

# **Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza**

## Technology Appraisal Guidance 67

### Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza

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#### This guidance is written in the following context:

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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# 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.

## 2 Clinical need and practice

- 2.1 Influenza occurs mainly in the winter months and affects all age groups. It causes significant morbidity and increased mortality. The average number of deaths attributed directly to influenza in the UK each year between 1987 and 1995 (non-epidemic years) was about 600, but the number of excess deaths occurring at the time of the influenza outbreaks during these years was about 6000 (these excess deaths are likely to be indirectly attributable to influenza). In epidemic years, the direct and indirect death rates were each about three times as high again, although the figures vary widely. Some estimates of indirect influenza deaths in both epidemic and non-epidemic years are even higher than those quoted above.
- 2.2 There are three main types of influenza virus: influenza A, B and C. Only types A and B are known to cause significant morbidity in humans. Influenza A occurs more frequently and is more virulent than influenza B. There have been significant outbreaks of influenza A in England and Wales in 9 of the 11 years from 1990 to 2000. There are several subtypes of influenza A, of which H3N2 and H1N1 have co-circulated in humans since 1978. Outbreaks of influenza B occurred in England and Wales in 4 of the 11 years from 1990 to 2000, and there were outbreaks of both influenza A and B in two of these years. Since 1990, about 74% of influenza has been caused by the influenza A virus, but this has varied between 20% and 97% from season to season.
- 2.3 Although the incubation period for influenza can range from 1 to 7 days, it usually lasts for 2 to 3 days. Typical symptoms for uncomplicated influenza are cough, malaise, fever/chills, headache, nasal congestion, sore throat and aching muscles. However, presentation can range from asymptomatic infection, through respiratory illness (particularly bronchitis and pneumonia), to multi-system complications affecting the heart, lungs, brain, liver, kidneys and muscles. Influenza-associated death usually results from viral or bacterial pneumonia.
- 2.4 People who present with ILI may not be suffering from true influenza, because a similar symptom complex can occur in association with various other viral infections, such as respiratory syncytial virus infection. At present, the diagnosis of influenza is based principally on clinical grounds (symptoms and physical signs). However, when influenza virus is circulating, it is more likely that a person presenting with ILI has true influenza.

- 2.5 The symptoms and outcomes of influenza are more severe in elderly people, infants and people in at-risk groups. People living or working in residential care establishments are at greater risk of infection. Health and care professionals who work in residential care establishments can spread the disease from group to group.
- 2.6 Otherwise healthy individuals with uncomplicated ILI are encouraged not to seek medical help but to follow self-management strategies such as resting, increasing their fluid intake, and using simple analgesics and over-the-counter symptomatic remedies.
- 2.7 Estimates of the frequency of hospital admissions among those aged 75 years or older are 1 in every 89 people with influenza for low-risk patients and 1 in 24 for high-risk patients; for patients aged 65 to 75 years, the figures are 1 in 230 for low-risk patients and 1 in 42 for high-risk patients; and for people aged 16 to 64 years the figures are about 1 in 4000 for low-risk patients and 1 in 250 for high-risk patients. For people in residential care establishments, the frequency of hospital admissions for those contracting influenza appears to be about 1 in 8 for those who have been vaccinated, rising to 1 in 5 for those who have not been vaccinated.
- 2.8 Vaccination offers a very cost-effective first line of defence against influenza. In England and Wales, annual vaccination is offered free through the NHS to people aged 65 years or older, members of other at-risk groups, and health professionals expected to be in contact with those who contract influenza. In an average year, vaccination is about 70% effective in preventing the disease in the vaccine recipients, although this may range from 30% to 90%, depending on the influenza virus in circulation. The surface of the virus may change antigenically from year to year through mutation. The body responds to the antigens of the vaccine, which are similar to the surface antigens of the virus. When the vaccine and viral antigens do not correspond, the body will not produce the appropriate antibodies and this renders the vaccine less effective.
- 2.9 Change in the influenza virus occurs either as antigenic drift or antigenic shift. Antigenic drift, which is the more common, arises as a result of gene mutations that are selected for in response to immune pressure from hosts. Antigenic shift occurs when two different subtypes of influenza A, one from humans and the other from a different host species, co-infect a single host. Within the co-infected host, the viral genes mix to form a new human

subtype of virus that has some of the properties of both 'parental' strains. Such a subtype may be infectious in humans but have a sufficiently new surface that humans lack immunity to it. Such a subtype might cause pandemics because resistance in the population would be low.

2.10 Pandemics of influenza have occurred over the past 200 or so years at intervals of about 25 years. In the pandemic of 1918, more than 20 million people are estimated to have died worldwide. Vaccines, which tend to be protective against particular strains, are unlikely to afford much, if any, protection against sufficiently different new strains of influenza virus.

2.11 Influenza vaccines are currently produced in embryonated hens' eggs and the supply is limited within a given season.

2.12 Routine vaccination of at-risk individuals is currently recommended in the UK. For vaccination, at-risk individuals are defined slightly differently from those defined as at-risk for the purposes of this document. For vaccination, at-risk individuals are considered to be:

- all people aged 65 years or older
- people of any age with chronic respiratory disease (including asthma), chronic heart disease, chronic renal disease, diabetes mellitus or immunosuppression (due to treatment or illness, including asplenia or splenic dysfunction)
- all those living in long-stay residential care establishments.

In 2001/02, vaccination rates for individuals aged 65 years or older were 68% in England and 61% in Wales. The uptake rate for younger people in at-risk groups is not known.

### 3 The technologies

- 3.1 Currently, two drugs are licensed for the prophylaxis of influenza in adults: amantadine (Lysovir, Symmetrel Syrup) and oseltamivir (Tamiflu).
- 3.2 Anti-influenza drugs appear to act independently of vaccination, and provide additional barriers to the influenza virus where the vaccine does not work. It is not known how well antiviral drugs would perform in pandemics.
- 3.3 Anti-influenza drugs are licensed for prophylaxis in two different ways. For post-exposure prophylaxis, treatment is initiated only after the individual has come into close contact with someone who is suspected of suffering from influenza. Treatment is continued for a short period of time, usually 7 to 10 days, following exposure. For seasonal prophylaxis, when influenza is known to be circulating within the community, those considered to be at risk begin prophylactic treatment irrespective of whether they have been exposed to someone suffering from influenza. Treatment is continued throughout the influenza season, usually for around 6 weeks.
- 3.4 Diagnostic tests for influenza are not widely available, nor do the currently available diagnostic kits seem any better at detecting true influenza than an experienced GP when influenza viruses are known to be circulating in the community. However, near-patient test kits may have value at a population level during the early period of the influenza season to confirm that influenza has started to circulate in the local community.

#### Amantadine

- 3.5 Amantadine is administered orally and excreted renally. It inhibits the M2 membrane protein ion channel activity of the influenza A virus, but has no effect on influenza B. Amantadine is licensed for seasonal and post-exposure prophylaxis of influenza A. The licence suggests that it be given to people particularly at risk such as:
  - those with chronic respiratory disease or debilitating conditions
  - the elderly
  - other family members, where one family member has contracted influenza

- institutionalised people, where there has been an outbreak of influenza in the institution
- unvaccinated essential service personnel.

The licence recommends that amantadine be administered daily for as long as protection from infection is required. In most instances this is expected to be for up to 6 weeks for seasonal prophylaxis.

It is implicit in the Summary of Product Characteristics that amantadine is not licensed for children younger than 10 years.

- 3.6 Amantadine is contraindicated in individuals subject to convulsions, with a history of gastric ulceration or severe renal disease, or who are pregnant or breastfeeding. It should be used with caution in individuals in confused or hallucinatory states, with underlying psychiatric disorders, or with liver, kidney or cardiovascular disorders. It also has a number of drug interactions. For full details of contraindications, warnings and adverse reactions see the Summary of Product Characteristics.
- 3.7 Some strains of the influenza A virus rapidly become resistant to amantadine. Currently in the UK, about 2.3% of circulating influenza viruses exhibit amantadine resistance. When outbreak control with amantadine has failed in closed communities, amantadine-resistant virus has been isolated. However, when amantadine has been widely used for treatment, as in Japan, there is evidence to show that there is limited circulation of resistant virus.
- 3.8 Amantadine (Lysovir) 100-mg capsules cost £2.40 for a pack of five and £4.80 for a pack of 14 (excluding VAT; *British National Formulary* 45, March 2003). The dosage for prophylaxis is one capsule daily for 2 to 3 weeks after vaccination, or without vaccination, for as long as protection against infection is required (usually 6 weeks). Amantadine is also available as Symmetrel syrup, for which a 150-ml pack, providing 15 daily doses of 100 mg of amantadine, costs £5.05 (excluding VAT; *British National Formulary* 45, March 2003). Costs may vary in different settings because of negotiated procurement discounts.
- 3.9 In adults aged 65 years or older renal function may be impaired and, where appropriate, the dose may be reduced.

- 3.10 In 1995, a dosage of 100 mg/day replaced the previously licensed dosage of 200 mg/day. The 200 mg/day dosage is not currently licensed.

## Oseltamivir

- 3.11 Oseltamivir is a neuraminidase inhibitor that can be taken orally (as oseltamivir ethyl ester, which is converted to oseltamivir carboxylate, the active drug, after absorption). It is excreted mainly through the kidneys. Oseltamivir is licensed for the post-exposure prophylaxis of influenza A and B in people aged 13 years or older who have had contact with a clinically diagnosed influenza case, when influenza is circulating within the community. The once-daily dose is 75 mg for at least 7 days. Therapy should begin within 48 hours of exposure. Oseltamivir is also licensed for seasonal prophylaxis. The licence suggests use should be determined on a case-by-case basis by the circumstances and the population requiring protection, and that in exceptional circumstances (for example, in case of mismatch between circulating and vaccine virus strains, or a pandemic situation), seasonal prophylaxis could be considered in adults or adolescents aged 13 years or older. The licensed dosage for the prevention of influenza during a community outbreak is 75 mg oseltamivir once daily for up to 6 weeks. The dose of oseltamivir should be adjusted downwards for people with moderate to severe renal impairment. For full details of warnings and adverse reactions see the Summary of Product Characteristics.
- 3.12 To date, viral resistance to oseltamivir has not been widely encountered. In cases where it has been encountered, the mutated virus does not appear to have been pathogenic to humans.
- 3.13 Oseltamivir (Tamiflu) 75-mg capsules cost £18.80 for a pack of ten (excluding VAT; *British National Formulary* 45, March 2003). Oseltamivir is also available as Tamiflu suspension, which allows smaller doses to be given more easily to children. The cost of 900 mg of powder suspended in 75 ml of water is £18.18 (excluding VAT; *British National Formulary* 45, March 2003). Costs may vary in different settings because of negotiated procurement discounts.

## 4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (Appendix B).

### 4.1 *Clinical effectiveness*

#### **Amantadine for post-exposure prophylaxis**

- 4.1.1 A review of amantadine in adolescents and healthy adults found two randomised controlled trials (RCTs) that compared amantadine 100 mg/day with placebo for the post-exposure prophylaxis of influenza A. The first study, carried out in 1970, was in 1927 healthy unvaccinated males aged 18–30 years and reported on two subgroups of individuals. The endpoint was ILI. The meta-analysis of the two subgroups gave an odds ratio (OR) for treated versus placebo groups of 0.44 (95% confidence interval [CI], 0.27 to 0.71). The second study, carried out in 1984, was in 536 vaccinated adolescents aged 13 years or older in a boys' boarding school. This produced an OR for treated versus placebo groups of 0.09 (95% CI, 0.02 to 0.31). The pooled OR for the two studies was 0.34.
- 4.1.2 No RCTs of amantadine at a dosage of 100 mg/day in at-risk adults were identified.

#### **Amantadine for seasonal prophylaxis**

- 4.1.3 One RCT in a vaccinated elderly population in residential care looked at seasonal prophylaxis, using 100 mg amantadine daily for 9 weeks. Prophylaxis was given to 89 individuals and there was a control group of 99 individuals. There were no outbreaks of influenza in either group.

#### **Oseltamivir for post-exposure prophylaxis**

- 4.1.4 Two trials of post-exposure prophylaxis among unvaccinated healthy adults and adolescents were identified, each using a dose of 75 mg/day, one published in 2001 and the other not yet published. The pooled rates of influenza attack were 15 out of 899 in the oseltamivir group, and 74 out of 857 in the placebo group (pooled OR 0.20; 95% CI, 0.05 to 0.74).

## Oseltamivir for seasonal prophylaxis

- 4.1.5 Two trials of seasonal prophylaxis among unvaccinated healthy adults (aged 18–65 years) were found. In one study, the rates of influenza attack were 7 out of 535 in the oseltamivir group, and 19 out of 268 in the placebo group (OR 0.15; 95% CI, 0.04 to 0.51). In the second study, influenza attack rates were 6 out of 505 in the oseltamivir group, and 6 out of 251 in the placebo group (OR 0.49; 95% CI, 0.12 to 1.99). The pooled OR of the two studies was 0.26 (95% CI, 0.08 to 0.84).
- 4.1.6 A single trial was found of seasonal prophylaxis among elderly people (aged 64–96 years) in residential care, 80% of whom were vaccinated. The influenza attack rates were 1 out of 276 in the oseltamivir group, and 12 out of 272 in the placebo group (OR 0.08; 95% CI, 0.01 to 0.61).

## 4.2 Adverse events

### Amantadine

- 4.2.1 Long-term use of amantadine (used as a treatment for Parkinson's disease) at dosages higher than 100 mg/day has been associated with a wide variety of adverse events affecting the central nervous, cardiovascular and gastrointestinal systems, and the skin, eye and urinary tract. In a Cochrane Review on the use of amantadine and rimantadine for the treatment and prophylaxis of influenza A, an analysis of the rate of adverse effects with amantadine compared with placebo reported in prophylaxis RCTs (most of which used an amantadine dosage of 200 mg/day), produced a pooled OR of 1.66 (95% CI, 1.36 to 2.01). In these studies, 20% to 40% of elderly people in the amantadine arm of the trials reported adverse events including insomnia, light-headedness, hallucinations, dizziness, headache and falls. In healthy adults, the rates of adverse events in RCTs using amantadine 100 mg/day are lower than the rates in RCTs using 200 mg/day, but differences between trials and other difficulties of comparison make a quantification of the difference difficult. There is little evidence available on the effects of lower doses of amantadine in at-risk people. In two retrospective cohort studies using a dosage of 100 mg/day in at-risk people in nursing homes, the rate of adverse events was 41% in one study (n = 79) and 19% in the other (n = 156).

## Oseltamivir

- 4.2.2 In clinical trials, oseltamivir at the licensed dosage is generally well tolerated, but has been associated with a somewhat higher rate of nausea and vomiting compared with placebo, although the differences are not large (a 3 to 7 percentage point higher rate of nausea and up to 2 percentage points higher rate of vomiting with oseltamivir compared with placebo). During post-licensing experience, there have been very rare reports of elevated liver enzymes and hepatitis, and of skin rashes.

## 4.3 Cost effectiveness

- 4.3.1 For the prophylaxis of influenza, the Assessment Report found one cost-effectiveness study of oseltamivir. In addition, the two manufacturers of the technologies provided analyses for this appraisal, and the Assessment Group developed its own models for both seasonal and post-exposure prophylaxis, and commented on models in the literature.
- 4.3.2 The estimated cost effectiveness in the models varied considerably, depending on the assumptions made for some of the key parameters. The most important of these was whether a reduction in mortality was included. One variant of the model prepared by the Assessment Group examined the scenario where a benefit is assumed from averting death. The percentage reduction in post-influenzal pneumonia attributed to antiviral drug treatment was estimated, and the same percentage reduction in pneumonia deaths was inferred. Because pneumonia is the most common cause of death from complications of influenza, this provided a reasonable method of extrapolating the beneficial effect (for the purposes of cost effectiveness) of the antiviral drugs.
- 4.3.3 Different studies have made different assumptions about plausible values of several key variables, to which the estimates of cost effectiveness within the models are very sensitive. Apart from the inclusion or otherwise of the effect of the drugs on mortality, when used for prophylaxis, the key variables were:
- whether prophylaxis extends for the whole time that influenza is circulating (seasonal prophylaxis) or only for the few days following contact with a person with ILI symptoms (post-exposure prophylaxis)
  - whether the person/group of people has been vaccinated
  - the effectiveness of the vaccine and the attack rate of the virus.

### Cost effectiveness of post-exposure prophylaxis

- 4.3.4 The estimates of cost effectiveness for post-exposure prophylaxis are subject to great uncertainty. The difficulty of determining the clinical and cost effectiveness of post-exposure prophylaxis is that the frequency of a person's contact with the virus is unknown. It is likely that in a residential care establishment a person may be subject to continuing contacts over the period that influenza is circulating, while a person living in a family situation may be subject to no contacts or only a single period of contact.
- 4.3.5 For healthy adults and adolescents, the appropriate comparator is unvaccinated people. The cost per quality-adjusted life year gained (CQG) for amantadine against no treatment, modelled from the two pooled studies (see Section 4.1.1) was estimated to be £31,000 (for the case of a high probability of influenza A), while for oseltamivir against no treatment, the cost per CQG was estimated from the pooled results of the trials mentioned in Section 4.1.4 to be £28,000.
- 4.3.6 For both at-risk people and people in residential care establishments, the more appropriate comparator is vaccinated people. For vaccinated people, the estimated CQG for oseltamivir against no treatment was £29,000 for the at-risk group and £3000 for the at-risk residential care group. For unvaccinated groups, the estimated CQG for oseltamivir against no treatment for the at-risk group was £7000, while for the at-risk residential care group oseltamivir was cost saving.
- 4.3.7 For amantadine, because there was no RCT evidence of clinical effectiveness of post-exposure prophylaxis in the at-risk groups, the corresponding cost-effectiveness figures are not presented.

### Cost effectiveness of seasonal prophylaxis

- 4.3.8 For healthy adults and adolescents, the appropriate comparator is unvaccinated people, and for both groups the CQG for amantadine or oseltamivir was estimated to be more than £100,000.
- 4.3.9 For both the at-risk and elderly residential care groups, the estimated CQG for vaccinated people was more than £60,000 for oseltamivir.

- 4.3.10 For oseltamivir, the estimated CQG for the unvaccinated at-risk group was £80,000. The estimate of CQG for unvaccinated elderly people in residential care was £12,000 for oseltamivir. For amantadine, no results have been presented – see Section 4.3.7.

#### **4.4** *Consideration of the evidence*

- 4.4.1 The Committee reviewed the data available on the clinical and cost effectiveness of amantadine and oseltamivir for the prophylaxis of influenza, having considered evidence on the nature of the condition and the value placed on prophylaxis by clinical experts and those who represent users. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources.
- 4.4.2 The Committee concluded that antiviral drugs should be considered for prophylaxis only when influenza is known to be circulating in the community. At other times, the probability that ILI is influenza is too low to make prophylaxis cost effective.
- 4.4.3 The Committee considered that the assumptions linking influenza to morbidity and mortality were more realistic for at-risk groups, making prophylaxis more likely to be cost effective in these groups. All people aged 65 years or older were defined as 'at-risk' irrespective of whether they had other risk factors. This is because, even without other risk factors, people aged 65 or older have hospital admission rates for influenza similar to those for people aged 18–64 years in the other at-risk categories.
- 4.4.4 The Committee was aware that vaccination is the most cost-effective defence against influenza and that prophylaxis with an antiviral drug should not replace or discourage the uptake of vaccination. The possibility that recommending routine prophylactic use of an antiviral drug for at-risk groups might lead to a longer-term reduction in the uptake of vaccination within this population was a concern for the Committee, because this might more than negate the benefits of prophylaxis using antiviral drugs.
- 4.4.5 No RCT evidence was available on the clinical effectiveness of amantadine at a dose of 100 mg for at-risk groups for either seasonal or post-exposure prophylaxis. Although in healthy adults the frequency of adverse events at the dosage of 100 mg/day is lower than at the 200 mg dose, similar evidence is not available for at-risk groups. The Committee was

therefore unable to accept that the clinical effectiveness of amantadine at a daily dose of 100 mg for the prophylaxis of influenza A among at-risk people was sufficiently proven to allow its cost effectiveness to be considered.

- 4.4.6 The Committee considered that post-exposure prophylaxis is cost effective to at-risk people in a residential care establishment, firstly because the risk of contracting influenza is greatly increased among those living in close proximity to an infected person, and the risk increases as the number of these contacts increases. Secondly, in the main, people in residential care establishments are among the most frail and, whether they have been vaccinated or not, the probability of their being hospitalised as a result of contracting influenza is much higher than for any of the other groups considered in this appraisal. It was also considered to be impractical within a residential care setting to distinguish between those who had been vaccinated effectively and those who had not.
- 4.4.7 The Committee considered whether prisons and particular types of hospital wards should be considered as residential care establishments for the purposes of consideration of the use of oseltamivir in post-exposure prophylaxis. The Committee was persuaded that, in both cases, the guidance should not be amended to specifically include these situations, and that, in general terms, the current guidance and that previously issued for treatment of influenza was sufficient. Thus, the Committee considered that the prison population did not fall into the category of 'residential care' from the point of view of the NHS. They accepted, however, that there were circumstances in which at-risk individuals might be housed in close proximity to those not at risk (for example, in the same cell) and that the need for prophylaxis for these individuals was covered in the guidance for the use of oseltamivir in the home environment. For hospitals in general the Committee considered that it was impractical to recommend a policy that distinguished between different wards, as it was likely that at-risk individuals may be cared for, for differing periods of time in most areas of the hospital. They considered that these at-risk individuals would automatically qualify for use of the neuraminidase inhibitors under the treatment guidance previously published. For all other situations, particularly where the risk of spread of influenza to an at-risk individual or individuals (from another patient or a member of staff) was considered a potentially serious issue for certain categories of patients, this should be dealt with at the discretion of the clinical staff in charge of these wards.

- 4.4.8 The Committee also considered the situation of post-exposure prophylaxis for at-risk people not in residential care, who have not been vaccinated. The Committee was persuaded that oseltamivir provides little additional benefit for at-risk people who are not in residential care and who have been vaccinated, because the vaccination will already have provided substantial protection against the disease. The exception is that, in years where the vaccine strains do not match the strains that are circulating, vaccinated people will not be well protected. Post-exposure prophylaxis should then be considered for at-risk people who have been vaccinated, as well as for at-risk people who have not been vaccinated.
- 4.4.9 Within the context of post-exposure prophylaxis, the Committee carefully considered what it believed constituted the best basis for the clinical effectiveness of amantadine among healthy adults and adolescents. It considered that there was no reason to expect that the adolescent population aged 13–19 years in the boarding school study would respond substantially differently from the population in the study in healthy young adults (see Section 4.1.1). It therefore considered that a more robust estimate of effectiveness for this age group in general would be gained by pooling the results of the two studies.
- 4.4.10 The Committee considered the uncertainties underlying the various assumptions made in the economic analysis for post-exposure prophylaxis. These included the likelihood of more than one GP visit being required to treat several at-risk individuals in the same residential care situation; the possibility that the cost of the GP visit would be greater than the standard charge if it was at short notice; and the likelihood that in general clinical practice, should a drug for prophylaxis be made available, the probability that the illness was truly influenza would be lower than that modelled in the economic analysis. The Committee concluded that, given all these factors, it was likely that in reality the CQG would be higher than the point estimates suggested, and that neither oseltamivir nor amantadine should be recommended for post-exposure prophylaxis in healthy adults up to 65 years old.
- 4.4.11 Given the high CQG estimates for seasonal prophylaxis with oseltamivir in the at-risk population, the Committee felt that this treatment strategy could not be recommended, that is, no antivirals should be used for seasonal prophylaxis of influenza, even in the at-risk population.

## 5 Recommendations for further research

- 5.1 Currently, not enough is known about the effects of influenza in at-risk adults and children, and elderly people living in residential care establishments.
- 5.2 More needs to be known about quality-of-life measurement in people with influenza.
- 5.3 A systematic evaluation of the feasibility of near-patient testing for influenza and the type of influenza is strongly recommended.

## 6 Implications for the NHS

- 6.1 The cost to the NHS will vary depending on the severity of the outbreak in any one year.
- 6.2 The financial impact on primary care when oseltamivir is made available for influenza post-exposure prophylaxis to at-risk people in residential care establishments has been estimated as follows. On the basis of 362,000 prescriptions annually for the estimated number of at-risk people in residential care establishments (assuming an average of one prescription per person per year), this represents about 900 prescriptions per year for a primary care trust of 125,000 people, most of which would be issued in batches. The annual cost for England and Wales is estimated to be £6.6 million. Should the average number of prescriptions written per person each year exceed one, the annual cost will exceed £6.6 million by the same proportion. (The estimated cost for England and Wales is substantially more than the manufacturer's estimates, which range from £200,000 to £1.4 million per year, depending on the attack frequency. These estimates are based on the frequency of influenza derived from GP visits, and are therefore possibly an underestimate of the actual level of influenza cases.)
- 6.3 When oseltamivir is made available for influenza post-exposure prophylaxis to people aged 65 years or older who have not been vaccinated against influenza (excluding those in residential care establishments), the following estimates of the financial impact on primary care have been made. It was assumed that there are 8 million people in this age group, of whom 2.5 million will be unvaccinated. It was assumed that 1.5 million of these do not live alone. If 10% of these people are exposed to influenza in any one year (and there are no multiple exposures), this amounts to 150,000 cases of exposure, of which it is assumed that half – or 75,000 – may seek prophylaxis, at a cost of £1.4 million.

- 6.4 The total drug cost for prophylaxis is therefore estimated to be of the order of £8 million to £12 million per year, but this estimate is subject to wide variation, because the incidence of influenza varies considerably from one year to another and the calculations are based upon estimates of frequency of infection. In a year in which the vaccine is not well matched with the circulating viruses, for example, the costs estimated in Section 6.3 could be expected to be substantially higher because of the vaccinated group aged 65 years or older being eligible for prophylaxis.

## 7 Implementation and audit

- 7.1 In considering local implementation arrangements, the National Health Service will wish to take account of previous advice from the Department of Health and the National Assembly of Wales (now the Welsh Assembly Government) following NICE Guidance No. 15 (see Section 8.1 below), and any further advice from these bodies following the extension of guidance in the current document. Local action might include some or all of the following.
- Telephone advice and information by a practice nurse or other healthcare professional with reference to a protocol containing appropriate and standard diagnostic questions.
  - Patient Group Directions for direct supply by nurses and pharmacists from community pharmacies, including those working from NHS walk-in centres in England.
  - NHS prescriptions issued by GPs in the standard way following consultations or home visits.
- 7.2 GPs should review their current practice and policies for the care of at-risk people who have been exposed to influenza-like illness (ILI), to take account of the guidance set out in Section 1.
- 7.3 Local guidelines, protocols or care pathways that refer to the care of at-risk people who have been exposed to ILI should incorporate the guidance.
- 7.4 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.
- 7.4.1 Oseltamivir is prescribed for the post-exposure prophylaxis of influenza in the following circumstances.

- 7.4.1.1 The individual is at-risk, is aged 13 years or older, is not effectively protected by vaccination, has been exposed to someone with ILI and is able to begin prophylaxis within 48 hours of exposure, or
- 7.4.1.2 The individual is at-risk and lives in a residential care establishment where a resident or staff member has ILI, whether or not the individual has been vaccinated.
- 7.4.2 Oseltamivir is not prescribed for post-exposure prophylaxis in a healthy individual who is up to age 65 years.
- 7.4.3 Oseltamivir is not prescribed for the seasonal prophylaxis of influenza.
- 7.4.4 Amantadine is not prescribed for either post-exposure or seasonal prophylaxis of influenza.

## 8 Related guidance

- 8.1 The Institute issued guidance on the use of zanamivir in October 1999 and November 2000: National Institute for Clinical Excellence (2000) Guidance on the use of zanamivir (Relenza) in the treatment of influenza. *NICE Technology Appraisal Guidance* No. 15. London: National Institute for Clinical Excellence.
- 8.2 The Institute issued guidance on the use of oseltamivir, zanamivir and amantadine for the treatment of influenza in February 2003: National Institute for Clinical Excellence (2003) Guidance on the use of oseltamivir, zanamivir and amantadine in the treatment of influenza. *NICE Technology Appraisal Guidance* No. 58. London: National Institute for Clinical Excellence.

## 9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.
- 9.2 The guidance on this technology will be reviewed in August 2006.

Andrew Dillon  
Chief Executive  
September 2003

A version of this guidance for the public is available from the NICE website ([www.nice.org.uk](http://www.nice.org.uk)) or from the NHS Response Line (telephone 0870 1555 455 and quote reference number N0294 for an English version and N0295 for a version in English and Welsh).

## Appendix A

### Appraisal Committee members and NICE project team

#### A. Appraisal Committee members

**NOTE** The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declaration of interests, are posted on the NICE website.

**Dr Jane Adam**

Radiologist, St George's Hospital, London

**Dr Sunil Angris**

General Practitioner, Waterhouses Medical Practice, Staffordshire

**Dr Darren Ashcroft**

Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

**Professor David Barnett (Chair)**

Professor of Clinical Pharmacology, University of Leicester

**Professor John Brazier**

Health Economist, University of Sheffield

**Professor John Cairns**

Professor of Health Economics, Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen

**Professor Mike Campbell**

Statistician, Institute of General Practice & Primary Care, Sheffield

**Dr Mark Chakravarty**

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK) Ltd, Egham, Surrey

**Dr Peter I Clark**  
Consultant Medical Oncologist,  
Clatterbridge Centre for  
Oncology, Wirral, Merseyside

**Dr Mike Davies**  
Consultant Physician, University  
Department of Medicine &  
Metabolism, Manchester Royal  
Infirmary

**Professor Jack Dowie**  
Health Economist, London  
School of Hygiene and Tropical  
Medicine

**Dr Paul Ewings**  
Statistician, Taunton & Somerset  
NHS Trust, Taunton

**Ms Sally Gooch**  
Director of Nursing, Mid-Essex  
Hospital Services NHS Trust,  
Chelmsford

**Professor Trisha Greenhalgh**  
Professor of Primary Health  
Care, University College London

**Miss Linda Hands**  
Clinical Reader in Surgery,  
University of Oxford

**Ms Ruth Lesirge**  
Lay Representative; previously  
Director, Mental Health  
Foundation, London

**Dr George Levvy**  
Lay Representative; Chief  
Executive, Motor Neurone  
Disease Association,  
Northampton

**Dr Gill Morgan**  
Chief Executive, NHS  
Confederation, London

**Professor Miranda Mugford**  
(up to November 2002)  
Health Economist, University of  
East Anglia, Norwich

**Ms Siân Richards**  
(up to December 2002)  
Chief Executive, Cardiff Local  
Health Board

**Professor Philip Routledge**  
Professor of Clinical  
Pharmacology, College of  
Medicine, University of Wales,  
Cardiff

**Dr Stephen Saltissi**  
Consultant Cardiologist, Royal  
Liverpool University Hospital

**Mr Miles Scott**  
Chief Executive, Harrogate  
Health Care NHS Trust

**Professor Andrew Stevens  
(Vice-Chair)**  
Professor of Public Health,  
University of Birmingham

**Professor Ray Tallis**  
(up to January 2003)  
Consultant Physician, Hope  
Hospital, Salford

**Professor Mary Watkins**  
Professor of Nursing, University  
of Plymouth

**Dr Norman Waugh**  
Senior Lecturer and Public  
Health Consultant, University of  
Southampton

## **B. NICE Project Team**

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

**Dr Alastair Fischer**  
Technical Lead,  
NICE project team

**Nina Pinwill**  
Project Manager,  
NICE project team

## Appendix B

### Sources of evidence considered by the Committee

The following documentation and opinions were made available to the Committee:

- A** The assessment report for this appraisal was prepared by the Departments of Epidemiology and Public Health & Microbiology and Immunology, University of Leicester and ScHARR, University of Sheffield:

Turner D, Wailoo A, Nicholson K, et al, *Systematic Review and Economic Decision Modelling for the Prevention and Treatment of Influenza A and B*, April 2002

- B** The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the appraisal consultation document. Consultee organisations were provided with the opportunity to appeal against the FAD:

- I. Manufacturer/sponsors:
  - Alliance Pharmaceuticals Ltd
  - Roche
  
- II Professional/specialist and patient/carer groups:
  - Age Concern Cymru
  - Age Concern England
  - British Geriatric Society
  - British Thoracic Society
  - Counsel and Care for the Elderly
  - Department of Health and Welsh Assembly Government
  - Health Protection Agency
  - Institute for Ageing and Health
  - National Pharmaceutical Association
  - Public Health Laboratory Service
  - Royal College of General Practitioners
  - Royal College of Nursing
  - Royal College of Pathologists
  - Royal College of Physicians
  
- III Commentator organisations (without the right of appeal):
  - NHS Quality Improvement Scotland

**C** The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on oseltamivir and amantadine for the prophylaxis of influenza by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD:

- Dr D Honeybourne, Consultant Respiratory Physician, Birmingham Heartlands Hospital
- Dr Douglas Fleming, GP, Northfield Health Centre, Birmingham
- Dr Celia Aitken, Consultant Virologist, St Bartholomew's & Royal London School of Medicine & Dentistry
- Dr William Carman, Consultant Virologist, Regional Virus Laboratory, Gartnavel General Hospital, Glasgow

## Appendix C

### Detail on criteria for audit of the use of oseltamivir and amantadine for the prophylaxis of influenza

#### *Possible objectives for an audit*

An audit could be carried out to ensure that when influenza is circulating, oseltamivir and amantadine are used appropriately.

#### *Patients to be included in an audit and time period for selection*

An audit could be carried out on all people who have been prescribed oseltamivir or amantadine for the prophylaxis of influenza in a suitable time period, for example a 2-month period in which influenza is circulating.

Alternatively, or in addition, an audit could be carried out on all at-risk people aged 13 years or older who are not effectively protected by vaccination, have been exposed to someone with ILI and are able to begin prophylaxis within 48 hours of exposure, or who live in a residential care establishment where a resident or staff member has ILI. The objective of the audit would be to ensure that oseltamivir is being prescribed for individuals for whom it is indicated. However, it could be very time-consuming to identify the individuals referred to because individual records of all at-risk people aged 13 years or older, and all people living in a residential care establishment, would have to be searched for reference to exposure to someone with ILI.

## Measures that could be used as a basis for audit

The measures that could be used in an audit of the appropriateness of use of oseltamivir and amantadine are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. When influenza is circulating, oseltamivir is prescribed for an individual who meets the following:</p> <p>a. The individual:</p> <ol style="list-style-type: none"> <li>1) 'is at-risk' <b>and</b></li> <li>2) is aged 13 years or older <b>and</b></li> <li>3) is not effectively protected by vaccination <b>and</b></li> <li>4) has been exposed to someone with ILI <b>and</b></li> <li>5) can begin prophylaxis within 48 hours of exposure</li> </ol> <p>or</p> <p>b. The individual:</p> <ol style="list-style-type: none"> <li>1) is at-risk <b>and</b></li> <li>2) lives in a residential establishment where a resident or staff member has ILI</li> </ol>	<p>100% of the individuals for whom oseltamivir is prescribed</p>	<p>The individual declines treatment</p>	<p>'At-risk' means that the individual meets at least one of the following criteria:</p> <p>has chronic respiratory disease (including asthma and chronic obstructive pulmonary disease), has significant cardiovascular disease (excluding people with hypertension only), has chronic renal disease, is immunocompromised, has diabetes mellitus or is aged 65 years or older.</p> <p>'Not effectively protected by vaccination' means an individual for whom vaccination is contraindicated or has yet to take effect, or in whom vaccination has been carried out but the vaccine is not well matched to the strain of influenza virus circulating.</p> <p>An at-risk individual is considered to be 'exposed' if he or she has been in close contact with a person who lives in the same home environment and who has been suffering from symptoms of ILI.</p> <p>For the situation described in 1b, the individual may be prescribed oseltamivir whether or not he or she has been vaccinated.</p> <p>Clinicians should agree locally on how ILI symptoms are recorded for audit purposes.</p>

Criterion	Standard	Exception	Definition of terms
2. Oseltamivir is prescribed for post-exposure prophylaxis in a healthy individual who is up to age 65 years	0% of the individuals for whom oseltamivir is prescribed	None	Clinicians should agree locally on how the healthiness of an individual is recorded for audit purposes.
3. Oseltamivir is prescribed for the seasonal prophylaxis of influenza	0% of the individuals for whom oseltamivir is prescribed	None	Clinicians should agree locally on how the prescribing of oseltamivir for seasonal prophylaxis is recorded for audit purposes.
4. Amantadine is prescribed for any individual for the post-exposure or seasonal prophylaxis of influenza	0% of the individuals for whom a prophylaxis drug is prescribed	None	'A prophylaxis drug' is oseltamivir or amantadine.

## Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the criterion *plus* number of patients who meet any exception listed}}{\text{Number of patients to whom the measure applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.

## Appendix D

### Thresholds for levels of influenza infection

#### *1. Thresholds for National Sentinel Influenza Surveillance Schemes*

Clinical monitoring is currently operated through four GP sentinel schemes.

- The Royal College of General Practitioners (RCGP), Birmingham Research Unit, Weekly Returns Service, uses approximately 80 spotter practices throughout England, with a combined patient population of approximately 600,000. Information is reported for three regions: North, Central and South.
- CDSC Wales uses 33 spotter practices throughout Wales, with a combined patient population of approximately 225,000.
- Scottish Centre for Infection and Environmental Health (SCIEH, Scotland) uses 90 spotter GP practices, with a combined patient population of approximately 450,000.
- CDSC Northern Ireland uses 20 practices and covers a patient population of approximately 125,000. This scheme was started for the 2000/01 season and baseline values have not yet been determined.

Virological monitoring is currently operated through three schemes. These services receive clinical specimens from which virus is isolated and characterised.

- Health Protection Agency Enteric, Respiratory and Neurological Virus Laboratory (ERNVL).
- CDSC, which operates approximately 50 laboratories throughout England, Wales and Northern Ireland.
- SCIEH (Scotland).

Influenza activity in the UK is reported as number of consultations per 100,000 population, or as being within one of four categories:

- baseline – normal low consultation rate for the majority of the year
- normal seasonal activity – as seen most winters

- higher than average seasonal activity – this is seen less often, although this level of activity has been seen in England five times in the past 10 years
- epidemic – periods of unusually high influenza activity; the last epidemic in the UK according to this system was during the winter of 1989/90.

The four National Sentinel Schemes in the UK have different thresholds for the different stages of influenza activity. The Sentinel Scheme for Northern Ireland is only in its second year and thresholds have not yet been established. The thresholds used by the other three schemes are shown below.

Term used	Consultation rate per 100,000 population		
	RCGP (England)	CDSC (Wales)	SCIEH (Scotland)
Baseline activity	< 50	< 25	< 50
Normal seasonal activity	50–200	25–100	50–600
Higher than average seasonal activity	200–400	> 100–400	> 600–1000
Epidemic	> 400	> 400	> 1000

Monitoring bodies will usually declare that influenza is circulating whenever the baseline activity level is exceeded.

## 2. Pandemic

Pandemic influenza is considered imminent or exists when:

- there is antigenic shift
- a high proportion of the population lacks immunity to the new virus
- the new virus spreads from person to person causing disease
- there is rapid spread of the virus beyond the community in which it was first identified.









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