NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Amantadine, oseltamivir and zanamivir for the treatment of influenza (including a review of NICE technology appraisal guidance 58)

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 with 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 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 can be caused by a variety of infectious agents and is a clinical diagnosis based on symptoms which include fever, cough, sore throat, headache and myalgia. The causative agent for an influenza-like illness cannot be determined by clinical examination alone. 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 settings 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 to 200 such consultations, with greater than 200 defined as an epidemic. In Wales, the corresponding figures are 25 to 100, and greater than 400. There are also virological monitoring schemes based on influenza virus isolated 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. The average number of deaths attributed directly

to influenza in the UK in non-epidemic years is approximately 600. It is estimated that influenza, in an epidemic year, causes between 12,000 and 13,800 deaths in the UK.

The influenza virus undergoes constant genetic mutation. This means that the virus responsible for an epidemic is slightly different from that in the previous year (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

Influenza is a self-limiting illness, so management is supportive and consists of relieving symptoms while awaiting recovery. For periods when influenza is 'circulating in the community', current NICE guidance recommends treatment with the antiviral drugs oseltamivir and zanamivir only for people in 'at-risk' groups who can start therapy within 48 hours of the onset of an influenza-like illness. Amantadine is currently not recommended by the Institute for the treatment of influenza. Further details of the current guidance are included in appendix B and for full guidance see NICE technology appraisal guidance 58 (TA 58). The Assessment Group reported that in the UK rate of naturally occurring (that is outside clinical trials) resistance of influenza virus to oseltamivir in the 2007–8 season was 11%.The recommendations in TA 58 do 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.

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.

Vaccination is currently the mainstay of influenza prevention (prophylaxis) and is recommended before each influenza season for the clinical 'at-risk' populations and certain other target groups such as those aged 65 years and older (see Chief Medical Officer Update, 2008). Antiviral drugs can also be

used for prophylaxis. Prophylaxis may be seasonal, post-exposure or for control of outbreaks in residential care. NICE guidance (NICE technology appraisal guidance 67 [TA 67]) on the use of antiviral drugs for the prophylaxis of influenza is currently being reviewed.

When NICE technology appraisal guidance 58 was issued in 2003 zanamivir had UK marketing authorisation for the treatment of children aged 12 years and older. This has since changed to children aged 5 years or older.

2 The technologies

Table 1 Summary description of technologies

Non-proprietary name	Amantadine	Oseltamivir	Zanamivir
Proprietary name	Lysovir, Symmetrel	Tamiflu	Relenza
Manufacturer	Alliance Pharmaceuticals	Roche	GlaxoSmithKline
Dose (adults)	100 mg daily for 4 to 5 days	One 75 mg capsule twice daily for 5 days for people aged 13 or older. For children aged between 1 and 12 years, 30 mg, 45 mg, 60 mg or 75 mg (depending on child's weight) twice daily for 5 days.	10 mg twice daily for 5 days
Acquisition cost (BNF edition 55)	£2.40 for 5 capsules (100 mg each), £4.80 for 14 capsules, £16.88 for 56 capsules; £5.55 for 150 ml syrup (50 mg/5 ml)	£16.36 for 45 mg, 75 mg capsules and suspension (for a 5-day course), £8.18 for 30 mg capsules (for 10 capsules)	£24.55(£16.36[1])(for a 5-day course)

Amantadine

Amantadine acts against influenza A by inhibiting an ion channel and blocking viral replication. It has UK marketing authorisation for the treatment of adults and children (10 years and older) who have signs and symptoms of infection caused by influenza A virus. The summary of product characteristics (SPC)

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

states that treatment should be started as early as possible, and when treatment is started within 48 hours of the onset of symptoms, the duration of fever and other effects of influenza are reduced by 1 or 2 days. Amantadine is taken orally as syrup or capsules, but only the syrup formulation is licensed for the treatment of influenza.

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 UK marketing authorisation for the treatment of influenza in adults and children (1 year and older) who present with symptoms typical of influenza when influenza virus is circulating in the community. The SPC states that treatment should be initiated as soon as possible within the first 48 hours of the onset of symptoms of influenza. Oseltamivir is taken orally as syrup or capsules.

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 UK marketing authorisation for treatment of influenza A and B in adults and children (5 years and older) who present with symptoms typical of influenza when influenza is circulating in the community. The SPC states that the treatment should begin as soon as possible, within 48 hours of onset of symptoms for adults and within 36 hours of onset of symptoms for children. Zanamivir is taken by oral inhalation, using a Diskhaler device.

3 The evidence

3.1 Clinical effectiveness

The Assessment Group conducted a systematic search for randomised controlled trials (RCTs) conducted in people who presented with symptoms of typical influenza, whether influenza was reported as circulating in the community or not. Studies were included that compared the effectiveness of oseltamivir or zanamivir with each other, with placebo or with best

symptomatic care. The Assessment Group conducted a systematic search for evidence on the clinical effectiveness of amantadine; however no new evidence was identified that had not already been considered for the previous technology appraisal (TA 58).

A total of 29 RCTs were included in the final review, of which 14 were additional to the previous technology appraisal (TA 58). No RCTs that directly compared zanamivir and oseltamivir were included; a Bayesian indirect comparison using placebo as a common comparator was conducted. The trials generally compared zanamivir or oseltamivir with placebo. Concomitant therapies such as antipyretics and other symptomatic relief were banned, restricted or freely available. The Assessment Group stated that the studies were of variable quality and, despite the short duration of the trials, only half achieved follow-up of at least 95% of the participants.

Limited data were available on the number of vaccinated participants in each of the studies. Seven studies excluded or did not recruit people vaccinated within the previous 12 months. In the other studies, the proportions of vaccinated participants ranged from 9% (healthy adults) to 43% (older people), where reported. In 18 studies it was reported that influenza was circulating in the community before study recruitment; however, only six of the RCTs recruited participants from the UK and the definitions of threshold levels were generally not reported.

Data were generally available on the following outcomes: time to alleviation of symptoms; time to return to normal activities; adverse events and complications. The population was divided into the following categories: otherwise healthy adults; 'at risk'; older people; and children. Data from trials conducted in populations that could not be subdivided were analysed as 'mixed' populations. Most studies defined healthy adults as people aged between 18 and 65 years that were otherwise not 'at risk'. Data for the 'at risk' populations were often obtained from studies of mixed populations, and the definitions of 'at risk' included children and adults with comorbid conditions,

and older people. A total of 36% of participants in all studies were considered 'at risk' according to definitions in the Department of Health Green Book.

Analyses were reported for the ITT population (intention to treat; representative of the entire population recruited in the trials) and ITTI population (intention to treat, confirmed as being influenza positive) wherever possible.

All of the included trials (except one zanamivir and one oseltamivir trial) reported continuous outcomes in days, rounding to the nearest half-day. For dichotomous outcomes, odds ratios (OR) with 95% confidence intervals (CIs) were calculated, and for continuous outcomes (time to event data) median differences with 95% CIs were calculated. Median differences and the associated standard errors were pooled in meta-analyses to produce a weighted median difference (WMD). If standard errors around the individual medians were not reported, the Assessment Group contacted the manufacturers or used techniques for estimation wherever possible. Heterogeneity was assessed using the chi-squared and I-squared tests.

3.1.1 Amantadine

The Assessment Group did not identify any studies of the clinical effectiveness of amantadine that had not been included in TA 58 and no manufacturer's submission was provided.

3.1.2 Oseltamivir

The Assessment Group's systematic review identified 16 RCTs. Eight of these had been considered for TA 58 and eight were new studies that had been published since the review of evidence for TA 58. Two of the included studies recruited mixed populations, seven recruited only healthy adults, two recruited from general 'at risk' populations, two recruited only children and three recruited only older people. In all of the trials oseltamivir was compared with placebo. Follow-up periods ranged from 10 to 28 days.

Most trials reported time to alleviation of symptoms and time to return to normal activities (14 trials in total). Meta-analyses were considered appropriate, and were conducted by population category. The results of these meta-analyses, along with the corresponding results from TA 58, are presented in tables 2 and 3. Heterogeneity was assessed and, when identified, the possible causes were investigated by the Assessment Group (see pages 43–94 of the assessment report for details).

Alleviation of fever was reported in a small number of studies. Because the studies that reported alleviation of fever were generally conducted in healthy or mixed populations, meta-analyses were not presented by population category. All of the trials showed a reduction in the time to alleviation of fever. Overall, oseltamivir reduced the median time to alleviation of fever by 18.74 hours in the ITT population (95% CI 27.78 to 9.70) and 24.41 hours in the ITTI population (95% CI 31.64 to 17.17).

Two trials tested for viral resistance and one potential case of oseltamivir resistance was identified. The data on complications were sparse and only the use of antibiotics was significantly reduced for those who received oseltamivir compared with placebo (ITTI population, OR 0.62, 95%CI 0.46 to 0.83). Across all trials, there was no evidence of a difference in the incidence of overall, serious or drug-related adverse effects between oseltamivir and placebo. Among the nine trials that reported mortality, there was a single death in the placebo arm of a trial in an ‘at risk’ population; it was not clear whether this death was associated with influenza.

3.1.3 Zanamivir

The Assessment Group’s systematic review identified 13 RCTs. Six of these were new studies that had been published since the review of evidence for TA 58. Five of the studies recruited a mixed population (for which symptom data for healthy and ‘at risk’ adults were available separately), three recruited only healthy adults, two recruited from general ‘at risk’ populations, two recruited only children and one recruited only older people. In all trials

zanamivir was compared with placebo. Follow-up periods ranged from 5 to 29 days.

All trials reported time to alleviation of symptoms and time to return to normal activities. Meta-analyses were considered appropriate, and were conducted by population category. The results of these meta-analyses, along with the corresponding results from TA 58, are presented in tables 2 and 3. Heterogeneity was assessed and, when identified, the possible causes were investigated by the Assessment Group (see pages 43–94 of the assessment report for details).

Alleviation of fever was reported in four studies, and only one reported any measure of variance, so meta-analyses could not be conducted for this outcome. Across the studies that reported alleviation of fever, the median time to alleviation of fever was reduced by between 0.5 and 0 days for zanamivir compared with placebo.

Two trials tested for viral resistance, and no potential cases of zanamivir resistance were identified. Although the data on complications were sparse, the incidence of overall complications and the use of antibiotics were significantly reduced for those who received zanamivir compared with placebo (ITTI populations, OR 0.77, 95%CI 0.65 to 0.92 for zanamivir; OR 0.88, 95% CI 0.66 to 0.99 for placebo). Across all trials, treatment with zanamivir significantly reduced the incidence of overall adverse events compared with placebo (OR 0.85, 95% CI 0.75 to 0.96) but there was no evidence of a difference in the incidence of drug-related adverse events. Very few serious adverse events were reported and there were no deaths in any of the seven zanamivir trials that reported mortality.

Table 2 Key outcomes meta-analyses (intention to treat populations)

	Zanamivir WMD (95% CI)		Oseltamivir WMD (95% CI)	
Population	**TA 58 (2003)**	**R 58 (2008)**	**TA 58 (2003)**	**R 58 (2008)**
Time in days to alleviation of symptoms				
Healthy adults	−0.78 (−1.31 to −0.26)	−0.57 (−1.07 to −0.07)	−0.86 (−1.42 to −0.31)	−0.55 (−1.05 to −0.14)
At-risk adults	−0.93 (−1.90 to 0.05)	−0.95 (−1.83 to −0.07)	−0.35 (−1.40 to 0.71)	−0.59 (−1.70 to 0.54)
Healthy children	−1.00 (−1.50 to −0.50)	−1.00 (−1.50 to −0.50)	−0.87 (−1.49 to −0.25)	−0.88 (−1.41 to −0.26)
At-risk children	−2.00 (−6.90 to 2.90)	−2.00 (−6.94 to 2.94)	NR	−0.88 (−1.94 to 0.17)
All children	NR	−0.94 (−1.43 to −0.46)	NR	−0.88 (−1.41 to −0.35)
Older people	NR	−1.13 (−2.90 to 0.63)	NR	−0.41 (−1.87 to 1.05)
All 'at risk'	NR	−0.98 (−1.84 to −0.11)	NR	−0.74 (−36.20 to 0.52)
Whole population	−0.94 (−1.23 to −0.65)	−0.71 (−1.01 to −0.41)	−0.80 (−1.18 to −0.41)	−0.68 (−0.95 to −0.41)
Time in days to return to normal activities				
Healthy adults	−0.51 (−1.04 to 0.02)	−0.37 (−0.84 to 0.09)	−1.33 (−1.96 to −0.71)	−1.33 (−1.96 to −0.71)
At-risk adults	−0.09 (−0.95 to 0.78)	−1.07 (−2.81 to 0.68)	−2.45 (−4.86 to −0.05)	−2.45 (−4.86 to −0.05)
Healthy children	−0.50 (−1.30 to 0.30)	−0.50 (−1.26 to 0.26)	−1.25 (−1.80 to −0.70)	−1.25 (−1.81 to −0.70)
At-risk children	−1.00 (−3.50 to 1.50)	−1.00 (−3.46 to 1.46)	NR	NR
All children	NR	NR	NR	NR
Older people	NR	NR	NR	−4.09 (−7.12 to −1.05)
All 'at risk'	NR	−0.96 (−2.32 to 0.41)	NR	NR
Whole population	−0.37 (−0.74 to −0.01)	−0.44 (−0.84 to −0.05)	−1.32 (−1.73 to −0.91)	−1.32 (−1.73 to −0.91)

WMD – weighted median difference; CI – confidence interval; TA 58 (2003) – model prepared by the Assessment Group for NICE technology appraisal 58; R 58 (2008) – model prepared by the Assessment Group for this NICE technology appraisal; NR – No results available.

Table 3 Key outcomes meta-analyses (intention to treat, confirmed influenza populations)

	Zanamivir: WMD (95% CI)		Oseltamivir: WMD (95% CI)	
Population	**TA 58 (2003)**	**R 58 (2008)**	**TA 58 (2003)**	**R 58 (2008)**
Time in days to alleviation of symptoms				
Healthy adults	−1.26 (−1.93 to −0.59)	−0.96 (−1.38 to −0.54)	−1.38 (−1.96 to −0.80)	−0.92 (−1.56 to −0.29)
At-risk adults	−1.99 (−3.08 to −0.90)	−1.96 (−3.05 to −0.86)	−0.45 (−1.88 to 0.97)	−0.84 (−2.35 to 0.68)
Healthy children	−1.00 (−1.60 to −0.4)	−1.00 (−1.59 to −0.41)	−1.49 (−2.22 to −0.76)	−1.50 (−2.23 to −0.77)
At-risk children	−3.80 (−7.60 to 0.10)	−3.75 (−7.59 to 0.09)	NR	−0.43 (−1.61 to 0.74)
All children	NR	NR	NR	−1.20 (−1.82 to −0.58)
Older people	NR	−1.85 (−4.77 to 1.07)	NR	−1.00 (−2.83 to 0.83)
All 'at risk'	NR	−1.83 (−2.81 to −0.86)	NR	−0.59 (−1.51 to 0.34)
Whole population	−1.26 (−1.616 to −0.90)	−1.07 (−1.39 to −0.74)	−1.33 (−1.77 to −0.90)	−0.95 (−1.39 to −0.50)
Time in days to return to normal activities				
Healthy adults	−0.46 (−0.90 to −0.02)	−0.39 (−0.84 to 0.06)	−1.64 (−2.58 to −0.69)	−2.63 (−4.13 to −1.14)
At-risk adults	−0.20 (−1.19 to 0.79)	−1.77 (−4.40 to 0.86)	−3.00 (−5.88 to −0.13)	−2.95 (−5.70 to −0.20)
Healthy children	−0.50 (−1.40 to 0.40)	−0.50 (−1.36 to 0.36)	−1.86 (−2.65 to −1.06)	−1.86 (−2.66 to −1.06)
At-risk children	−2.50 (−4.40 to −0.60)	−2.50 (−4.37 to −0.63)	NR	−0.50 (−1.51 to 0.46)
All children	NR	NR	NR	−1.33 (−1.95 to −0.71)
Older people	NR	NR	NR	−3.07 (−6.30 to 0.16)
All 'at risk'	NR	−1.89 (−3.95 to 0.17)	NR	−0.80 (−1.73 to 0.13)
Whole population	−0.37 (−0.72 to −0.02)	−0.71 (−1.24 to −0.19)	−1.64 (−2.11 to −1.17)	−1.51 (−2.02 to −1.01)

WMD – weighted median difference; CI – confidence interval; TA 58 (2003) – model prepared by the Assessment Group for NICE technology appraisal 58; R 58 (2008) – model prepared by the Assessment Group for this NICE technology appraisal; NR – No results available.

3.1.4 Indirect comparison of zanamivir and oseltamivir

The Assessment Group identified one direct comparison of zanamivir and oseltamivir but excluded this trial because it did not report usable outcome data. Therefore, the Assessment Group performed an indirect comparison of zanamivir and oseltamivir using a multi-parameter Bayesian approach. The comparison characterised the joint distribution of the efficacy of zanamivir and oseltamivir in terms of symptom duration (that is, time to alleviation of symptoms and time to return to normal activities). The probabilities that each treatment was 'best' were calculated for the following population subgroups: otherwise healthy adults; otherwise healthy children and an 'at-risk' group that combined 'at-risk' children, 'at-risk' adults and older people (see section 6, pages 105–113 of the assessment report for further details).

The results from the Bayesian indirect comparison were broadly consistent with the results from the standard meta-analyses; however, the precision of the estimates was better. Across all of the analyses, the probability that either treatment was more effective than placebo was 100%. There was variation across population subgroups as to whether zanamivir or oseltamivir had a higher probability of being most effective. The probability of each treatment being the 'best' and the median and mean number of days to alleviation of symptoms and return to normal activities for the ITT and ITTI populations are presented in tables 4 and 5. The Assessment Group noted that the 'best' treatment for healthy children was zanamivir for the ITT populations and oseltamivir for the ITTI populations.

Table 4 Bayesian analysis (intention to treat population)

Subgroup	Treatment	Probability 'best'	Median (95% credibility interval)	Mean (95% credibility interval)
Number of days to the alleviation of symptoms				
Healthy adults	placebo	0.00	5.48 (2.04, 12.08)	9.88 (3.69, 21.82)
	zanamivir	0.05	4.99 (1.86, 11.04)	8.99 (3.35, 19.91)
	oseltamivir	0.95	4.43 (1.63, 9.88)	7.98 (2.93, 17.72)
'At risk'	placebo	0.00	8.29 (3.15, 18.15)	14.92 (5.65, 32.78)
	zanamivir	0.89	6.67 (2.51, 14.66)	12.01 (4.54, 26.43)
	oseltamivir	0.11	7.65 (2.9, 16.76)	13.78 (5.21, 30.31)
Healthy children	placebo	0.00	3.79 (1.25, 8.77)	6.82 (2.26, 15.89)
	zanamivir	0.74	2.96 (0.98, 6.91)	5.33 (1.76, 12.48)
	oseltamivir	0.26	3.19 (1.03, 7.52)	5.74 (1.87, 13.52)
Number of days to return to normal activities				
Healthy adults	placebo	0.00	6.50 (2.25, 14.79)	11.71 (4.03, 26.69)
	zanamivir	0.05	5.91 (2.04, 13.38)	10.66 (3.67, 24.28)
	oseltamivir	0.95	5.25 (1.80, 12.01)	9.46 (3.24, 21.66)
'At risk'	placebo	0.00	9.81 (3.49, 22.21)	17.68 (6.23, 40.3)
	zanamivir	0.89	7.89 (2.77, 17.89)	14.23 (4.97, 32.42)
	oseltamivir	0.11	9.06 (3.16, 20.65)	16.33 (5.7, 37.67)
Healthy children	placebo	0.00	4.49 (1.39, 10.97)	8.09 (2.51, 19.66)
	zanamivir	0.74	3.51 (1.08, 8.62)	6.32 (1.94, 15.46)
	oseltamivir	0.26	3.78 (1.16, 9.27)	6.81 (2.08, 16.82)

Table 5 Bayesian analysis (intention to treat, confirmed influenza population)

Subgroup	Treatment	Probability 'best'	Median (95% credibility interval)	Mean (95% credibility interval)
Number of days to the alleviation of symptoms				
Healthy adults	placebo	0.00	5.36 (2.47, 10.12)	8.96 (4.11, 16.89)
	zanamivir	0.12	4.58 (2.09, 8.64)	7.66 (3.49, 14.46)
	oseltamivir	0.88	4.12 (1.86, 7.86)	6.88 (3.12, 13.15)
'At risk'	placebo	0.00	8.28 (3.84, 15.84)	13.83 (6.41, 26.45)
	zanamivir	0.99	5.47 (2.48, 10.53)	9.13 (4.14, 17.59)
	oseltamivir	0.01	7.34 (3.33, 14.24)	12.27 (5.53, 23.70)
Healthy children	placebo	0.00	5.80 (2.32, 12.03)	9.69 (3.88, 20.22)
	zanamivir	0.26	4.74 (1.83, 10.13)	7.92 (3.07, 16.86)
	oseltamivir	0.74	4.22 (1.61, 9.04)	7.06 (2.69, 15.18)
Number of days to return to normal activities				
Healthy adults	placebo	0.00	6.80 (2.91, 13.42)	11.37 (4.83, 22.66)
	zanamivir	0.12	5.81 (2.47, 11.44)	9.72 (4.12, 19.28)
	oseltamivir	0.88	5.22 (2.22, 10.38)	8.73 (3.68, 17.54)
'At risk'	placebo	0.00	10.50 (4.51, 21.03)	17.56 (7.49, 35.39)
	zanamivir	0.99	6.93 (2.91, 14.01)	11.59 (4.85, 23.46)
	oseltamivir	0.01	9.32 (3.92, 18.92)	15.58 (6.54, 31.64)
Healthy children	placebo	0.00	7.36 (2.73, 15.90)	12.31 (4.57, 26.78)
	zanamivir	0.26	6.02 (2.15, 13.43)	10.06 (3.57, 22.34)
	oseltamivir	0.74	5.36 (1.92, 11.86)	8.97 (3.20, 19.95)

3.2 Cost effectiveness

3.2.1 Review of cost-effectiveness studies

The Assessment Group identified 22 cost-effectiveness studies that assessed oseltamivir or zanamivir for the treatment of influenza, and met the inclusion criteria outlined in the protocol. The manufacturer of oseltamivir, Roche Products, also provided a de novo economic model. No cost-effectiveness analyses were submitted by the manufacturers of amantadine or zanamivir. The majority of the identified studies were conducted primarily from a healthcare or payer perspective, of which seven were from the perspective of the NHS (including the assessment for TA 58 and the current manufacturer's submission from Roche).

The decision-tree model developed by the Assessment Group for TA 58 was designed to compare amantadine, oseltamivir and zanamivir with usual care for the treatment and prophylaxis of influenza. The following four separate groups were considered: otherwise healthy adults; high-risk adults; children; and older people in residential care. For each of the population groups, amantadine compared with usual care had the lowest incremental cost-effectiveness ratios (ICERs), which ranged from £4535 to £6190 per quality-adjusted life-year (QALY) gained. However, the Committee was unable to accept that the clinical effectiveness of amantadine was sufficiently proven and so it was not recommended for the treatment of influenza A. The ICERs for oseltamivir compared with usual care ranged from £19,015 to £22,502 per QALY gained. The ICERs for zanamivir compared with usual care ranged from £16,819 to £31,529 per QALY gained.

Of the five other studies conducted from the UK NHS perspective, two compared zanamivir with usual care in both healthy and 'at risk' adults, two compared oseltamivir with usual care in healthy children and healthy adults and one compared oseltamivir, zanamivir and usual care in healthy adults. The estimated ICERs for zanamivir compared with usual care ranged from £78,490 to £54,000 per QALY gained for 'at risk' adults and £65,000 per QALY gained for otherwise healthy adults. The estimated ICERs for oseltamivir compared with usual care ranged from oseltamivir being dominant to £11,173 per QALY gained for healthy children, and £225 to £5600 for adults per QALY gained. In the only comparison of oseltamivir with zanamivir (in healthy adults), zanamivir was dominated.

3.2.2 Manufacturer's model (Roche)

The manufacturer of oseltamivir (Roche) submitted an economic model that estimated the cost effectiveness of oseltamivir compared with zanamivir and usual care for the treatment of influenza, using separate pairwise comparisons (table 6). The model considered the following population subgroups separately: otherwise healthy adults, 'at risk' adults (including older adults), otherwise healthy children aged 1–12 years and otherwise healthy children

aged 1–5 years. A decision-tree structure was used and the analyses were primarily conducted from an NHS perspective. For the comparison of oseltamivir with zanamivir it was assumed that both drugs are equally effective and a cost-minimisation approach was used.

The model started when a patient presented to a GP with an influenza-like illness when influenza was reported to be circulating in the community. The probability that the illness was influenza was assumed to be 31% in all populations modelled. In the model people with an influenza-like illness were assumed to either recover or experience one of the following complications: bronchitis, pneumonia or (for children only) otitis media.

The health state utility for influenza-like illness without complication was assumed to be 0.840; this was taken from Harvard utility scores and was assumed not to differ between populations. The relative improvement in utility associated with zanamivir and oseltamivir was assumed to be 11.52%, which resulted in a utility value of 0.937. The estimated percentage improvement in utility was derived from the oseltamivir clinical trials. The resource-use data cover costs associated with GP visits, diagnostic tests, antibiotic treatments and hospital visits. The total cost of a course of zanamivir was assumed to be £0.19 higher than that of oseltamivir. The Assessment Group stated that this was an error in the manufacturer's economic model.

Table 6 Base-case cost-effectiveness results from Roche's submission

Population	Treatment strategy	Incremental cost (£)	Incremental QALY	Incremental cost-effectiveness ratio (£)
Healthy adults	Oseltamivir vs. usual care	11.75	0.00216	5452
	Oseltamivir vs. zanamivir	−0.19	0	Oseltamivir dominates
Children (aged 1–12)	Oseltamivir vs. usual care	9.34	0.00156	5992
	Oseltamivir vs. zanamivir	−5.65	0	Oseltamivir dominates
Children (aged 1–5)	Oseltamivir vs. usual care	8.17	0.00174	4687
'At risk' adults	Oseltamivir vs. usual care	11.54	0.0177	652
	Oseltamivir vs. zanamivir	−0.19	0	Oseltamivir dominates

A number of one-way sensitivity analyses were performed to investigate the sensitivity of the cost-effectiveness estimates to parameter variations. The key drivers in the model were the probability that an influenza-like illness is true influenza and the probability that patients presented to a GP within 48 hours.

3.2.3 Assessment Group's economic analysis

Model structure

The Assessment Group developed estimates of the cost effectiveness of oseltamivir and zanamivir for the treatment of influenza compared with usual care without antiviral treatment using an incremental, rather than pairwise, approach. The Assessment Group did not develop estimates of the cost effectiveness of amantadine for the treatment of influenza because it is not widely used and was not recommended for use in TA 58. The decision-tree model evaluated costs from an NHS and personal social services perspective. Because all the costs and benefits occurred within a single influenza season, the time horizon was 1 year; therefore there was no discounting, except for life years lost as a result of premature death caused by influenza and its complications. The model was probabilistic: parameters were entered into the model as probability distributions in order to reflect the uncertainty in the mean

estimates (see section 7.2, pages 160–164 of the assessment report for further details).

The model started when a patient presented to a healthcare professional with an influenza-like illness and was considered suitable for treatment with either oseltamivir or zanamivir. Each patient was then assumed to progress through the decision tree and could experience either recovery, resistance to oseltamivir or zanamivir, respiratory or non-respiratory tract complications, hospitalisation or death as a result of a complication (see page165 of the assessment report for further details of complications included in the model).

Cost-effectiveness estimates for influenza treatment were presented for five separate population groups:

- otherwise healthy children aged 1–14 years
- 'at risk' children aged 1–14 years
- otherwise healthy adults aged 15–64 years
- 'at risk' adults aged 15–64 years
- 'elderly' (defined as adults older than 65 years).

In the model it was assumed that oseltamivir and zanamivir were used only according to their UK marketing authorisations. This meant that patients were assumed to present and be able to start treatment within 48 hours of symptom onset for oseltamivir and 36 hours for zanamivir. The model also assumed that oseltamivir and zanamivir would be prescribed only when influenza was known to be circulating in the community, based on national surveillance schemes (this was assumed to be defined as 30 new GP consultations for influenza-like illness per 100,000 population).

Model parameters

The probability that an influenza-like illness is influenza was derived from national surveillance data provided by the Royal College of General Practitioners. Across all weeks that data were collected, the crude average probability that influenza-like illness was influenza was 0.495 (622/1256). The Assessment Group developed a Bayesian hierarchical model to estimate the

probability that the illness was true influenza across the separate age groups. Results from the model estimated the probabilities to be 0.56 (95% credibility interval [CrI] 0.26 to 0.79) in people younger than 15 years and 0.41 (95% CrI 0.21 to 0.66) in people aged 15 and older (see pages 169–171 of the assessment report for further details).

The effectiveness of oseltamivir and zanamivir was derived from the overall duration of symptoms for the different subgroups applied in the model. These were taken directly from the mean ITTI results from the indirect Bayesian multi-parameter evidence synthesis model performed by the Assessment Group. The same mean duration of symptoms was applied to each of the separate 'at-risk' populations considered in the economic model. Sensitivity analyses were performed using the median estimates and using time to return to normal activities. The relative effectiveness estimates from the ITTI populations were assumed to be independent of previous vaccination or prophylactic use of antivirals. The relative effectiveness of oseltamivir and zanamivir was assumed to be the same for both influenza type A and B. Both treatments were considered to be effective only in patients with true influenza.

A systematic search of the literature was undertaken to identify suitable health-related quality of life data. Although the Assessment Group identified some studies, none of these presented comparable estimates for different risk groups and there were limitations in the methods used in the identified studies. In the absence of robust data, utility values were based on those applied in TA 58. The data used in TA 58 were derived from the transformation of visual analogue scale (VAS) data reported in some of the oseltamivir trials into time trade off utilities over a 21-day period. These data were then augmented with symptom duration estimates from the full range of RCTs identified in the current clinical effectiveness review. Separate values were reported for otherwise healthy adults and 'at risk' adult populations and the total quality of life days and years gained are reported in table 7.

Table 7 Total quality of life days and years gained for healthy adults and 'at risk' groups receiving oseltamivir or placebo

	Healthy adults			'At-risk' groups		
	Placebo	**Oseltamivir**	**Difference**	**Placebo**	**Oseltamivir**	**Difference**
Total quality-adjusted life days gained	14.456835	15.220211	0.763376	10.29142	10.867186	0.575766
Total quality-adjusted life-years gained	0.002223	0.002257	0.000035	0.001718	0.001784	0.000067

No separate figures were available for people receiving zanamivir treatment so these were estimated using relative effectiveness estimates from the indirect Bayesian comparison applied to the placebo arm. In the absence of comparable estimates for otherwise healthy children and 'at risk' children, the values corresponding to the equivalent adult populations were applied in the model. Adverse effects from oseltamivir and zanamivir were assumed to be mild and self-limiting and were not assumed to impact on a person's health-related quality of life.

The model assumed that all patients with influenza-like illness (whether influenza or not) had a probability of developing a complication. Estimates of the baseline probabilities of developing each complication (and subsequent mortality) were derived separately for each subgroup from data reported in a large UK population-based study. The probability of any type of complication ranged from 7.55% (healthy adult subgroup) to 17.59% ('at-risk' children subgroup). The most common complication was assumed to be a respiratory tract infection; of which, bronchitis was most probable in children and pneumonia in adults. In the model, it was possible for patients to experience more than one complication; the probability of this was estimated per patient in each subgroup.

All patients who develop complications as a result of influenza and influenza-like illness were assumed to present to a healthcare provider for treatment and could be prescribed antibiotics. Only complicated cases were assumed to lead to hospitalisation and death. Premature death as a result of influenza was assumed to occur only following a secondary complication (irrespective of whether a patient was hospitalised). Given limitations in the evidence base, it was assumed that hospitalisations occurred only as a result of respiratory tract infections. There were no robust estimates of the relative treatment effects in relation to complications as a whole (including hospitalisations and mortality), so estimates of how effective the different treatments were at reducing the incidence of complications were based on a single estimate of the relative effect, namely the relative risk of antibiotic use (see table 8). Quality of life estimates were decreased specifically according to type of complication.

Table 8 Relative risks of complications (based only on antibiotic use)

Population	Comparison	Relative risk (95% confidence interval)
Healthy adults	Zanamivir vs. placebo	0.71 (0.34 to 1.45)
	Oseltamivir vs. placebo	0.57 (0.24 to 1.35)
'At risk'	Zanamivir vs. placebo	0.74 (0.35 to 1.57)
	Oseltamivir vs. placebo	0.69 (0.50 to 0.93)
Children	Zanamivir vs. placebo	0.78 (0.45 to 1.35)
	Oseltamivir vs. placebo	0.56 (0.36 to 0.87)

The model includes the costs of managing secondary complications. It is assumed in the model that each patient developing a complication requires a single GP visit and faces a higher probability of requiring antibiotics than a patient who does not develop a complication. Costs and likelihood of hospitalisation as a result of each type of complication were also included in the model (see pages 178–179 of the assessment report for further details of the costs associated with complications).

The model assumed that all patients who develop a complication face a subsequent probability of mortality. This probability was assumed to vary only

by population subgroup, not by treatment strategy or previous hospitalisation. Mortality was assumed not to incur any cost, but it was assumed to result in loss of potential QALYs. In each population age group (children, adults and older people), the expected age of death from complications related to an influenza-like illness was derived from data from the national statistics reporting influenza deaths by age group.

The acquisition cost of oseltamivir (£16.36) was based on the 'British national formulary' (edition 55) list price, with identical estimates applied for zanamivir based on the revised price agreement. It was assumed that any remaining powder from the use of oral suspension (oseltamivir) in children would not be re-used and hence the full cost was assumed throughout in each subgroup.

Sensitivity analyses

A total of 12 scenario analyses were investigated by the Assessment Group. These analyses included investigation of assumptions such as those made about complications, the probability that an influenza-like illness was true influenza and the relative efficacy of oseltamivir and zanamivir (see table 7.24, page184 of the assessment report for further details of the scenario analyses conducted).

3.2.4 Results of Assessment Group's economic analysis

The base-case results of the economic analysis are summarised in table 9 below and table 7.25 of the assessment report (page 185).

Table 9 Assessment Group's base-case results

Strategy	Mean cost	Mean quality-adjusted life-years gained	Incremental cost-effectiveness ratio
Healthy children			
Usual care	£5.03	24.9629	Not applicable
Zanamivir	£18.60	24.9641	Dominated
Oseltamivir	£18.21	24.9647	£7035
'At risk' children			
Usual care	£8.60	24.9600	Not applicable
Zanamivir	£20.04	24.9666	£1752
Oseltamivir	£19.89	24.9638	Extendedly dominated
Healthy adults			
Usual care	£3.29	14.6671	Not applicable
Zanamivir	£17.83	14.6692	Dominated
Oseltamivir	£17.68	14.6697	£5521
'At risk' adults			
Usual care	£6.82	11.0038	Not applicable
Zanamivir	£19.36	11.0093	£2270
Oseltamivir	£19.25	11.0073	Extendedly dominated
Older people			
Usual care	£13.13	4.1939	Not applicable
Zanamivir	£22.07	4.2098	£562
Oseltamivir	£21.84	4.2081	Extendedly dominated

In each population, the ICER for both oseltamivir and zanamivir (relative to standard care) is less than £20,000 per QALY gained, and across the separate populations ranged from £562 to £7035 per QALY gained. In healthy children and healthy adults oseltamivir dominated zanamivir, with ICERs of £7035 and £5521 per QALY gained respectively. In 'at risk' children, 'at risk' adults and older people zanamivir extendedly dominated oseltamivir (that is, treatment with zanamivir is expected to cost more and result in more QALYs gained than oseltamivir). The ICERs were £1752 per QALY gained for 'at risk' children, £2270 for 'at risk' adults and £562 for older people. At a willingness to pay threshold of £20,000 per QALY gained, the probability that zanamivir was cost effective ranged from 23% (healthy children) to 90% ('at risk' adults) and the probability that oseltamivir was cost effective ranged from 10% ('at risk' adults) to 77% (healthy adults). The probability that usual care was cost effective at the same threshold was 0–4% (healthy children).

Sensitivity analyses

Across the 12 scenario analyses performed by the Assessment Group, the overall conclusions and ICERs in the 'at risk' populations appeared robust to a wide range of assumptions. The ICERs appeared more sensitive in the otherwise healthy populations; however, zanamivir remained consistently dominated by oseltamivir in both healthy adults and healthy children across the separate scenarios. The base-case estimate of the ICER of oseltamivir compared with standard care was sensitive to a number of key assumptions; namely:

- the exclusion of hospitalisation and mortality benefits with antiviral treatment (these were included in the base case)
- the probability that an influenza-like illness is true influenza (this was 0.495 in the base case)
- the potential link between a positive recommendation, increased consultations with healthcare providers and the subsequent estimate of the probability that an influenza-like illness is influenza (this was also an important factor considered in TA 58)
- the decrement applied to quantify the impact of influenza on quality of life and the assumption about when the mean reductions in symptom durations were being achieved (that is, across the entire illness period or closer to the beginning or end of the illness) with antiviral treatment compared with standard care.

For full details of the results of the sensitivity analyses performed by the Assessment Group, see section 7.2.5.2 (pages 185–201) of the assessment report.

3.2.5 Comparison of the Assessment Group's model, Roche's model and the model for TA 58

Tables 10 and 11 present comparisons of results from three different models: the model submitted by the manufacturer of oseltamivir (referred to as the Roche model); the Assessment Group's model for TA 58 (referred to as the

TA 58 model); and the Assessment Group's model for the current appraisal (referred to as the R 58 model). The base-case results from each model are presented separately for each population group, both including and excluding hospitalisation and mortality benefits.

In contrast to the R 58 model, separate pairwise comparisons of the interventions of interest were presented in the TA 58 model and hospitalisation and mortality benefits were included in the Roche model. Therefore, to allow a simultaneous comparison of oseltamivir, zanamivir and usual care across the models, the Assessment Group applied similar decision rules from the R 58 model to the TA 58 model, and estimated ICERs with exclusion of hospitalisation and mortality benefits by setting the probability to zero in the Roche model.

Table 10 Comparison of results from the three models; including hospitalisation and mortality benefits

Subgroup	Incremental cost-effectiveness ratio	
	Oseltamivir	**Zanamivir**
R 58 (Assessment Group economic model for current appraisal)		
Healthy children	£7035	Dominated
'At risk' children	Extendedly dominated	£1752
Healthy adults	£5521	Dominated
'At risk' adults	Extendedly dominated	£2270
Older people	Extendedly dominated	£562
TA 58 (Assessment Group economic model for previous appraisal)		
Children (healthy and 'at risk' children not analysed separately)	£11,381	Dominated
Healthy adults	£4729	Dominated
'At risk' adults	£3,205 vs. zanamivir	£3016 vs. usual care
Older people in residential care	Dominated by zanamivir	Dominates usual care
Roche model for this appraisal		
Healthy children 1–5 years	£4687	Not relevant comparator (due to license of zanamivir)
Healthy children 1–12 years	£5992	Dominated
'At risk' children	Not reported separately	Not reported separately
Healthy adults	£5452	Dominated
'At risk' adults	£652	Dominated
Older people	Not reported separately	Not reported separately

For a comparison of results from the different models, excluding hospitalisation and mortality benefits, see table 11 and page 207 of the assessment report.

Table 11 Comparison of results from the three different models, excluding hospitalisation and mortality benefits

Subgroup	Incremental cost-effectiveness ratio	
	Oseltamivir	Zanamivir
R58 (Assessment Group economic model for current appraisal)		
Healthy children	£7,852	Dominated
'At risk' children	Extendedly dominated	£3,327
Healthy adults	£13,985	Dominated
'At risk' adults	Extendedly dominated	£4,850
Older people	Extendedly dominated	£4,763
TA 58 (Assessment Group economic model for previous appraisal)		
Children (healthy and 'at risk' children not analysed separately)	£19,461	Extendedly dominated
Healthy adults	£19,015	Dominated
'At risk' adults	Extendedly dominated	£17,289
Older people in residential care	Extendedly dominated	£16,819
Roche model for this appraisal*		
Healthy children 1–5 years	£12,152	Not relevant comparator
Healthy children 1–12 years	£18,144	Dominated
'At risk' children	Not reported separately	Not reported separately
Healthy adults	£20,283	Dominated
'At risk' adults	£8,937	Dominated
Older people	Not reported separately	Not reported separately
* Not presented by Roche – results based on Assessment Group re-analysis		

The ICERs estimated by Roche consistently reported zanamivir to be dominated by oseltamivir in all populations considered. However, the ICERs estimated by the Assessment Group's TA 58 and R 58 models showed oseltamivir extendedly dominated by zanamivir for 'at risk' children and adults, and older people.

The Roche model assumed the lowest probability that an influenza-like illness was true influenza (31% in all populations). However, quality of life benefits related to symptoms, application of US hospitalisation rates and the estimated remaining life expectancy, resulted in the most favourable ICERs for oseltamivir compared with zanamivir for all populations in the Roche model. The Assessment Group also highlighted that the consistent finding that

oseltamivir dominated zanamivir could also be attributed to the assumption of equivalent clinical effectiveness for both oseltamivir and zanamivir and the error regarding the revised price of zanamivir in the Roche model.

The separate models were also compared excluding the potential benefits of hospitalisation and mortality. In this scenario, the ICER estimates for all models were higher; however, the estimates from the Roche model were substantially increased compared with those from the equivalent set of results using the TA 58 and R 58 models. The Assessment Group stated that this difference demonstrates that the assumptions applied to these elements are key drivers of the base-case results presented by Roche.

There was also a marked difference between the TA 58 estimates and the R 58 estimates when hospitalisation and mortality benefits were excluded. The Assessment Group stated that these differences were likely to be owing to the following key reasons: the probability that an influenza-like illness was true influenza was assumed to be higher in the R 58 model than in the TA 58 model; the duration of symptoms, including the data and methods employed, were different in the two models; and different approaches were used to value the QALY gains resulting from symptomatic benefits in the two models. The Assessment Group also highlighted that the drug acquisition costs in the R 58 model were lower than those used in the TA 58 model.

4 Issues for consideration

4.1 Effect of an increase in GP consultations

The higher the probability that an influenza-like illness is true influenza, the more successful the antiviral treatment because these drugs are only effective against true influenza. Would the drugs be given for more cases of influenza-like illness (and therefore a lower proportion of true influenza) if a positive recommendation is given? In the Assessment Group model, assuming a 15% increase in GP consultations and a decrease of 15% in the probability that an influenza like illness was true influenza, increased the ICER from £7,850 to £14,420 per QALY gained for healthy children (oseltamivir dominates) and

from £13,990 to £28,950 per QALY gained for healthy adults (oseltamivir dominates) when hospitalisation and mortality benefits were excluded. See tables 7.32 and 7.33 (page 194) of the assessment report.

4.2 Hospitalisation and mortality benefits

Have reasonable assumptions been made about inclusion/exclusion of hospitalisation and mortality benefits derived from oseltamivir and zanamivir for all subgroups? If these are excluded then ICERs are much higher.

4.3 Quality of life considerations

Is the decrement applied to quantify the impact of influenza on quality of life appropriate?

4.4 Threshold level for circulating influenza

It has been suggested that consultation rates with GPs in the Royal College of General Practitioners sentinel scheme are not a reliable indicator of when influenza viruses are circulating. What are the implications of this for the review of TA 58?

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 affect cost-effectiveness estimates?

4.5 Regional differences

Surveillance schemes operate nationally/regionally. What other considerations might need to be taken into account for localised outbreaks with high attack rates or for outbreaks within residential communities that do not occur in the influenza season?

4.6 Viral resistance

How does viral resistance affect considerations of the evidence?

4.7 Flu attack rate

The model started at the point that a patient presents to a healthcare professional with an influenza-like illness. What effect would uncertainty about the influenza attack rate have on generalisability of results from this model?

4.8 Route of administration of zanamivir

Should any consideration be given to the route of administration of zanamivir? In consultee comments, it was suggested that a small number of patients taking zanamivir experienced bronchospasm.

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

A The assessment report for this appraisal was prepared by CRD/CHE Technology Assessment Group, University of York.

- Burch J, Paulden M, Conti S, et al. Antiviral drugs for the treatment of influenza: A Systematic Review and Economic Evaluation, June, 2008.

B Additional references used:

- Chief Medical Officer Update, 2008: PL CMO (2007)3: Influenza Immunisation Programme 2007/2008. [http://www.dh.gov.uk/AboutUs/Ministersanddepartmentleaders/ChiefMedicalOfficer/CMOPublications/CMOLetters/fs/en]

Appendix B: Guidance on the use of oseltamivir and amantadine for the treatment of influenza. NICE technology appraisal guidance 58 (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 1.6).

1.1 Zanamivir and oseltamivir are not recommended for the treatment of influenza in children or adults unless they are considered to be 'at risk'.

1.2 At-risk adults and children 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 Amantadine is not recommended for the treatment of influenza.

1.4 Within their licensed indications, zanamivir and oseltamivir are recommended for the treatment of at-risk adults who present with influenza-like illness (ILI) and who can start therapy within 48 hours of the onset of symptoms.

1.5 Within its licensed indications, oseltamivir is recommended for the treatment of at-risk children who present with ILI and who can start therapy within 48 hours of the onset of symptoms.

1.6 Community-based virological surveillance schemes should be used to indicate when influenza virus is circulating in the community. Community-based virological surveillance schemes, such as those organised by the Royal College of General Practitioners and the Public Health Laboratory Service, should be used to indicate when influenza virus is circulating in the community. Such schemes should ensure that the onset of the circulation of influenza virus (A or B) within a defined area is identified as rapidly as possible.