NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of NICE technology appraisal guidance 67)

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Influenza is an acute infection of the respiratory tract caused by the influenza A and B viruses. The symptoms of influenza are a fever accompanied by respiratory symptoms such as sneezing, coughing, runny nose and sore throat and systemic symptoms such as malaise, myalgia, chills and headaches. Gastrointestinal symptoms such as nausea, vomiting and diarrhoea are also common.

Influenza infection is usually self-limiting and lasts for 3–4 days, with some symptoms persisting for 1–2 weeks. The severity of the illness can vary from asymptomatic infection to life-threatening complications. The most common complications are secondary bacterial infections such as otitis media, pneumonia and bronchitis. Other respiratory complications include viral pneumonia and exacerbation of chronic respiratory diseases such as asthma.

Non-respiratory complications include encephalopathy, transverse myelitis, pericarditis, myocarditis, Reye's syndrome and toxic shock syndrome. Complications are more common in 'at-risk' groups, including people aged 65 years and older, infants (particularly in infants with congenital abnormalities), people with chronic respiratory, cardiovascular, neurological, liver or renal disease, people with diabetes mellitus and people who are immunosuppressed.

Influenza-like illness (ILI), which can be caused by a variety of infectious agents, is a clinical diagnosis made on the basis of symptoms including fever, cough, sore throat, headache and myalgia. The causative agent for an influenza-like illness cannot be routinely determined clinically and diagnosis requires laboratory testing. Influenza can be confirmed by viral culture or polymerase chain reaction (PCR) of nose, throat or nasopharyngeal secretions, or by rising serum antibody titres.

Influenza occurs in a seasonal pattern with epidemics in the winter months, typically between December and March. The illness is highly contagious and is spread from person to person by droplets of respiratory secretions produced by sneezing and coughing. Influenza is commonly transmitted through household contacts, with the highest attack rates in children. People who live in residential accommodation and those who work in healthcare are at a higher risk of infection.

Influenza activity is monitored through surveillance schemes, which record the number of new general practitioner (GP) consultations for influenza-like illness per week per 100,000 population. In England, normal seasonal activity is 30–200 such consultations, with greater than 200 defined as an epidemic. In Wales, the corresponding figures are 25–100, and greater than 400. In addition there are virological monitoring schemes based on the isolation of the virus from clinical specimens. The incidence of influenza is called the attack rate. It is expressed as the proportion of people at risk who develop the disease, during the period under consideration. The influenza attack rate

depends on the circulating level of influenza. It is estimated that yearly influenza epidemics in the UK cause between 12,000 and 13,800 deaths.

The influenza virus undergoes constant genetic mutation, meaning that the antigenic type of virus responsible for each yearly epidemic is slightly different from that in previous years (antigenic drift). Occasionally, the virus can mutate into a completely different subtype to which there is no immunity in the human population, giving rise to pandemics of influenza (antigenic shift).

1.2 Current management

As influenza is a self-limiting illness; management is supportive and consists of relieving symptoms while awaiting recovery. Also, for people in at-risk groups who can start therapy within 48 hours of the onset of an influenza-like illness, current NICE guidance recommends treatment with the anti-viral drugs oseltamivir and zanamivir (for full guidance see NICE Technology Appraisal Guidance 58). All people, but especially those in at-risk groups, need to be monitored for the development of complications. Complications require specific management, and antibiotics are used for secondary bacterial infections.

Prevention of influenza is most effectively achieved by vaccination. In the UK the Department of Health currently recommends that people who are at-risk of influenza infection or complications are vaccinated at the beginning of each winter. Such people are those with chronic respiratory, cardiovascular or renal disease, people with diabetes, people who are immunosuppressed, people aged 65 and above, people with chronic liver or neurological disease, individuals who work or live in residential care facilities, carers of at-risk people, healthcare and other essential workers and poultry workers.

Anti-viral drugs can also be used for the prevention of influenza. *Post exposure prophylaxis (PEP)* can be given to people who have been in contact with a person with ILI. *Seasonal prophylaxis* can be given in the absence of known contact but when it is known that influenza is circulating in the

community. It is given for longer periods of time to cover the duration of the influenza season. Seasonal prophylaxis is considered in exceptional situations such as an antigenic mismatch between circulating strains of the influenza virus and that used for vaccination which would mean that at-risk people are not adequately protected by vaccination. Prophylaxis can also be used to control *outbreaks* of influenza within a residential community. Current NICE recommendations for the use of oseltamivir and zanamivir for the prophylaxis of influenza are included in Appendix B (for full guidance see NICE Technology Appraisal Guidance 67).

2 The technologies

Table 1 Summary description of technologies

Non-proprietary name	Oseltamivir	Amantadine	Zanamivir
Proprietary name	Tamiflu	Lysovir, Symmetrel	Relenza
Manufacturer	Roche	Alliance Pharmaceuticals	GlaxoSmithKline
Dose (adults)	75 mg once daily for 10 days for PEP (up to 6 weeks for seasonal prophylaxis)	100 mg daily for up to 6 weeks	10 mg once daily for 10 days for PEP) (up to 4 weeks for seasonal prophylaxis)
Acquisition cost (BNF edition 54)	£16.36 (for a 10 day course)	£2.40 for 5 capsules (100mg each), £4.80 for 14 capsules; £5.55 for 150ml syrup (50 mg/5 ml)	£24.55(£16.55[1])(for a 10 day course)

Changes to marketing authorisations since NICE technology appraisal 67 was issued in 2003 include: a) that zanamivir now holds a marketing authorisation for prophylaxis whereas previously this was for treatment only; b) for

1 The manufacturer has informed the Institute of a reduction in the price of zanamivir, which has been approved by the Department of Health.

oseltamivir there was an extension to the therapeutic indication to be for children of 1 year of age or older, whereas previously this was limited to people aged 13 years or older.

Oseltamivir

Oseltamivir is a neuraminidase inhibitor that is active against influenza A and B. It prevents viral release and subsequent infection of adjacent cells. It has a marketing authorisation for post-exposure prevention in people aged 1 year or older following contact with a clinically diagnosed influenza case when influenza virus is circulating in the community. In exceptional situations (for example, in case of a mismatch between the circulating and vaccine virus strains, and a pandemic situation), seasonal prevention could be considered in people aged 1 year or older. PEP should be started within 48 hours of contact with an index case of influenza-like illness and continued for 10 days. Seasonal prophylaxis is given for up to 6 weeks. Oseltamivir is administered orally.

Amantadine

Amantadine acts against influenza A by inhibiting an ion channel and blocking viral replication. The marketing authorisation recommends amantadine for the prophylaxis of influenza in people who are particularly at risk. This can include those with chronic respiratory disease or debilitating conditions, older people and those living in crowded conditions. It can also be used for people in families where influenza has already been diagnosed, for control of institutional outbreaks, for people working in essential services who are unvaccinated, or when vaccination is unavailable or contraindicated. The Summary of Product Characteristics states that treatment is recommended for as long as protection from infection is required and that in most instances this is expected to be for 6 weeks. In clinical practice this corresponds to its use as seasonal prophylaxis; for PEP, amantadine is usually given for 4-5 days. Amantadine is administered orally.

Zanamivir

Zanamivir is a neuraminidase inhibitor that is active against influenza A and B. It prevents viral release and subsequent infection of adjacent cells. It has a marketing authorisation for PEP in adults and children (aged 5 years and older) following contact with a clinically diagnosed case in a household. In exceptional circumstances, it may be considered for seasonal prophylaxis of influenza A and B during a community outbreak (for example, in case of a mismatch between circulating and vaccine strains and a pandemic situation). PEP should be initiated within 36 hours of contact with an index case of influenza-like illness and continued for 10 days. Seasonal prophylaxis is given for up to 28 days. Zanamivir is administered by oral inhalation using an inhaler device.

3 The evidence

3.1 Clinical effectiveness

The Assessment Group conducted a systematic search for RCTs conducted in people exposed to a clinically diagnosed case of influenza or for whom seasonal prophylaxis would be appropriate (exceptional circumstances such as mismatch between vaccine and circulating virus strains). The population was divided into children, adults and elderly people, with each group being further subdivided into healthy or at-risk (of developing complications of influenza). The three drugs could be used as seasonal prophylaxis or PEP, with outbreak control referring to PEP in settings where individuals live or work in close proximity (for example in residential care). Trials in which volunteers were challenged with exposure to influenza were included as part of the clinical effectiveness review but the results of these were not used to inform the health economic modelling.

Twenty-two RCTs were identified by the systematic review and a further RCT was provided in a sponsor's submission. No head-to-head RCTs were identified. In most RCTs, the effectiveness of anti-viral drugs is measured as

cases prevented measured in terms of symptomatic laboratory-confirmed influenza (SLCI) or alternatively in terms of clinical illness. The efficacy outcome is presented as the relative risk and protective (or prophylactic or preventive) efficacy of developing influenza with and without prophylaxis. The relative risk is the ratio of the proportion of people developing influenza in the treatment group to the proportion developing influenza in the control group. The lower the relative risk the higher the efficacy of prophylaxis. The protective efficacy is the percentage of people for whom prophylaxis could prevent infection. It is calculated by subtracting the relative risk from 1 (expressed as a percentage). The background circulating levels of influenza for the duration of the individual RCTs described were often not reported clearly.

The available evidence for the effectiveness of antiviral prophylaxis in influenza is summarised in table 2 on page 11 of this Overview, and table 15, page 103 of the Assessment Report.

3.1.1 Oseltamivir

The systematic review yielded six RCTs of oseltamivir prophylaxis. Two seasonal prophylaxis RCTs were in healthy adults and one was in older people within a residential care setting. Two studies were of PEP in households with mixed adult and child populations. One RCT was of oseltamivir prophylaxis against experimentally induced influenza.

A meta-analysis of the two seasonal prophylaxis trials in adults resulted in a relative risk of developing symptomatic laboratory-confirmed influenza with oseltamivir prophylaxis of 0.27 (95% CI 0.09 to 0.83). The study of seasonal prophylaxis in older people showed a 92% protective efficacy for symptomatic laboratory-confirmed influenza ($p=0.002$), with an 86% relative reduction in secondary complications.

The two RCTs of PEP in households resulted in a protective efficacy against symptomatic laboratory-confirmed influenza of 89% ($p<0.001$) in one study and 73% in the other. For contacts of influenza-positive index cases (that is

those who developed confirmed influenza), the protective efficacy was 89% and 68% in each study, respectively. When the results of the two RCTs were pooled by meta-analysis, the resulting relative risk was 0.19 (95% CI 0.08 to 0.45) (therefore the protective efficacy was 81%). For the contacts of influenza-positive index cases, relative risk was 0.21 (95% CI 0.08 to 0.58), (protective efficacy 79%).

Analysis of data from one PEP trial limited to children aged 1–12 years resulted in a protective efficacy of 64% (relative risk of 0.36); and 55% (relative risk of 0.45) for influenza-positive cases. The trial of prophylaxis against experimentally induced influenza B showed a higher rate of infection in the treatment group; relative risk 1.06 (95% CI 0.83 to 1.36). Oseltamivir was of equivalent efficacy in vaccinated and unvaccinated people. Some trials tested for viral resistance, but no evidence of resistance was found, though recent evidence suggests that resistance is emerging in influenza A.

3.1.2 Amantadine

Eight RCTs were identified, none of which were conducted since the previous appraisal. Three trials were of seasonal prophylaxis: two trials in unvaccinated healthy adults and one trial in older people in residential care who were inadequately vaccinated. Two trials investigated outbreak control, one in healthy mostly vaccinated adolescents and one in healthy unvaccinated adults. Three trials were of prophylaxis against experimentally induced influenza in healthy unvaccinated adults. The studies of the efficacy of seasonal prophylaxis were limited by low attack rates. In one study in healthy adults, the relative risk for clinical symptoms with amantadine prophylaxis was 0.4 (95% CI 0.08 to 2.03). Another study in healthy military personnel found no difference in the incidence of acute respiratory illness.

A study of outbreak control in vaccinated adolescent males in a boarding school reported a relative risk of 0.17 (95% CI 0.08 to 0.37) for clinical influenza and a protective efficacy of 90% (95% CI 0.66 to 0.97) for symptomatic laboratory-confirmed influenza. This study also demonstrated

that the protective effect of amantadine prophylaxis is limited to the period of prophylaxis. The second study of outbreak control in unvaccinated adults in semi-isolated engineering schools reported a relative risk for clinical influenza of 0.59 (95% CI 0.49 to 0.70) with amantadine prophylaxis and showed some evidence that prophylaxis reduced the severity and duration of influenza illness.

The three studies of amantadine prophylaxis against experimentally induced influenza resulted in relative risks of 0.22 for symptomatic laboratory-confirmed influenza, 0.26 and 0.58 for clinical influenza and 0.14 for serologically confirmed influenza. The Assessment Group could not draw firm conclusions as to the impact of vaccination status on the efficacy of amantadine prophylaxis. No information was available from the RCTs on the degree of viral resistance. However, there are indications that viral resistance to amantadine is emerging, and therefore the results of the clinical effectiveness of these RCTs will need to be interpreted with caution.

3.1.3 Zanamivir

The Assessment Group's systematic review identified eight RCTs and a further RCT formed part of the sponsor submission. A trial of zanamivir as seasonal prophylaxis in healthy adults resulted in a protective efficacy of 68% (95% CI 37 to 83) against symptomatic laboratory-confirmed influenza. The trial was conducted in an influenza season where the vaccine and circulating strain were mismatched. In the unvaccinated subgroup, the protective efficacy was 60% (95% CI 24% to 80%). A second study of zanamivir seasonal prophylaxis in healthcare workers showed no statistically significant difference in the development of symptomatic laboratory-confirmed influenza. There was also a large-scale study of zanamivir seasonal prophylaxis in community-dwelling at-risk adolescents and adults (aged 12 years and above). For the intent-to-treat (ITT) population the protective efficacy against symptomatic laboratory-confirmed influenza was 83% and relative risk 0.17 (95% CI 0.07 to 0.44). The relative risk did not vary according to vaccination status. The relative risk for developing confirmed influenza with complications was 0.12

(95% CI 0.02 to 0.73). A trial of seasonal prophylaxis with zanamivir in people aged 65 and above, some of whom had further risk factors for influenza complications, resulted in a relative risk of 0.20 (95% CI 0.02 to 1.72).

A trial of zanamivir PEP given for 10 days to all household contacts (aged 5 years or older) of an index case with influenza-like illness resulted in a relative risk for symptomatic laboratory-confirmed influenza of 0.18 (95% CI 0.08 to 0.39). For contacts of influenza-positive index cases the relative risk was 0.20. A further trial of 10-day zanamivir PEP in household contacts resulted in a protective efficacy of 79% (95% CI 62% to 89%), (relative risk 0.21), and 81% protective efficacy in contacts of influenza-positive index cases (95% CI 62% to 90%), (relative risk 0.19). Fewer households in the treatment group had contacts who developed complications of laboratory-confirmed influenza (p=0.01). Two trials (reported jointly) investigated the use of zanamivir PEP for 5 days in household contacts. The relative risk for developing symptomatic laboratory-confirmed influenza was 0.33 during prophylaxis and the length of illness was shorter in the treatment group (p=0.016).

Two studies investigated the prevention of influenza outbreaks in older people in long-term residential care. The available data from one of these trials are limited. The second trial was conducted in mostly unvaccinated people and prophylaxis conferred a protective efficacy for symptomatic laboratory-confirmed influenza of 32% during influenza A outbreaks (95% CI 27 to 67). Some studies tested the susceptibility of viral isolates to zanamivir and no evidence of viral resistance was found.

3.1.4 Adverse events

RCT evidence indicates that in general oseltamivir, amantadine and zanamivir are well tolerated, with a relatively low occurrence of people experiencing drug-related adverse events and drug-related withdrawals. However the Assessment Group and consultees have noted the importance of considering adverse events associated with anti-viral drugs, particularly amantadine, and

particularly in people with comorbidity, such as diabetes mellitus, that could make them more susceptible to adverse effects. Adverse events commonly associated with all three drugs include nausea and skin rashes. Rare adverse events that may be associated with amantadine include convulsions and hallucinations; with zanamivir include bronchospasm, and with oseltamivir include neuropsychiatric disorders. For full details of side effects and contraindications, see the Summaries of Product Characteristics.

Table 2: Summary of efficacy of interventions in prophylaxis against symptomatic, laboratory-confirmed influenza

	Relative risk[a] of developing symptomatic, laboratory-confirmed influenza (95%C.I.)		
Prophylactic strategy	**Amantadine**	**Oseltamivir**	**Zanamivir**
Seasonal prophylaxis in healthy children	Dosage not established	NDA[b]	NDA
Seasonal prophylaxis in at-risk children	Dosage not established	NDA	NDA
Seasonal prophylaxis in healthy adults	0.40 (0.08 to 2.03)	0.27 (0.09 to 0.83)	0.32 (0.17 to 0.63)
Seasonal prophylaxis in at-risk adults and adolescents	NDA	NDA	0.17 (0.07 to 0.44)
Seasonal prophylaxis in healthy elderly subjects	No data reported	NDA	0.20 (0.02 to 1.72)
Seasonal prophylaxis in at-risk elderly subjects	No data reported	0.08 (0.01 to 0.63)	0.20 (0.02 to 1.72)
Post-exposure prophylaxis in mixed households	NDA	0.19 (0.08 to 0.45)	0.21 (0.13 to 0.33)
Post-exposure prophylaxis in healthy children	Dosage not established	0.36 (0.15 to 0.84)	NDA
Post-exposure prophylaxis in at-risk children	Dosage not established	NDA	NDA
Post-exposure prophylaxis in healthy adults and adolescents	0.10 (0.03 to 0.34)	NDA	NDA
Post-exposure prophylaxis in at-risk adults and adolescents	NDA	NDA	NDA
Post-exposure prophylaxis in healthy elderly subjects	NDA	NDA	NDA
Post-exposure prophylaxis in at-risk elderly subjects	NDA	NDA	0.68 (0.36 to 1.27) (85% at-risk)

a For details of RCT characteristics see Assessment Report table 3 (p.55), table 4 (p.59) and table 5 (p.63). In most RCTs the comparator is placebo. Index cases may or may not receive treatment.
b NDA indicates subgroup categories for which no data were available

3.2 Cost effectiveness

3.2.1 Review of cost-effectiveness studies

The Assessment Group identified seven cost-effectiveness studies that included oseltamivir, amantadine or zanamivir for the prophylaxis of influenza, including one sponsor submission from the manufacturer of oseltamivir. No cost-effectiveness analyses were submitted by the manufacturers of amantadine and zanamivir. Two cost-effectiveness studies were UK based and took an NHS perspective (including the assessment for the original appraisal), one was from Canada, one from continental Europe, one from the USA and one from the perspective of the Ministry of Defence in the UK. One study from the UK NHS perspective estimated that the cost-effectiveness oseltamivir PEP compared with no prophylaxis or treatment was approximately £30,000 per QALY gained and compared with no prophylaxis followed by oseltamivir treatment was about £52,000 per QALY gained. The second UK study, the assessment undertaken for the original appraisal, included vaccination as a prophylactic strategy. The model only related to seasonal prophylaxis. All three drug strategies were dominated by vaccination as a prophylactic strategy. When the drugs were combined with vaccination, they were most cost effective in the residential care population, with amantadine in this group having an estimated ICER per QALY gained of about £29,000 per QALY gained. The cost effectiveness estimates of amantadine for other groups and oseltamivir and zanamivir for all groups were much higher.

3.2.2 Manufacturer's model: oseltamivir

The submission from the manufacturer of oseltamivir reported a model to estimate the cost effectiveness of oseltamivir for seasonal and post-exposure prophylaxis of influenza, comparing it with amantadine, zanamivir and no prophylaxis for adults and children older than 12 years who were healthy or at-risk, and for children aged 1–12 years and 1–5 years. A cost-effectiveness analysis was undertaken for the comparison of oseltamivir with amantadine or

usual care. For the comparison of oseltamivir with zanamivir, it was assumed that both drugs are equally effective and a cost-minimisation analysis was undertaken.

Table 3: Results of economic analysis submitted by manufacturer of oseltamivir

Economic case		**Incremental cost effectiveness ratio (ICER) PEP**	**Incremental cost effectiveness ratio (ICER) Seasonal**
Otherwise healthy adults			
1.	Oseltamivir	£27,153	£163,671
	Usual care		
2.	Oseltamivir	£2,141	£237,055
	Amantadine		
3.	Oseltamivir	Oseltamivir is cost saving	Oseltamivir and zanamivir are equivalent
	Zanamivir		
Otherwise healthy children 1-12 years			
4.	Oseltamivir	£7,977	£90,551
	Usual care		
5.	Oseltamivir	Oseltamivir is therefore dominant.	£79,247
	Amantadine		
6.	Oseltamivir	Oseltamivir is cost saving	Oseltamivir is cost saving
	Zanamivir		
Otherwise healthy children 1-5 years			
7.	Oseltamivir	£5,610	£46,085
	Usual care		
At risk adults			
8.	Oseltamivir	£1,983	£11,437
	Usual care		
9.	Oseltamivir	£96	£16,127
	Amantadine		
10.	Oseltamivir	Oseltamivir is cost saving	Oseltamivir and zanamivir are equivalent
	Zanamivir		

The Assessment Group re-analysed the results from the manufacturer's model for oseltamivir to generate full incremental cost-effectiveness estimates (the manufacturer's submission presented pair-wise comparisons rather than a full incremental analysis). The results for PEP are in tables 17-20 on page 114 of the TAR. Oseltamivir PEP results in incremental cost-effectiveness ratios (ICERs) below £8000 per QALY gained for both groups of children, less than £2000 for at-risk adults and about £27,000 for healthy adults. The results for seasonal prophylaxis with oseltamivir are in tables 21-24 on pages 115 and 116 of the TAR. For children in both age groups the ICER for oseltamivir

is above £46,000 per QALY gained. For adults and children (older than 12 years) who are healthy or at-risk oseltamivir is dominated by zanamivir, and for the at-risk group the ICERs for amantadine and zanamivir are less than £16,000 per QALY gained. The model was sensitive to the changes in assumptions for attack rates and the number of GP visits per household.

3.2.3 Assessment Group economic analysis

Model structure

The Assessment Group conducted an independent economic assessment. The three drugs were cross compared with each other and with no prophylaxis for three age groups: children aged 1–14 years, adults aged 15–64 years and people older than 65 years. Each age group was further subdivided into healthy and at-risk, and each of these six subgroups were further divided on the basis of vaccination status.

As all the costs and benefits occurred within a single influenza season, the time horizon was 1 year and therefore there was no discounting, except for life years lost due to premature death caused by influenza and its complications. The model operates on the basis of influenza-like illness. The probability that a contact develops influenza depends on the influenza attack rate, the prophylactic efficacy of the intervention strategy and the person's vaccination status. In addition, for amantadine it also depends on the probability that influenza is of type A and the degree of resistance of the virus to the drug. Contacts who do develop influenza may seek medical treatment and receive treatment with oseltamivir and zanamivir if at risk, in line with current NICE recommendations (NICE technology appraisal 58). People who develop complications seek medical attention and receive antibiotics. A proportion are hospitalised and some may die.

The model assumes prophylaxis is only effective for the period the patient is taking the drug. It also assumes that the benefits of vaccination and prophylaxis are cumulative, and that prophylaxis would only be considered

when it is known that influenza is circulating in the community above a threshold of 30 new influenza-like illness GP consultations per 100,000 population. The model does not consider the benefits of prophylaxis in preventing transmission of influenza from the person who receives prophylaxis and avoids infection, to others who may have contracted the illness from this person.

Model parameters

The baseline *influenza attack rate* is the probability that an individual develops influenza over the influenza season. The model assumes this differs in each age group and within the seasonal and PEP models. These are summarised in table 28 on page 142 of the TAR. The *probability that ILI is true influenza* was derived from Royal College of General Practitioners (RCGP) data and estimated to be 0.5 across all subgroups for the duration when influenza is circulating in the community above the threshold of 30 new ILI GP consultations per week per 100,000 population. This figure is used together with the true influenza attack rate to calculate the ILI attack rate.

The *probability influenza is influenza A* was based on virological surveillance data for 12 influenza seasons (1995/6-2006/7). The probability that influenza A was the dominant strain in a given season was calculated at 0.75. The probability that a case was influenza A was calculated separately for years where influenza A was dominant (0.86) and for years where influenza B was dominant (0.30). The overall mean probability that a case of influenza is influenza A was estimated to be 0.72.

The *duration of the influenza season* was calculated as the period for which the number of new GP ILI consultations per week was above the threshold level of 30 (previously 50) per 100,000 population for the last 20 influenza seasons (1987/8-2006/7).The mean duration of the influenza season was calculated to be 5.71 weeks. It was assumed that vaccination is effective over the whole of the season but that drugs were only effective for the time they

were taken. Hence the preventive efficacy of antivirals was adjusted according to the proportion of the influenza season for which the drugs were taken.

The protective efficacies of vaccination, amantadine, oseltamivir and zanamivir were derived from the review of clinical effectiveness (and Cochrane reviews for vaccination). The model assumed that people who stopped prophylaxis did so at the beginning of the course and received no protective benefit. The protective efficacy of vaccination reduces the probability of developing influenza without prophylaxis in the model. The joint benefit of vaccination and prophylaxis is assumed to be cumulative – that is the effectiveness of prophylaxis is applied to only that proportion of the vaccinated population who are not effectively protected by vaccination.

There was a lack of clinical effectiveness evidence for a number of subgroups in the cost effectiveness analysis. Due to the lack of evidence the relative risk for seasonal prophylaxis with amantadine was taken from a study of unvaccinated healthy adults and applied to all population subgroups. For PEP with amantadine, efficacy was taken from a single study of outbreak control in vaccinated healthy adolescents and applied to all groups in the model. The model also assumed, based on data from the 2006/7 season that 37% of influenza cases are resistant to amantadine. For seasonal prophylaxis with oseltamivir the results of the study in healthy unvaccinated adults were applied to healthy and at-risk adults and paediatric age groups and the results of the trial in at-risk subjects in residential care were applied to healthy and at-risk elderly populations. For PEP with oseltamivir a metaanalysis of two trials from healthy adults was done and the results applied to the health and at-risk adult and elderly people and the results of the subgroup analysis for children in these trials were applied to healthy and at-risk children subgroups. For seasonal prophylaxis, trial in healthy and mostly unvaccinated adults was used to calculate the relative risk for the healthy adults and the at-risk and healthy children groups. A study of seasonal prophylaxis in at-risk adults supplied estimates for the at-risk adult and for the elderly populations. For PEP with zanamivir a metaanalysis of three trials in adults and children was

conducted and the results applied to all population groups. The relative risks used in the model for each subgroup are summarised in table 3.

Table 3: Summary of relative risks estimates used in the AG model

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

[a] Relative risk based on clinical trial evidence relating exclusively to model subgroup

[b] Relative risk based on clinical trial evidence that includes model subgroup and other subgroups

[c] Relative risk based on clinical trial evidence from other model subgroups (equal effectiveness assumed)

The model includes the probability of adverse effects from vaccination and amantadine only and the resulting costs and health effects. Adverse effects from oseltamivir and zanamivir were assumed to be mild and self-limiting and not impact on a person's health-related quality of life. The model also assumes a withdrawal rate from amantadine prophylaxis of 5.7% in children and healthy adults and 14.7% in at-risk adults and elderly and withdrawal from oseltamivir and zanamivir of 1.3% for all model subgroups.

Not all patients with ILI (who are at-risk) are assumed to be treated. The model estimates the probability that a person with ILI presents to a medical practitioner, The probability this is within 48 hours and the probability of treatment being prescribed. Eighty-nine percent of treatments with a neuraminidase for ILI were assumed to be treated with oseltamivir and 11% with zanamivir in line with market research.

The relative risk for complications following treatment was the same as that used in TA67. The model also included the probability of developing

complications from influenza or ILI, the probability of receiving antibiotics, the probability of hospitalisation due to a complication (including intensive care treatment) and the probability of death due to an ILI-related complication.

The model operates in terms of QALYs lost over the influenza season and the difference in QALYs lost between prophylactic options is the estimate of QALYs saved. QALYs are lost for adverse effects, influenza and ILI episodes, complications of influenza and ILI and premature death due to complications. Estimates of health-related quality of life were obtained from oseltamivir studies. The method for obtaining utility values used in the model is non-reference case, derived from measures on a 10-point scale, and is described on pages 164 and 165 of the Assessment Report. It is the same approach as was used in the Assessment Report for TA67. The adverse effects of amantadine were assumed to cause a 0.2 utility decrement for a mean duration of 5 days. Health utility decrements associated with ILI complications were derived from a study that used committee consensus to reach estimates and were assumed to operate for the duration of complications in clinical trials for oseltamivir.

The model includes costs for acquisition and administration of vaccination and antiviral prophylaxis and treatment, costs associated with the management of adverse effects, consultation costs, antibiotics and costs of hospitalisation including intensive care. The model assumes that each prescription of prophylaxis requires a GP consultation but explores the possibility of prescribing multiple courses of prophylaxis (for example for family contacts) at a single visit.

Sensitivity analyses

Sensitivity analyses were carried out using the lower price for zanamivir, which the manufacturer informed the Institute has been approved by the DH. The effect of multiple prescriptions per GP consultation was examined. Seasonal prophylaxis would be considered in the exceptional event of a mismatch between circulating and vaccine virus strains. In such a situation the

protective efficacy of vaccination would decrease, the extent of such a decrease being determined by the degree of mismatch. This was explored by analyses where the absolute relative risk for vaccination was 0.5 and 0.75. As the trials for oseltamivir and zanamivir occurred in different settings with differing circulating levels of influenza, virus strains and populations – the differing estimates of efficacy are not strictly comparable. To explore the impact of this an analysis was conducted where both drugs were considered to be of equal efficacy. Further analyses exploring the effect of assuming resistance to oseltamivir and varying the influenza attack rates were also conducted.

3.2.4 Results of Assessment Group economic analysis

The results of the economic analysis are summarised in table 4 on page 21 of this Overview, and table 68, page 192 of the Assessment Report.

Seasonal prophylaxis

In healthy children, oseltamivir economically dominates amantadine and zanamivir. That is, treatment with oseltamivir is expected to cost less and result in more QALYs gained. For unvaccinated children the ICER was £44,007 per QALY gained and for vaccinated children it was £129,357 per QALY gained. For at-risk children oseltamivir dominated the other drugs, with an ICER of £16,630 per QALY gained for unvaccinated children and £51,069 per QALY gained for vaccinated children. In healthy adults oseltamivir dominates the other drugs, with ICERs of £147,505 in unvaccinated adults and £427,184 in vaccinated adults. For at-risk adults oseltamivir again dominates the other drugs, with ICERs of £63,552 in unvaccinated people and £186,651 in vaccinated people. For healthy older people oseltamivir dominates the other drugs, with ICERs of £49,742 in unvaccinated people and £121,728 in vaccinated people. In at-risk older people oseltamivir dominates the other drugs, with ICERs of £38,098 per QALY gained for unvaccinated people and £93,763 for vaccinated people.

PEP

In healthy children zanamivir economically dominates oseltamivir and amantadine, with ICERs of £23,225 per QALY gained in unvaccinated children and £71,648 per QALY gained in vaccinated children. For at-risk children zanamivir dominates the other drugs, with ICERs of £8233 for unvaccinated children and £27,684 for vaccinated children. For healthy adults oseltamivir dominates zanamivir and amantadine, with ICERs of £34,181 for unvaccinated people and £103,706 for vaccinated people. For at-risk adults oseltamivir dominates the other drugs, with ICERs of £13,459 per QALY gained for unvaccinated adults and £43,970 for vaccinated adults. In healthy older people oseltamivir dominates zanamivir and amantadine, with an ICER of £10,716 per QALY gained for unvaccinated people and £28,473 for vaccinated people. For at-risk older people oseltamivir again dominates, with ICERs of £7866 for unvaccinated people and £21,608 for vaccinated people.

Sensitivity analyses

When the lower price of zanamivir is used in the economic model it has little impact on the outcome of the comparisons made in the base case for seasonal prophylaxis except for at-risk adults. In this group zanamivir is no longer dominated; the ICER in £53,159 per QALY gained. For PEP the price reduction leads to improvements in the cost effectiveness of zanamivir for healthy and at-risk children. In general, the estimates for cost effectiveness were sensitive to the influenza attack rates, the level of viral resistance, vaccine efficacy, the threshold to describe when influenza is circulating in the community, the relative efficacy of oseltamivir and zanamivir and the risk of hospitalisation in uncomplicated cases. For seasonal prophylaxis, the estimates were sensitive to the discount rate and for PEP they were sensitive to the use of multiple prescriptions for prophylaxis per GP visit.

Table 4: Baseline Assessment Group cost effectiveness results (ICER of cost per QALY gained) for prophylaxis strategies, in each age group divided by risk and vaccination status.

Vaccination strategy & group		**Amantadine**	**Zanamivir [a]**	**Oseltamivir**
Seasonal Prophylaxis				
Healthy children	Unvaccinated	Ext[b] dominated	Dominated	£44,007[c]
	Vaccinated	Dominated	Dominated	£129,357
At-risk children	Unvaccinated	Ext dominated	Dominated	£16,630
	Vaccinated	Ext dominated	Dominated	£51,069
Healthy adults	Unvaccinated	Ext dominated	Ext dominated	£147,505
	Vaccinated	Dominated	Ext dominated	£427,184
At-risk adults	Unvaccinated	Ext dominated	Ext dominated	£63,552
	Vaccinated	Dominated	Ext dominated	£186,651
Healthy elderly	Unvaccinated	Ext dominated	Ext dominated	£49,742
	Vaccinated	Dominated	Ext dominated	£121,728
At-risk elderly	Unvaccinated	Ext dominated	Ext dominated	£38,098
	Vaccinated	Ext dominated	Ext dominated	£93,763
Post-exposure prophylaxis				
Healthy children	Unvaccinated	Ext dominated	£23,225	Ext dominated
	Vaccinated	Ext dominated	£71,648	Ext dominated
At-risk children	Unvaccinated	Ext dominated	£8,233	Ext dominated
	Vaccinated	Ext dominated	£27,684	Ext dominated
Healthy adults	Unvaccinated	Ext dominated	Dominated	£34,181
	Vaccinated	Ext dominated	Dominated	£103,706
At-risk adults	Unvaccinated	Ext dominated	Dominated	£13,459
	Vaccinated	Ext dominated	Dominated	£43,970
Healthy elderly	Unvaccinated	Ext dominated	Dominated	£10,716
	Vaccinated	Ext dominated	Dominated	£28,473
At-risk elderly	Unvaccinated	Ext dominated	Dominated	£7,866
	Vaccinated	Ext dominated	Dominated	£21,608

a these results use the current BNF price for zanamivir – for results using the lower price, see Assessment Report, table 68, page 192
b Ext. = extendedly
c for breakdown of ICERs into expected incremental costs and QALYs, see tables 44 to 67, pp. 175 to 190 of Assessment Report

4 Issues for consideration

1. Threshold level for circulating influenza

- It has been suggested that consultation rates with general practioners in the Royal College of General Practitioners sentinel scheme (as used in TA67) are not a reliable indicator of when influenza viruses are circulating. What are the implications of this for the review of TA67?

- Would the results of RCTs, during which the background level of circulating influenza is unknown or variable, be generalisable to current and future periods, based on UK surveillance scheme thresholds? To what extent might the exact circulating level impact on cost effectiveness estimates?

2. Extrapolation of relative risks to subgroups

- PEP model attack rates are mostly derived from studies in mixed households. Would the attack rates be applicable to other subgroups?

- RCTs were in different countries, in seasons with different circulating strains of virus and different level of influenza activities. How does this affect inferences about relative effectiveness?

3. As surveillance schemes operate nationally/regionally, what are the considerations regarding localised outbreaks with high attack rates or for outbreaks within residential communities that do not occur in the influenza season?

4. For seasonal prophylaxis vaccine efficacy is affected by exact degree of mismatch between circulating and vaccine virus strains. What is the appropriate relative risk for vaccination that should be assumed in the case of such a mismatch?

5. How do considerations of viral resistance impact on considerations of the evidence?

6. What are the implications of the Social Value Judgements principles for this appraisal in which the evidence base is divided into subgroups on the basis of age?

5 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The Assessment Group (AG) report for this appraisal was prepared by The University of Sheffield, School of Health and Related Research (ScHARR):

- Tappenden P., Jackson R., Cooper K. et al. Oseltamivir, amantadine and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67), February 2008

B Submissions from the following organisations:

I Manufacturer/sponsor

- Roche
- GlaxoSmithKline

II Professional/specialist, patient/carer and other groups:

- Health Protection Agency
- British Thoracic Society
- Diabetes UK

C Additional references used:

- Technology Appraisal No. 58. February 2003. Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza.
- Technology Appraisal No. 67 September 2003. Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza.
- Summaries of Product Characteristics for oseltamivir, amantadine and zanamivir as at 8 April 2008
- Oseltamivir European Public Assessment Report, accessed 8 April 2008 at http://www.emea.europa.eu/humandocs/Humans/EPAR/tamiflu/tamiflu.htm

Appendix B:

Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza. Technology Appraisal 67, September 2003.

1 Guidance

This guidance has been prepared in the expectation that vaccination against influenza is undertaken in accordance with national guidelines. Vaccination is the most effective way of preventing illness from influenza, and the drugs described in this guidance are not a substitute for vaccination. This guidance does not cover the circumstances of a pandemic, impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no community resistance.

This guidance pertains only to circumstances where it is known that either influenza A or influenza B is circulating in the community (see Section 1.7).

1.1 Oseltamivir is recommended for the post-exposure prophylaxis of influenza in at-risk people aged 13 years or older who are not effectively protected by vaccination and who have been exposed to someone with influenza-like illness (ILI) and are able to begin prophylaxis within 48 hours of exposure. People who are not effectively protected by vaccination include those who have not been vaccinated since the previous influenza season, or for whom:

• vaccination is contraindicated, or has yet to take effect

• vaccination has been carried out but the vaccine is not well matched to the strain of influenza virus circulating. (The Department of Health and the Welsh Assembly Government, acting on information from the Health Protection Agency, issue advice nationally each year on whether the vaccine and the circulating influenza virus are well matched.)

Exposure to ILI is defined as being in close contact with someone who lives in the same home environment as a person who has been suffering from symptoms of ILI.

1.2 At-risk people are defined, for the purpose of this guidance, as those who are in at least one of the following groups. People who:

• have chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)

• have significant cardiovascular disease (excluding people with hypertension only)

• have chronic renal disease

• are immunocompromised

• have diabetes mellitus

• are aged 65 years or older.

1.3 Oseltamivir is recommended for the post-exposure prophylaxis of influenza in at-risk people, aged 13 years and older and who can begin prophylaxis within 48 hours, whether or not they have been vaccinated, if they live in a residential care establishment where a resident or staff member has ILI. For the purposes of this guidance, a residential care establishment is defined as a place where the at-risk person resides in the long term in order to be provided with continuing care alongside a number of other individuals.

1.4 Oseltamivir is not recommended for post-exposure prophylaxis in healthy people up to age 65 years.

1.5 Oseltamivir is not recommended for the seasonal prophylaxis of influenza.

1.6 Amantadine is not recommended for either post-exposure or seasonal prophylaxis of influenza.

1.7 Community-based virological surveillance schemes should be used to determine when influenza virus is circulating in the community. Such schemes, including those organised by the Royal College of General Practitioners and the Health Protection Agency, should ensure that the onset of the circulation of influenza virus (A or B) within a defined area is identified as rapidly as possible. In Appendix D, definitions and numerical values of threshold levels for different categories of influenza activity are given.