated 95% CIs. The results show oseltamivir to be cost saving when using the mean time to return to normal activities and zanamivir costs £18,000 per QALY gained.

High-risk adult treatment models
The results shown in Appendix 23 for the sensitivity analyses for the high-risk treatment model reflect similar issues as those discussed above in relation to the healthy adult treatment models.

In addition, *Table 166* and the companion acceptability curve in *Figure 56* indicate that zanamivir and oseltamivir generate similar and relatively low cost-effectiveness ratios in the extrapolated model. The results of the base case model are sensitive to the QALY data used to inform the valuation of length of influenza illness. The 7-day model results, shown in *Table 167*, indicate that the mean cost-effectiveness ratios for oseltamivir and zanamivir rise to £63,175 and £53,691, respectively.

In both the base case and extrapolated case, the impact of the relative risk of pneumonia has a substantial impact. In the extrapolated model both treatments generate negative health benefits when the upper 95% CI value is used.

Residential care elderly treatment models
Many of the results for this model mirror those described above for the high-risk adult models, particularly the impact of 7-day QALY values; see *Table 173* in Appendix 24.

Extrapolation of base case results to incorporate morbidity and hospitalisation effects produces cost saving mean results for both oseltamivir and zanamivir; see *Table 172*. *Figure 58* translates the results of probabilistic sensitivity analysis on this extrapolated model on to an acceptability curve. It is interesting that the curves for both oseltamivir and zanamivir plateau at around 70% probability of cost-effectiveness at a very low WTP. This is because the CIs for the effect of NIs on pneumonias are wide. This means that in the extrapolated models there are a large number of simulations where the OR for the effect of NIs in reducing pneumonias is >1 and hence the effect of NIs on QALYs generated will be negative. This is a product of the uncertainty surrounding the effect of NIs on pneumonias (and hence hospitalisations and deaths in our extrapolated model) and the importance of hospitalisations and death reductions in the residential care model.

No one-way analysis was done on this patient group since the majority of values used are common to the high-risk patient group.

Children's treatment models
The extrapolated children's model shown in *Table 175* in Appendix 25 indicates mean incremental cost effectiveness ratios of £6117, £11,318 and £19,127 for amantadine, oseltamivir

and zanamivir, respectively. Zanamivir is dominated by oseltamivir. The models utilising 7-day QALY values, *Tables 176* and *177*, do not differ substantially from their 21-day equivalents, although the one-way sensitivity analyses utilising the O'Brien and colleagues[11] QALY difference, *Tables 178* and *179*, indicate substantially reduced cost-effectiveness for all three drug treatments.

Prophylaxis

A series of one-way sensitivity analyses were run on each of the four prophylaxis models described in the section 'Prophylaxis models' (p. 128). The parameters varied were attack rate, probability of hospitalisation, cost of hospitalisation, the QALY loss associated with each influenza case, probability that influenza is strain A, probability of death, time off work for the receipt of vaccination (healthy adult model only) and time off work due to influenza (healthy adult model only). Selected results are shown in Appendix 26. Results are not shown if they had no substantial impact on the results. *Table 180* and *Figure 61* show the effect of varying the attack rate of influenza in adults. The cost-effectiveness of all prophylaxis strategies is sensitive to the attack rate. *Table 180* also shows the effect of varying the probability of death. It can be seen that the deterministic cost per QALY ratio is just above £30,000 per QALY for vaccination even if no deaths due to influenza are assumed.

Sensitivity analyses of most interest to the residential population are also shown in Appendix 26, *Table 181*. In the residential care elderly model for previously vaccinated individuals, an attack rate of 20% corresponds to ICERs of approximately £19,000 and £14,000 for zanamivir and oseltamivir, respectively. Also important in the residential care setting is the probability of death from influenza. If this level is 30% then the incremental cost-effectiveness of zanamivir and oseltamivir in previously vaccinated people improves to £26,344 and £19,501, respectively. The result is also sensitive to the QALY value placed on avoided deaths. *Table 181* shows that if the QALY value of an avoided death is changed to 1 QALY then the cost-effectiveness of zanamivir and oseltamivir in addition to vaccine is £247,469 and £183,187, respectively. If the values for adverse events for amantadine are added, it can be seen that amantadine in addition to vaccination is less cost-effective, moving from £4,883 per QALY to £46,251 per QALY. *Table 182* shows the effect of assuming a higher cost for vaccination. If the cost of administering vaccination is £18.40 rather than the base case value of £8.40, then it can be seen that the cost per QALY values for all models increases. For the residential population vaccination is still assumed to be cost saving.

Discussion

This chapter has combined data from Chapters 3 and 4 with additional data sources within decision analytic models to estimate the cost-effectiveness of treatment and prophylactic strategies for influenza from a UK perspective. For each patient group we present a base case model that is derived predominantly from existing evidence.

For treatment of influenza, the mean base-case results indicate that NIs generate relatively favourable cost-effectiveness ratios. However, the degree of uncertainty that is illustrated through probabilistic sensitivity analysis indicates that these mean base case results must be treated with caution.

In the healthy adult model, the acceptability curve for oseltamivir plateaus at around 65%. Zanamivir generates a slightly lower reward. The probability that amantadine is cost-effective is lower than either NI except at very low levels of WTP for additional health benefits. There are two parameters which contribute substantially to these findings: first, the uncertainty associated with the QALY values for influenza, and second, the adverse events associated with amantadine. Since amantadine generates less incremental benefits, albeit at lower incremental cost, in a large proportion of the probabilistic samples adverse events outweigh the benefits of reducing influenza. This pattern is repeated across all four treatment models. In the high-risk and residential elderly models amantadine adverse events are greater, both in frequency and in severity.

The base case focuses primarily on the health benefits generated by influenza treatments through their reduction in the length of influenza. However, it is conceivable that influenza treatments could have an effect on the rate of serious complications that result from influenza. The base case model includes a valuation for the health effects of pneumonia (and otitis media in the children's model) based on rates observed in the trials. However, it does not include the cost of hospitalisations or the health benefits of reduced mortality. Only limited evidence was available for any effects of antivirals on hospitalisations (see Chapter 3, *Table 49*). As for mortality rates, deaths from influenza were rare in trials of NIs.

Therefore, suitable data on mortality were not available from these sources. In the sensitivity analysis, we presented models that extrapolated the observed reductions in pneumonia to hospitalisations and deaths. This was done on the basis that pneumonia is a serious complication commonly associated with influenza mortality. Since we had no equivalent evidence for the effect of amantadine on pneumonia, this extrapolation was not carried out for amantadine. In all four models the cost-effectiveness of NIs is substantially improved by this extrapolation. This was true for both the deterministic and probabilistic analyses. Clearly, the impact on deaths and hospitalisations of NIs has a potentially important effect on cost-effectiveness.

Two other variables with marked effects on the cost-effectiveness ratios are the proportion of all ILIs that are influenza and any increase in the propensity to consult a GP caused by the availability of antiviral drugs. Decreases in the proportion of ILI that are influenza cause the cost-effectiveness ratios to rise rapidly as this increases the number of people who have a drug from which they can receive no benefit. Increasing the extra numbers of people who visit their GP also causes cost-effectiveness ratios to rise.

For prophylaxis, antiviral drugs were compared with vaccination as preventative strategies. In all cases the cost-effectiveness ratios for vaccination were either low or cost-saving. The antiviral strategies were dominated by vaccination, that is, they were both more costly and less effective. Largely, this is because antivirals are only protective whilst being taken. The model was based on a 6-week course of prophylaxis. Since antivirals as a sole strategy were dominated, we investigated the use of a combination of vaccination with antivirals. These had high cost-effectiveness ratios in the majority of cases. The exception was prophylaxis in a residential elderly population where rates of hospitalisations and mortality are high. Although in the base case the cost-effectiveness of antivirals was relatively unfavourable, there were scenarios relating to the elderly residential care model where antivirals as an additional strategy could be cost-effective. In situations where attack rates or mortality rates are substantially higher than in these base case models, short-term prophylaxis may be an efficient strategy.

Limitations of model

The QALY values applied to influenza illness were generated from patient-reported data in trials of oseltamivir. The advantage of this approach is that it recognises the fact that days of illness with influenza are not homogeneous (see *Tables 93* and *94*). However, since these trials only report values for oseltamivir and placebo patients, the values for zanamivir and amantadine had to be imputed based on length of illness. Furthermore, amantadine trials report outcomes in terms of fever days, which in turn had to be converted to illness days. This creates several stages of uncertainty in generating QALY values in addition to that which is incorporated in the probabilistic sensitivity analysis. The QALY data used in the base case model were patient values over 21 days from the onset of illness. The sensitivity analyses examined the impact of censoring these data at 7 days. In O'Brien and colleagues[11] similar 7-day data were used for healthy adults. The unadjusted trial scores reported by O'Brien and colleagues show a difference of 0.35 QALDs between placebo and treatment influenza positive patients. In the placebo arm the sample size was 630 and in the treatment arm 908. The data were from trials WV15730, WV15670, WV15671 and M76001 (the last study was excluded from the meta-analysis in Chapter 3). The sample size for the QALY data used in the treatment models was lower than that reported by O'Brien and colleagues (n = 387 in placebo group, 339 in treatment group; subjects were healthy adults) since patients were selected only from the first three trials listed above. This generates a larger difference in the unadjusted scores. The difference between placebo and treatment groups was 0.45 QALDs in this healthy adult group. Whether such differences would also be apparent in the 21-day patient valuations is not clear, but it is likely that the variance used in the probabilistic sensitivity analysis is larger than it would have been if larger sample sizes had been used. Inclusion of the additional trial data cited by O'Brien and colleagues may have a crucial impact on the mean ICERs and/or the uncertainty reflected in our estimates.

Since amantadine is not a new influenza treatment, much of the evidence relating to its effectiveness is relatively old, not from RCTs and not comparable to more recent evidence for NIs. Furthermore, if only trials using a dose rate of 100 mg per day are used, then the evidence base is considerably reduced. In order to estimate cost-effectiveness, several assumptions have had to be made. For example, the QALY values that we used for amantadine adverse events were based on assumed EQ-5D states. Given the frequency of adverse events in the elderly, this is a significant assumption.

The model extrapolates data on the effectiveness of zanamivir in adult and high-risk groups to model a residential care population. However, there is uncertainty regarding the ability of frail elderly people to use a Diskhaler (see Appendix 21 for a discussion of available evidence).

The effectiveness of prophylactic strategies that combine vaccination with antivirals has been assumed to equal the additive effectiveness of the two independent strategies. Furthermore, whereas the models have made use of evidence that patients developing influenza having been vaccinated suffer less severe influenza, no comparable evidence relating to antivirals was identified.

Children's models have focused on those aged ≤ 12 years as a single group. There may be merit in further subgroup analysis given the greater rate of some severe influenza complications in very young children, such as otitis media. Zanamivir is only licensed for children aged >12 years at this time and the very young may experience problems with the use of the inhaler were this licence to be extended.

Differences in rates of pneumonia observed in clinical trials, used to extrapolate results to include impacts on deaths and hospitalisations, are rarely statistically significant (see *Tables 35* and *48*). The results of these models must therefore be treated with caution.

Comparisons of results with previous evidence

It is important that the results presented here are viewed in relation to those generated in previous studies, outlined in the section 'Existing economic evidence' (p. 105). However, such comparisons must be cautious in relation to non-UK studies. For this reason, the report by Burls and colleagues[2] is the central focus of this section, although the two Canadian studies of oseltamivir by O'Brien and colleagues[11] and Husereau and colleagues[7] are useful comparators.

Treatment models differ in the assumptions made relating to the inclusion of health impacts of treatments on mortality and severe complications of influenza. The closest comparisons are likely to occur between measures of cost per IDA which strips out these health impacts.

In the healthy adult model, our mean figures of £20.01 and £33.24 for oseltamivir and zanamivir, respectively, appear favourable. The Burls and Brady reports estimated a figure for zanamivir approximating £50 per IDA. Our estimate in relation to oseltamivir approximates that made in the O'Brien report (£26.28) but is favourable in comparison with the Husureau report. Our estimates also appear favourable in the high-risk models.

A key difference between studies that is likely to impact this result is the base-case value used for diagnostic accuracy. We used a figure of 46% for healthy adults when influenza is circulating compared with 34% in both the Brady and Burls reports and 69% in the O'Brien report.

Cost per QALY estimates also differ in the base-case treatment models. The Burls base case result for healthy adults estimated a base-case cost per QALY of £65,000 compared with our estimate of £31,000 for zanamivir and £19,000 for oseltamivir. In the high-risk groups the Burls report estimated an ICER of £47,000 in the original version, which was subsequently revised to £31,500 in the supplementary analysis and shown to fall to £21,000 if deaths and hospitalisations reduce in the same proportion to antibiotic use. Although diagnostic accuracy affects this result somewhat, several other differences are worthy of note.

First, the 21-day QALY score generates substantially greater differences between treatment versus no treatment than the QALY valuations used in the Burls report. For zanamivir a median reduction in length of illness of 1.384 days was multiplied by (0.8 – 0.516) to generate a QALD gain of 0.39 in the Burls report. The difference between zanamivir and no treatment in our base case is 0.6 of a QALD. Our results are much less favourable when similar QALY scores are utilised and a similar pattern occurs in the elderly models.

Second, our model includes valuations for pneumonia-related QoL but does not include either mortality reductions or hospitalisations in the base case model. The extrapolated models include these effects and produce favourable results for both NI treatments. However, these reductions were extrapolated on the basis of observed reductions in pneumonia rather than antibiotic use. Whilst the assumed relationship between pneumonia and other severe events is more tenable than that between antibiotic use and severe events, it should be noted that pneumonia is a rare event in clinical trials (see *Tables 35* and *48*) and was recorded in fewer trials than antibiotic use for zanamivir, (see *Table 13*). However, note that the reduction in antibiotic use for zanamivir

in at-risk patients is not statistically significant (*Tables 33* and *34*). Furthermore, the unit cost for hospitalisation used in this study was higher than that used in the Burls report.

Third, as described in Appendix 3, meta-analysis results used in this model were based on mean, rather than median, times to recovery.

In comparison with O'Brien and colleagues,[11] our results indicate more favourable base-case results for oseltamivir in healthy adults despite the lower rate of diagnostic accuracy we used. In part this is again dependent on the larger QALY differences but the price of oseltamivir is also greater in Canada.

In summary, no significant structural differences between the base case treatment models used in this report and those reported in previous studies are apparent. In the sensitivity analysis our model includes a structural difference in that the decision to consult a GP is included. Key differences between our work and other studies are the assumptions made regarding mortality, the probability that ILI is influenza, serious complications and hospitalisations and the QALY scores used to value influenza illness. The probabilistic sensitivity analysis presented in this chapter supports the sensitivity analyses presented by Burls and colleagues in highlighting the substantial degree of uncertainty that surrounds estimates of cost-effectiveness for treatments of influenza.

Broadly, the results of the prophylaxis models substantiate the findings of Scuffham and West.[8] They found that, in elderly persons, vaccination is a cost-saving strategy and that it dominates any solitary antiviral prophylactic strategy. Although not cost saving in the high-risk models presented here, vaccination is associated with an extremely low ICER (£500) and dominates. Key differences between this model and the one presented here are the attack rate (assumed to be 10% by Scuffham and West) and the use of life-years gained as the primary outcome measure in cost-effectiveness.

Chapter 7
Discussion

This report includes new systematic reviews regarding the effectiveness of oseltamivir and zanamvir for treatment and prophylaxis of influenza A and B. These reviews used data from all published sources identified and further unpublished data from both published and unpublished trials made available to us by the manufacturing pharmaceutical companies. In addition, a further systematic review of the published literature on the use of amantadine in children and the elderly was carried out. These reviews and previous systematic reviews in other relevant areas were used to inform an economic decision model which evaluates a variety of treatment and prevention strategies. Where no previous systematic review evidence was available to inform model input parameters, alternative and, where possible, multiple sources of information were consulted, and in many cases further meta-analyses were carried out.

Summary of main results

Amantadine treatment

Systematic review

No trials met the inclusion criteria for elderly patients and only two met the criteria for children. As a result of both clinical and methodological heterogeneity found in the trials, no formal quantitative synthesis was undertaken.

Economic decision model

The incremental costs per QALY gained in the base-case **treatment** analysis of amantadine for treatment of influenza A were:

- £6190 per QALY for the **otherwise healthy adult** population
- £4535 per QALY for the **high-risk** population
- £5057 per QALY for the **residential** population
- £6117 per QALY for the **children** population.

Uncertainty analysis suggests a probability of approximately 60% of a cost per QALY below £30,000 for any of four populations considered.

Amantadine prevention

Systematic review

Two trials met the inclusion criteria for elderly patients and three met the criteria for children. As a result of both clinical and methodological heterogeneity found in the trials, no formal quantitative synthesis was undertaken.

Economic decision model

In the base-case **prophylaxis** analysis, the incremental cost per QALY gained for the residential population was £28,920. For all of the remaining populations the incremental cost per QALY gained was much higher, ranging from £124,854 to £909,210.

Oseltamivir treatment

Systematic review

Oseltamivir 75 mg twice daily for 5 days was found to **reduce** the median duration of symptoms in the influenza positive group by:

- 1.38 days (95% CI 0.80 to 1.96) for the **otherwise healthy adult** population
- 0.50 days (95% CI –0.96 to 1.88) for the **high-risk** population
- 1.5 days (95% CI 0.8 to 2.2) for the **children** population.

Economic decision model

The incremental costs per QALY gained in the base-case **treatment** analysis of oseltamivir were:

- £19,015 per QALY for the **otherwise healthy adult** population
- £22,502 per QALY for the **high-risk** population
- £21,781 per QALY for the **residential** population
- £19,461 per QALY for the **children** population.

Uncertainty analysis suggests a probability between approximately 55 and 60% of a cost per QALY below £30,000 for any of four populations considered.

Oseltamivir prevention

Systematic review

Oral oseltamivir 75 mg once daily for 6 weeks was found to **reduce** the cases of influenza by between approximately 75 and 90% depending on the strategy adopted and the population under consideration.

Economic decision model

In the base-case **prophylaxis** analysis, oseltamivir was dominated by vaccine. For both oseltamivir and vaccine the incremental cost per QALY gained for the residential population was £64,841 compared with vaccine. For all of the remaining populations the incremental cost per QALY gained was much higher, ranging from £251,004 to £1,693,168 per QALY. Uncertainty analysis suggests a probability of 3% of an incremental cost per QALY below £30,000 in the residential population. None of the other populations have a probability of more that 1% of an incremental cost per QALY below £30,000.

Zanamivir treatment

Systematic review

Inhaled zanamivir 10 mg twice daily for 5 days was found to **reduce** the median duration of symptoms in the influenza positive group by:

- 1.26 days (95% CI 0.59 to 1.93) for the **otherwise healthy adult** population
- 1.99 days (95% CI 0.90 to 3.08) for the **high-risk** population
- 1.3 days (95% CI 0.3 to 2.0) for the **children** population (high-risk and otherwise healthy combined).

Economic decision model

The incremental costs per QALY gained in the base-case **treatment** analysis of zanamivir were:

- £31,529 per QALY for the **otherwise healthy adult** population
- £17,289 per QALY for the **high-risk** population
- £16,819 per QALY for the **residential** population
- £30,825 per QALY for the **children** population.

Uncertainty analysis suggests a probability between approximately 50 and 68% of a cost per QALY below £30,000 for any of four populations considered.

Zanamivir prevention

Systematic review

Inhaled zanamivir 10 mg once daily for 6 weeks was found to **reduce** the cases of influenza by between approximately 70 and 90% depending on the strategy adopted and the population under consideration.

Economic decision model

In the base-case **prophylaxis** analysis, zanamivir was dominated by vaccine. For zanamivir in addition to vaccine the incremental cost per QALY gained for the residential population was £84,682 compared with vaccine. For all of the remaining populations the incremental cost per QALY gained was much higher, ranging from £324,414 to £2,188,039 per QALY. Uncertainty analysis suggests a probability less than 1% of a cost per QALY below £30,000 for all populations.

Vaccine prevention

Economic decision model

The incremental cost per QALY gained in the base-case **prophylaxis** analysis of vaccine were:

- £10,184 per QALY for the **otherwise healthy adult** population
- £2333 per QALY for the **high-risk** population
- –£769 (cost saving) per QALY for **residential** population
- £5024 per QALY for the **children** population.

Assumptions, uncertainties and limitations

Systematic reviews and meta-analyses

Treatment

Specific limitations with the oseltamivir and zanamivir systematic reviews and meta-analyses for treatment (Chapter 3) included the statistical issues surrounding the quantitative synthesis of time-to-event data and, in particular, the derivation and use of an estimate for the mean time. However, this particular issue is not only an important one for this report, but is in fact more general, and one which requires methodological investigation. A second limitation of the treatment meta-analyses for complications is the use of a marginal analysis, which does not allow for between-study heterogeneity.

Prevention

In several of the oseltamivir and zanamivir prophylaxis trials, a proportion of the trial populations had received vaccine in the same influenza season, hence making the prophylactic effect of only oseltamivir or zanamivir very difficult to establish.

General comments

In both the systematic reviews of oseltamivir and zanamivir for treatment and prophylaxis, a number of issues arose. First, we know of unpublished results and whole trials evaluating oseltamivir and zanamivir that were not made available to ourselves in the appropriate format before the deadline of 31 December 2001 (although study reports were included in the NICE

submission in February 2002), and hence the possibility of publication bias and particularly time-lag bias (i.e. the trials currently not published may show the drugs to be less favourable than those published) cannot be ruled out. Second, it was difficult to evaluate the quality of the primary studies for oseltamivir and zanamivir, and scores given reflected the completeness of the trial report available rather than any true underlying quality score. The quality of the amantandine studies was low, and in highly specific populations (e.g. children were largely institutionalised with learning difficulties and the elderly populations were limited to those hospitalised and living in residential care).

Economic analysis

Neuraminidase inhibitors

- The NI prophylaxis randomised evidence is limited, spread thinly across four different preventative strategies (most had only one study available), bringing the generalisability of the results into question.
- No NI prophylaxis randomised evidence was available specifically isolated to children; hence the effectiveness in this population group was extrapolated from other evidence.

Amantadine

- In the model, amantadine is assumed to have no impact on hospitalisation since its impact on hospitalisation is largely unknown.
- Amantadine has a more serious adverse event profile than the NIs, but this is difficult to model accurately (see the section 'Amantadine', p. 23).

General – model inputs

- For the **treatment** economic decision models, a series of one-way sensitivity analyses revealed that the probability that patients presenting with ILI are influenza positive, the probability that patients presenting with ILI after 48 hours receive active treatment and the QALY values used for an influenza day are all important model inputs across the various treatment strategies.
- For the prophylaxis economic decision model, a series of one-way sensitivity analyses revealed that the model results for an elderly residential care population appeared to be the most susceptible to uncertainty in model inputs, and particularly so with respect to the attack rate and the QALY values used for avoided deaths.
- No randomised evidence compares the different antivirals/strategies evaluated in the model directly. Hence, all evidence which informs the decision model is indirect, and because of this model results should be interpreted with caution.
- Different definitions were used for the main efficacy end-points for amantadine, oseltamivir and zanamivir. Therefore, there was a need to transfer all outcomes on to a common scale. The uncertainty in performing this transformation is not propagated through the model.
- In addition to different outcome definitions, outcomes were measured on different metrics (e.g. hours or days), which meant that conversion to a common metric was necessary. This rounding may have introduced bias into the analysis.
- The evidence on vaccine, amantadine and the NIs was collected in different periods (1950s to 2001). Standards in trial design and conduct have changed considerably across this period, as have patient populations. Hence caution should be exercised when interpreting the results of indirect intervention comparisons made by the model.
- We relied on previous meta-analyses for some NI outcomes, vaccine and amantadine results. In some instances this was due to limited resources (e.g. amantadine effectiveness in a healthy population), and in others it was because primary data was not available to us (e.g. complications of NIs). The latter used a marginal method of meta-analysis which has a number of deficiencies.
- It was necessary to convert median times to event end-points to mean times. This required making certain assumptions (see Appendix 3).
- For model input parameters not informed by our or previous systematic reviews, although meta-analyses were often carried out to inform, these were not done under a strict systematic review framework. However, we believe that we have been more comprehensive than previous models in the evidence we have included.
- For modelling purposes, we assumed that QoL data supplied by Hoffman La Roche did not include pneumonia complications as this was modelled separately. Only this QoL evidence informed the model, hence further evidence on the QoL would mean that extrapolation of these data to other interventions would not be necessary.
- There is always a concern that favourable trial results cannot be translated into similar benefits in general practice. In particular, the practical implications of getting to see a GP <48 hours after symptom onset and the accuracy of the GP's diagnosis of influenza may reduce the impact of the NIs in practice.

- There was no randomised evidence on the impact of treatments on deaths, hence we extrapolated from hospitalisations and pneumonia data. This is an important issue, hence further evidence on the impact on mortality of the treatments is desirable.
- The model assumes that a person dying from influenza would otherwise live to their average age expectancy. This may be an overestimate of the life-years gained as people at high risk of dying from influenza may, on average, have a shorter life expectancy than the average population.

General – model structure

- The modelling approach modelled at a macro influenza season level. A more complex model would have taken into account the dynamics of an influenza epidemic. Models such as this could address issues such as whether an epidemic could be alleviated or controlled by the blanket use of prophylaxis strategies. Hence the proportion of persons who have influenza at a particular instance in an epidemic and the impact of this number on the probability of other persons contracting influenza are not addressed here.
- We have modelled an 'average influenza season'. In practice, influenza is caused by different types and strains (virulence), with different proportions of influenza types A and B circulating, different lengths of epidemics being observed and background level of immunity existing. Evaluation of treatment and prevention strategies for epidemics with certain characteristics have not been considered.
- A key variable in the model is the proportion of persons presenting to the GP before 48 hours who actually have influenza. If NI treatment for influenza were available widely, then this may change individuals' behavioural patterns (e.g. more persons may present to the GP with ILI but the percentage with true influenza would actually be reduced). Although this issue has been partly addressed in the sensitivity analysis, no changes in behaviour have been factored specifically into the model since sensible prediction would be difficult.
- No modelling of resistance of influenza to amantadine (or indeed other strategies) was carried out. This is likely to be of considerable relevance in residential care when amantadine is used for both treatment and prophylaxis.
- We model the average effectiveness of vaccine, and it should be noted that its effectiveness will change year to year depending how good a match it is to circulating influenza type and strain.
- Although we tried to keep to strictly defined patient groups, there was some overlap in children/adult/high-risk studies with respect to age band definitions used by the trials.
- It is contentious as to whether elderly residential people can reliably inhale zanamivir using the Diskhaler device.[558] We have reviewed the available data on the use of zanamivir in residential care (and those admitted to hospital for acute elderly care) (Appendix 21). The data indicate that approximately 80% of elderly people in residential care or admitted to hospital for acute elderly care are able to use the device.

Implications for future research

Prophylaxis

Although the use of both oseltamivir and zanamivir appears to be of potential benefit in preventing influenza, there is a dearth of evidence and, as a result, considerable uncertainty exists in both the clinical and cost-effectiveness of these drugs. Further studies should therefore be conducted, particularly in residential settings.

Treatment

Although this report presents updated evidence compared with that of the last report for NICE,[559] there is still an imbalance in terms of the number of high-risk patients entered into the treatment trials, and this is reflected in terms of the uncertainty in both the systematic reviews and the economic model results. In addition, there still remain relatively few data on hospitalisation and death following treatment.

General comments

A general limitation of all the economic analyses undertaken in this report is the reliance on data for the utility values of days with influenza that are less than perfect. In the sensitivity analyses reported, this model input was shown to have a considerable impact on the results. Hence a priority for future research in this area should be to obtain high-quality utility data from a sufficiently large and diverse group of individuals.

Implications for assessment of findings

Given the limitations of the systematic reviews and meta-analyses undertaken, the structural

limitations of models developed and the sensitivity of model results to specific inputs, around which there may be considerable uncertainty, caution has to be exercised when making policy decisions based on the evidence presented in this report.

Prophylaxis

Vaccination dominates all independent antiviral strategies. Vaccination of the elderly residential care population was cost saving, but low ICERs were computed beyond the groups currently recommended to receive vaccine by the Chief Medical Officer. Vaccination policies vary from country to country. In Ontario, Canada, for example, universal vaccination is recommended. In the USA, the Advisory Committee on Immunization Practices (ACIP) recommends influenza vaccination more broadly including persons aged 50–64 years. ACIP also recommends vaccination for persons who live with or care for persons at high risk (e.g. healthcare workers and household members who have frequent contact with persons at high risk and can transmit influenza infections to these persons at high risk), and vaccination of children is currently under consideration.

In the UK, there is no recommendation for healthy working age adults to be vaccinated. The Joint Committee on Vaccination and Immunisation (JCVI) advises that there is currently insufficient evidence (e.g. reduction of nosocomial transmission or absenteeism) on which to base a clear recommendation about the routine immunisation of all healthcare workers. However, the Secretary of State's announcement on 23 May 2000, and the national criteria for local winter planning issued by the Department of Health (DH) through the Winter and Emergency Services capacity planning team (WEST), make it clear that NHS employers should include influenza immunisation in their winter planning, and offer it to certain of their front-line employees. Social care employers were instructed to consider similar action. Recently, DH invited tenders to support a range of studies to support policy development on immunising healthcare workers against influenza. Vaccine coverage of healthcare workers remains poor, possibly in part because of differing messages for healthcare workers and the wider population. The results presented here suggest that vaccination of healthy adults generates a relatively low incremental cost per QALY although with considerable uncertainty. Conceivably, a further change to the UK policy to include younger otherwise fit people – and healthcare workers who are more likely to be exposed to influenza – could be reviewed.

Current evidence on the prophylactic use of NIs, in both seasonal and outbreak contexts, is severely limited, which, when combined with the acknowledged limitations and deficiencies of the decision model that has been developed, means that the results presented cannot be considered to be robust, which therefore limits their use to determine policy without further targeted research being undertaken. None the less, outbreaks of influenza are not infrequent in residential care facilities despite high levels of immunisation. Given the burden of influenza in residential facilities, the potential for a considerable reduction in the risk in developing influenza with both a seasonal and outbreak use of NIs and their apparent safety, post-exposure prophylaxis (i.e. outbreak control) might reasonably be expected to yield important benefits (e.g. reduced morbidity, winter admissions and deaths) to patients and the health service.

The cost per QALY gained for seasonal prophylaxis of the residential population with amantadine in comparison with no intervention was relatively low (approximately £5000) – less than half the estimated cost per QALY for oseltamivir and less than one-third of that for zanamivir. However, this must be balanced against the requirement to assess renal function of elderly patients before treatment (to reduce the risk of troublesome adverse reactions), and the considerable potential for the development of drug resistance, particularly when used for both 'treatment' and prophylaxis. Moreover, the evidence on amantadine was collected several decades ago and the amantadine prophylaxis randomised evidence is limited, being based on only two trials. The results are further complicated by the fact that influenza did not occur in one of the two studies. In the model, amantadine is assumed to have no impact on hospitalisation since its impact on hospitalisation is largely unknown. Hence the data cannot be considered sound and further research is strongly recommended prior to policy decisions, preferably a head-to-head comparison with the NIs.

Treatment

Although there is considerable RCT evidence now available on the use of NIs for the treatment of influenza, and the mean base-case results indicate that NIs generate relatively favourable cost-effectiveness ratios, the degree of uncertainty that is illustrated through probabilistic sensitivity

analysis indicates that the results must be treated with caution. It should be noted that the cost-effectiveness of all alternatives to no treatment are particularly sensitive to the probability that patients presenting with ILI are influenza positive. Our base case utilised data on influenza diagnoses collated by the RCGP sentinel practitioner network, with laboratory confirmation using the polymerase chain reaction by the PHLS. It is conceivable that the ability of these GPs to identify clinical influenza is sufficiently different to many other GPs, and this could therefore have implications for the generalisability of the results presented here.

In addition to the uncertainties inherent in the economic modelling, note must also be taken of the delays between onset of illness and consultation by a substantial number of patients with ILI, particularly by the elderly (*Table 148* in Appendix 12). Fever occurs less frequently in the elderly with influenza. Influenza may also present with respiratory syndromes other than ILI, and deterioration may be rapid in those who die. These factors, together with the cost-effectiveness data presented on vaccines, underscore the importance of the Chief Medical Officer's annual recommendation on vaccination.

Although new rapid diagnostic tests for influenza are available, they have evidently not yet reached a high enough level of clinical usefulness (taking into consideration factors including their unit cost, and/or the time required to obtain specimens and carry out the tests, and/or their sensitivity and specificity) to guide the use of antivirals in individual cases. However, the new tests – in concert with RCGP consultation rates of ≥ 50 per 100,000 for ILI – could play an extremely important role in identifying the early presence of influenza in a given locality, thereby facilitating the optimal use of antivirals. Further appraisal and development of rapid diagnostic tests for influenza should be encouraged, particularly in the light of the considerable reduction in the mean cost per QALY in the sensitivity analyses when the probability of ILI being influenza exceeds 0.7. Moreover, with increasing levels of immunisation and public awareness of drugs for influenza, rapid diagnostic testing may ultimately become necessary if the pool of patients with influenza is steadily diluted with increasing consultations for other respiratory infections.

Should the current NICE recommendation on treatment with zanamivir be reaffirmed and extended to include other drugs or other indications, then heightened virological surveillance is recommended for several reasons: first, to define periods when treatment and prophylaxis are appropriate; second, to relate virological findings to clinical diagnosis; third, to gather more information on the incidence of serious complications of influenza; and finally, to monitor the evolution of antiviral resistance. Each is considered imperative in informing future economic evaluations and clinical practice. Furthermore, given the uncertainty concerning the efficacy of NIs and amantadine to prevent complications and deaths – and concerns about their possible inappropriate use in patients with early influenza-like symptoms of life-threatening bacterial infections – we suggest that cohort studies be carried out using large clinical databases.

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David Turner assisted in developing the research protocol for this review, worked on the economic decision model and carried out the amantadine systematic review. Allan Wailoo assisted in developing the research protocol for this review, worked on the economic decision model and worked on the review of previous economic evaluations in the area. Karl Nicholson led the development of the research protocol, provided clinical expertise and input to all stages of the assessment, wrote the clinical background and contributed to all sections of the review document. Nicola Cooper worked on the systematic review of neuraminidase inhibitors, provided further statistical and economic support for the economic model and contributed to the writing and collating of the other sections of the report. Alexander Sutton assisted in developing the research protocol for this review, worked on the systematic review of neuraminidase inhibitors and contributed to the writing of and commented on other sections of the report. Keith Abrams assisted in developing the research protocol for this review, provided statistical advice for the systematic review of neuraminidase inhibitors and economic decision model, contributed to the discussion and read and commented on other parts of the draft report.

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