

# Treatment and Prevention of Influenza: Swedish Recommendations

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The introduction of the 2 neuraminidase inhibitors (NAIs) zanamivir and oseltamivir has offered new options for the prevention and treatment of influenza. This article summarizes a Swedish consensus guidance document on the rational use of antiviral drugs in the management of influenza virus infections. Vaccination remains the cornerstone for influenza prophylaxis. Target groups for the annual vaccination programme are the 'at-risk' individuals, i.e. elderly patients ( $\geq 65$  y) and patients with chronic pulmonary disease or cardiovascular disease or other chronic diseases predisposing for a complicated course of influenza. Antiviral drugs are not a substitute for influenza vaccination, but could be used as adjuncts. Currently, 3 drugs have been approved for the treatment of influenza, including zanamivir and oseltamivir and the M2 inhibitor amantadin. Amantadin has come to very limited use, has recently been withdrawn from the Swedish market and is available only on a named patient basis. Compared with amantadin, the NAIs have clear advantages because of their broader anti-influenza activity against both type A and B, improved safety profiles and low potential for inducing drug resistance. The NAIs are therefore recommended as first options in the treatment of influenza. Oseltamivir can be taken orally, whereas zanamivir is for oral inhalation. Limited *in vitro* and *in vivo* data suggest that oseltamivir is less potent against influenza B, whereas zanamivir seems equally effective against influenza A and B. In influenza-positive healthy adults and children, treated within 48 h after symptom onset, the NAIs shorten the duration of illness by about 1 d. No significant effect on the duration of symptoms has been documented in treated at-risk patients with influenza. Owing to their limited therapeutic benefit, general use of the NAIs in the treatment of influenza is not recommended, but they can be advocated on an individualized basis for patients with severe influenza who can start therapy within 48 h of the onset of symptoms. Zanamivir is the preferred choice in a confirmed influenza B epidemic. For prevention of influenza, 2 drugs are approved, oseltamivir in adults above 12 y old and amantadin in people above 10 y old. The 70–90% protective efficacy of oseltamivir for household postexposure prophylaxis and for seasonal prophylaxis is comparable to that reported for amantadin. Oseltamivir is the preferred drug for prophylactic use. Chemoprophylaxis is targeted at high-risk groups and should be considered on a case-by-case basis depending on the circumstances and the population requiring protection. A broader preventive use of oseltamivir can be advocated in at-risk groups during seasons when there is a poor antigenic match between the epidemic strains and the vaccine strains. Oseltamivir prophylaxis is otherwise recommended for patients unable to be vaccinated and for families exposed to influenza which include a member of the at-risk groups. In high-risk hospital units and in institutions caring for the elderly, oseltamivir prophylaxis, in combination with vaccination, can be recommended as measures to control an influenza outbreak.

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## INTRODUCTION

In June 2002 the Swedish Medical Products Agency arranged an expert meeting resulting in national recommendations for the use of antiviral drugs in the prevention and treatment of influenza. A new antiviral agent, oseltamivir (Tamiflu®) was licensed in Europe in June 2002 and new information was available on zanamivir. Therefore, it was considered important to provide formulary committees and prescribing physicians with an update of previous recommendations.

## BACKGROUND

Influenza is a viral respiratory tract infection, which spreads rapidly and occurs annually as seasonal epidemics. In temperate climate influenza is seen mainly during the winter months, with outbreaks lasting for 6–16 weeks. Between 2 and 15% of the population, corresponding to 175,000 to 1,300,000 people in Sweden, contract the infection each year. The highest incidence is seen among children and adolescents, who are also the main sources for dissemination of the infection. In otherwise healthy people influenza causes considerable morbidity and absenteeism from school and work. Complications, most commonly bacterial pneumonia, occur mainly in patients with underlying cardiovascular or pulmonary disease and in people aged > 65 y. These individuals constitute the 'at-risk' groups, who have increased incidences of hospitalization and death during influenza outbreaks. In Sweden about 1000–4500 excess deaths were registered in 1993–2002 during periods with influenza activity compared with corresponding periods without influenza activity in other years (Fig. 1). For adequate prevention and treatment, it is essential that individuals belonging to the at-risk groups are informed about the possible consequences of an influenza virus infection.

Influenza viruses are RNA viruses belonging to the family Orthomyxoviridae. Three types of influenza are distinguished (A, B and C), influenza A being the most common source of epidemics. Influenza B can also cause epidemics, while influenza C typically results in mild upper respiratory tract infections. The influenza virus particle has 2 surface antigens, haemagglutinin, which mediates attachment of the virus to host cell receptors, and neuraminidase, which has an enzymatic receptor-destroying function essential for the release of progeny virus from infected cells and for the spread of virus in the respiratory secretions. Both haemagglutinin and neuraminidase change continuously over time by mutations and infrequently by genetic recombination in pigs between human and avian influenza viruses. A minor change in the antigens is called antigenic drift and a major change resulting in a new haemagglutinin is called antigenic shift. A shift may result in an influenza pandemic. Influenza viruses from pigs or fowl may also infect humans without recombination, as was the case in 1918 (Spanish flu) and in 1997 in Hong Kong (H5N1), respectively. These 2 outbreaks

have so far been the most serious ones in terms of mortality. However, the Hong Kong avian influenza virus seemed unable to spread from person to person and only 18 cases, 6 of whom died, were reported in 1997. Influenza B virus only undergoes minor antigenic changes and usually causes smaller outbreaks.

Influenza A and B infections cause similar symptoms (Table I). The outcome of influenza infection can range from an asymptomatic infection to a very severe illness. In general, symptoms are more severe in the elderly, infants and people at risk. The viruses replicate in the respiratory tract epithelial cells. Influenza is spread via saliva drops, aerosol or contact. The excretion of viral particles peaks during the period 24 h before and 48 h after onset of symptoms. Children who experience their first influenza infection excrete viruses for a longer period than adults. The amount of viruses excreted correlates to the increase in body temperature. The incubation time is short, usually 1–3 d.

## LABORATORY DIAGNOSIS OF INFLUENZA

For the diagnosis of influenza, the optimal sample is a nasopharyngeal aspirate obtained by a suction catheter, which is flushed with 2–3 ml of saline. However, nasopharyngeal, nasal and throat swabs as well as bronchial and tracheal secretions may be useful, and the choice of specimens partly depends on the laboratory methods used. Rapid diagnosis of influenza A and B infections is, in Sweden, usually obtained by the demonstration of influenza antigen in cells in a nasopharyngeal aspirate using the immunofluorescence technique. Commercial rapid diagnostic kits and sensitive and rapid nucleic acid amplification techniques are being introduced.

The reference virological technique involves the isolation of influenza virus in cell cultures or fertilized hen's eggs. Virus isolation is of particular value in the early phase of an epidemic, when it is essential to gain information about the circulating epidemic strain and its similarity to the viruses used for vaccine production. In the future, virus isolation may be replaced by techniques for amplification of viral nucleic acid, e.g. polymerase chain reaction (PCR). Serology has no value in the early diagnosis of influenza.

Sampling for laboratory confirmation of the influenza diagnosis is recommended for the index case to verify the presence of influenza in the community or in an institution. After the confirmation of an influenza outbreak, sampling of typical cases is not necessary. However, virological verification is of continued value in atypical disease, in hospitalized patients, often for logistic reasons, and in patients with severe illness. It may also be indicated in some at-risk patients. In general, the laboratory results can be obtained within 1 d, but the decision on antiviral treatment usually has to be made before the laboratory confirms the diagnosis. Commercial point-of-care assays often have lower sensitivity than the methods used in the laboratories, but may be valuable in certain situations (1).

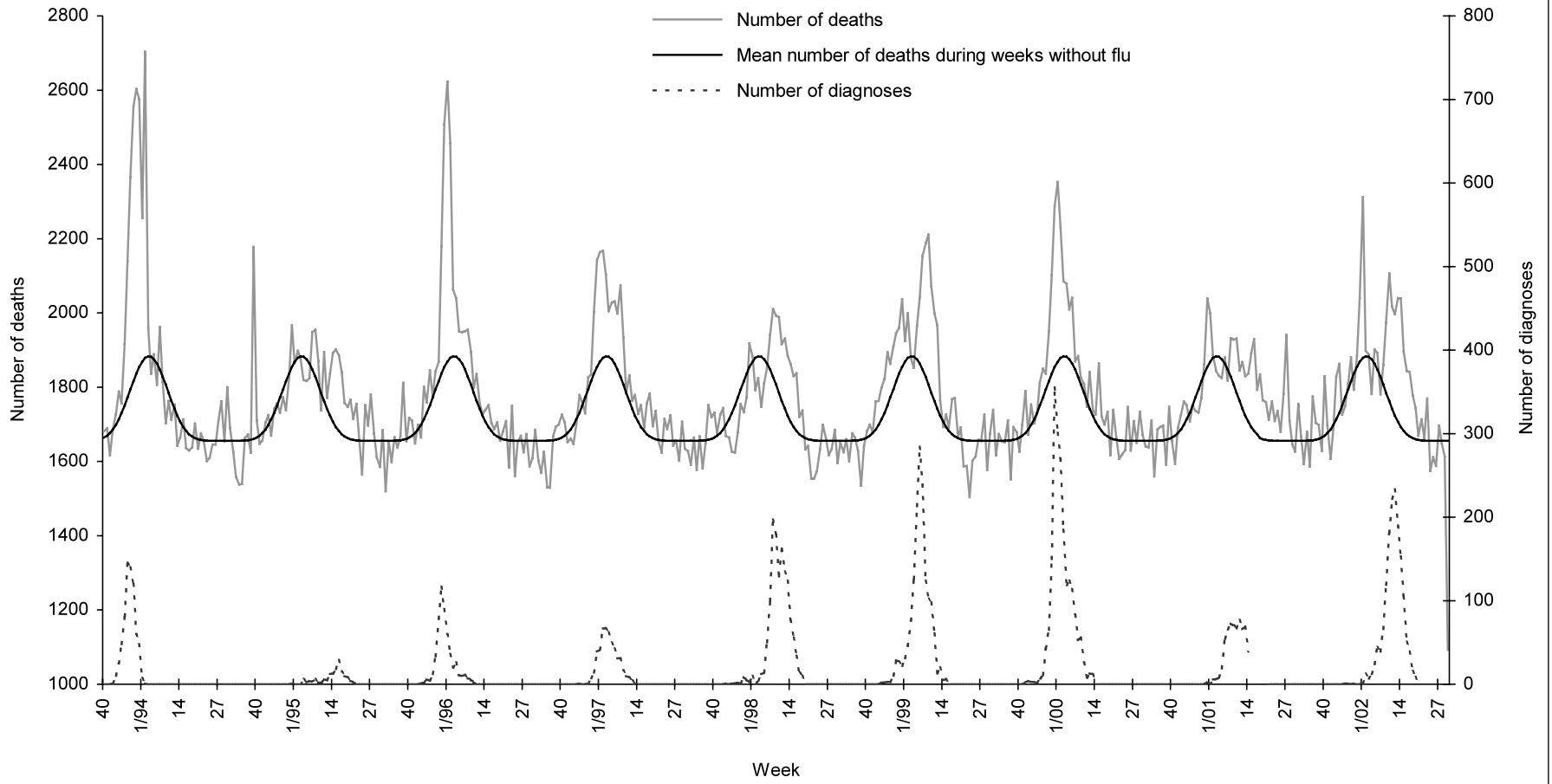


Fig. 1. Weekly death rates related to number of influenza diagnoses from Swedish laboratories, from week 40 1993 to week 30 2002.

Table I. *Clinical signs and symptoms of an infection with influenza A or B virus*

Patient category	Symptoms
Children <2 y	Drowsiness, feeding difficulties, skin colour changes, irritability
Children 2–12 y	Fever, febrile seizures, vomiting, diarrhoea, feeding difficulties, cough
Adolescents and adults	Rapid onset, chills, high fever/chills, headache, myalgia, mild respiratory symptoms followed by non-productive cough with retrosternal pain, nasal congestion and sore throat

## EPIDEMIOLOGICAL SURVEILLANCE

Since 1999, 2% of the Swedish general practitioners have participated in a weekly sentinel surveillance of influenza reporting patients with influenza-like illnesses to the Swedish Institute for Infectious Disease Control (SIIDC). The sentinel system is run by the County Medical Officers in the 21 counties of Sweden. In addition, 20 clinical microbiological laboratories report weekly the numbers of verified influenza diagnoses. These results are compiled every week on the SIIDC's website (<http://smittskyddsinstitutet.se>) and are also sent to the World Health Organization (WHO) and the European Influenza Surveillance Scheme (EISS).

## PROPHYLAXIS BY VACCINATION

Annual vaccination of patients at risk of serious complications is the most important and effective tool to reduce the medical consequences of an influenza epidemic. Antiviral drugs may serve as supplements, but do not replace a vaccination programme.

### *Vaccines*

The presently used vaccines each contain antigens from 2 strains of influenza A and 1 strain of influenza B. Virus strains to be included in the vaccines are decided annually by the WHO. Vaccines used are produced from virus cultured in fertilized hen's eggs. Subunit vaccines contain only the virus haemagglutinin and neuraminidase, whereas split vaccines contain purified proteins from the whole virus. The 2 types of vaccine are regarded as comparable. Vaccines with adjuvants to increase immunogenicity, targeted mainly at the elderly population, have started to appear on the market.

### *Protective efficacy of vaccines*

The efficacy of an influenza vaccine depends on the antigenic similarity between the strain causing the epidemic and the strains included in the vaccine. The efficacy also depends on host factors such as age and immunological competence (2). Against that background it is not surpris-

ing that studies have shown protection after influenza vaccination varying between 0 and 90%. For immunocompetent people below 65 y of age, and a good antigenic match between vaccine strains and epidemic strains, the protection rate varies between 70 and 90% (3). When years with a less good match were included in the Cochrane report, the efficacy against confirmed influenza was 68% [95% confidence interval (95% CI) 49–79%] (4). Protection against influenza illness is considerably lower in the elderly (5). However, in at-risk patients, a meta analysis has shown that vaccination results in a reduction in the frequency of pneumonia and the rate of hospitalization by 53% (95% CI 35–66%) and 50% (95% CI 28–65%) respectively, as well as a reduction in the mortality by 68% (95% CI 56–76%) (6).

### *Target groups for vaccination*

The recommendations for the annual use of influenza virus vaccines are developed by the Swedish National Board of Health and Welfare. They are targeted at preventing the serious consequences of influenza, i.e. severe disease, hospitalization and death. The target groups for whom vaccination is recommended include people at high risk for a complication of influenza:

- patients with chronic pulmonary disease or cardiovascular disease, in particular those with reduced pulmonary function and cardiac insufficiency;
- people aged 65 y and older: this indication is strengthened with increasing age and the presence of underlying diseases;
- patients with other chronic diseases, such as chronic metabolic disease, e.g. diabetes mellitus, or patients with immunosuppression (disease or medication related) should also be considered for vaccination, although the benefits of vaccination are less convincingly proven in these groups.

It has been estimated that 1.5 million Swedes are at risk for a complicated course if they contract influenza. The intensity of campaigns to encourage vaccination of at-risk groups as well as the prices for vaccination vary between the Swedish counties. In 13 counties studied, the vaccination coverage among people aged > 65 y was between 32 and 58% in 2001. Data on uptake rates for other risk groups are lacking. Thus, further efforts are needed to achieve better vaccination coverage in the at-risk groups.

Otherwise healthy individuals below 65 y of age have a low risk of serious complications of influenza. Since, as a mean, each individual contracts influenza every 10th to 20th year, there are no clear medical motives for vaccination. However, adverse reactions to the vaccine are mild, there are no contraindications other than egg allergy, and there is no evidence of negative effects caused by annual influenza vaccinations.

Children belonging to the at-risk groups should be vaccinated. This includes children with serious metabolic diseases other than diabetes mellitus, as well as those with severe malformations requiring repeated surgery and children with severe neuromuscular disorders. The vaccine can be given from 6 months of age, and as primary immunization 2 doses with at least a 2 week interval are recommended. Children with risk factors who are younger than 6 months can be protected by vaccination of the family and the nursing staff.

Influenza vaccination of hospital staff has been shown to decrease the risk of nosocomial dissemination of the infection (7). Influenza vaccination of hospital staff, especially those caring for patients belonging to the high-risk groups, should be considered.

#### ANTIVIRAL TREATMENT OF INFLUENZA

At present 2 antiviral drugs, zanamivir and oseltamivir, are approved in Sweden for the treatment of influenza. Both have the same mechanism of action, affecting the replication of influenza virus by inhibiting neuraminidase (8, 9). The M2 inhibitor amantadin has recently been withdrawn from the Swedish market, but is still available on a named patient basis.

It is important to point out that since viral replication is most intense before and shortly after the onset of symptoms, antiviral treatment must start as early as possible and within 48 h after the first symptoms of an influenza infection. Clinical trials have demonstrated that in previously healthy patients no benefits are achieved compared with placebo if treatment is started later. It has also been shown that efficacy is improved the earlier after symptom onset the treatment is started (10), and also in patients with more severe influenza (11).

The efficacy of antiviral treatment has been evaluated in 2 ways: as efficacy in patients with virologically verified influenza [per protocol (PP) analysis] and as efficacy in all patients enrolled into a trial based on clinical symptoms compatible with acute influenza virus infections [intention-to-treat (ITT) analysis]. The latter approach is probably the most relevant to the situation in common practice. Published studies on zanamivir and oseltamivir have evaluated the efficacy of antiviral treatment using the median time to alleviation of influenza symptoms as the primary endpoint. So far no studies have had sufficient statistical power to allow evaluation of the effects on mortality or frequencies of complications.

##### *Zanamivir*

Zanamivir inhibits neuraminidase and is active against both influenza A and B viruses. It is administered by oral inhalation using a specific device (Diskhaler®), which requires careful instructions to be given to the patient. The recommended dose is 2 inhalations twice daily for 5 d. Each dose contains 5 mg of zanamivir powder.

In 3 randomized placebo-controlled phase III trials, including otherwise healthy patients with influenza symptoms, PP analyses showed a 1–2.5 d (mean 1.5 d) reduction in time to alleviation of illness in zanamivir-treated patients compared with placebo (10, 12–14). In the ITT population a 1 d treatment benefit was observed (95% CI 0.5–1.5). The severity of influenza-related symptoms was also reduced. The majority of the patients in these trials had influenza A infections. A pooled PP analysis of patients with confirmed influenza B ( $n = 163$ ) showed that zanamivir shortened the duration of symptoms by 2.0 d (95% CI 0.50–3.50,  $p = 0.029$ ). Thus, zanamivir seemed equally effective against both influenza A and B (15). One paediatric trial has been performed and the efficacy results were similar to those in adults (16). However, data are still limited and the drug has not yet gained approval in Europe for use in children.

Documentation of the efficacy of zanamivir in patients belonging to high-risk groups is limited. In 1 trial 525 patients with mild or moderate asthma or chronic obstructive pulmonary disease (COPD) were randomized to treatment with zanamivir or placebo (17). A significant 1.5 d reduction in the duration of symptoms was seen in the PP analysis, while the ITT analysis showed a non-significant 1.0 d reduction. The incidence of secondary complications was not significantly reduced in the zanamivir-treated patients. In another trial recruiting only elderly patients (> 65 y), treatment with zanamivir did not result in any significant benefit compared with placebo. Owing to slow recruitment this trial was terminated prematurely after 358 patients had been included.

In the clinical trials zanamivir was generally well tolerated, with the number, nature and severity of adverse events similar to placebo. During the postmarketing period, rare serious adverse events such as acute bronchospasm, decline in respiratory function and throat tightness or constriction have been reported.

##### *Oseltamivir*

Oseltamivir is a neuraminidase inhibitor active against influenza A and B viruses. In vitro studies have shown that the drug has lower inhibitory activity against influenza B than against influenza A. The limited clinical experience also suggests that oseltamivir is less effective against influenza B (18–20). The drug is administered orally as capsules (75 mg) or as a suspension (12 mg/ml). To increase its oral bioavailability, oseltamivir is given as an ethyl ester, which is converted by hepatic esterases to the active metabolite (oseltamivir carboxylate) after absorption. The adult dosage of oseltamivir is 75 mg twice daily for treatment and 75 mg once daily for prophylaxis. The recommended dose for children is 2 mg/kg twice daily for treatment. The drug is eliminated by renal excretion and dose adjustment is recommended for patients with severe renal impairment. Oseltamivir is approved for the treatment of influenza A and B in adults and children aged 1 y or older and for the

prevention of influenza in adults and adolescents 13 y or older.

The placebo-controlled pivotal clinical trials of oseltamivir included several different populations such as previously healthy adults ( $n = 1355$ ) and children ( $n = 698$ ), patients aged  $> 65$  y ( $n = 741$ ), children with asthma ( $n = 334$ ) and adult patients with cardiac or pulmonary diseases ( $n = 404$ ) (20–23). In the trials in healthy people, the reduction in time to symptom alleviation varied between 1.0 and 1.5 d in the PP analyses and 0.7 and 0.9 d in the ITT analyses. In adults no significant effects were seen on the incidence of complications of influenza. In children the frequency of otitis media was significantly reduced from 27% in the placebo group to 16% in those treated with oseltamivir (23).

The majority of patients enrolled in the above-mentioned trials had influenza A infection. A pooled analysis of patients infected with influenza B (15% of those with confirmed infections) demonstrated that oseltamivir reduced the median duration of illness by 0.7 d (95% CI 0.1–1.6 d) (20).

In the at-risk groups, i.e. elderly patients  $> 65$  y, adult patients with chronic pulmonary and/or cardiac disease, and children with chronic asthma, the primary endpoint, median time to alleviation of symptoms, was not significantly different between oseltamivir-treated patients and placebo (20). The duration of fever, a secondary endpoint, was, however, significantly reduced by 1.0 d in those randomized to oseltamivir. The incidence of lower respiratory tract complications requiring antibiotic treatment, mainly bronchitis, was significantly reduced in the influenza-positive elderly patients treated with oseltamivir (12% compared with 19% in the placebo group). No such reduction in the incidence of complications was observed in patients with underlying chronic cardiac and/or pulmonary conditions. Importantly, no studies have been conducted with the primary objective of assessing the reduction in the risk of influenza-associated complications or deaths.

The most common drug-related adverse events were nausea and vomiting, reported in about 10% of treated subjects. The frequencies of adverse events varied with age, and vomiting were relatively more common in children than in adults. The safety profile in the elderly population was similar to that in younger adults. Most adverse events were mild to moderate and reversible within 1–2 d.

#### *Amantadin*

Amantadin was originally developed for the treatment of Parkinson's disease, but has also been approved for the treatment and prevention of influenza A. It inhibits the M2 protein ion-channel activity of the influenza A virus, but has no effect on influenza B. The recommended dosage is 100 mg/d in adults up to 65 y and 50 mg/d in elderly patients. Treatment must be started within 48 h after onset of symptoms. In clinical studies including healthy adults,

amantadin shortened the duration of illness by 1 d (24). Because of the rapid emergence of resistance to amantadin in influenza A virus strains and the high frequencies of central nervous system side-effects, the drug has never been widely used in Sweden.

#### *Resistance to antiviral agents*

As mentioned above, resistance to amantadin is commonly induced: some 30% of viruses shed from individuals treated with amantadin have been found to be resistant (25). Viral resistance to neuraminidase inhibitors has so far been demonstrated infrequently and its clinical importance is unknown (26). There are no clinical data on possible cross-resistance between zanamivir and oseltamivir. In clinical trials oseltamivir-resistant variants have been recovered from 0.3% (4/1177) of adult patients and from 4.5% (17/374) of children (23). No rebound of illness, atypical symptoms or prolonged virus shedding were observed in the patients with drug-resistant variants. Only a single case of resistance to zanamivir has been reported. A resistant influenza B virus was isolated from a severely immunocompromised child receiving prolonged zanamivir treatment (27). The risk of development of resistance to neuraminidase inhibitors is kept under close surveillance by an international network.

#### *Recommendations*

General use of antiviral agents in patients with influenza is not recommended, since influenza in previously healthy adolescents and adults  $< 65$  y of age is normally a self-limiting infection with low frequencies of complications. Symptomatic treatment with analgesics, rest and increase of fluid intake is advised. Studies in at-risk groups have demonstrated little or no benefit from antiviral therapy and therefore no general recommendation could be advocated in this population.

On an individualized basis, antiviral drugs can be recommended for those suffering a severe influenza illness with high fever and poor general condition, if the following prerequisites are fulfilled:

- an influenza epidemic has been virologically confirmed in the community
- clinical symptoms are typical for influenza
- other serious infections have been excluded
- treatment can be started at the latest 48 h after the onset of symptoms.

Antiviral drugs are not indicated for individuals with mild or non-febrile influenza-related illnesses.

The use of a neuraminidase inhibitor is advocated before the use of amantadin, owing to its broader antiviral activity, improved safety profile and lower potential for inducing resistance. If influenza B is confirmed or surveillance data indicate that influenza B is the predominant circulating strain, zanamivir is recommended as the first choice.

When zanamivir is prescribed, patients must receive careful instructions on how to use the inhalation device. In patients with mild to moderate asthma or COPD, zanamivir should be used restrictively and bronchodilating therapy must be administered before inhalation of zanamivir. Zanamivir should not be used in patients with persistent asthma or severe COPD.

Until further information is available, neuraminidase inhibitors should not be used in pregnant women. Animal studies do not indicate harmful effects on the pregnancy or the foetus, but relevant documentation on the use of neuraminidase inhibitors during pregnancy is lacking.

Children above the age of 1 y may be treated with oseltamivir. In Europe zanamivir is not approved for the treatment of influenza in children below the age of 12 y. For amantadin the age limit is 10 y.

No documentation on the efficacy and safety of the neuraminidase inhibitors in immunosuppressed patients is yet available. However, since it is probable that the viral load is higher and the duration of virus excretion is longer in these patients, the potential benefits of treatment may be larger than in other patient groups. In such patients there may also be reasons to start treatment even if more than 48 h has elapsed since the onset of symptoms.

#### PROPHYLAXIS WITH ANTIVIRAL DRUGS

Vaccination is the mainstay in influenza management and is the most important way to reduce the medical consequences of influenza infections. Antiviral drugs are not a substitute for vaccination, but could be used as an adjunct to the vaccine. Only oseltamivir is approved for prophylaxis against both influenza A and B infections in adults and adolescents aged 13 y or more using single daily doses of 75 mg. Amantadin is approved for prophylaxis in adults against influenza A, but the drug is only available on a named patient basis in Sweden. Zanamivir has been studied as a prophylactic agent, but has not yet been approved in this indication (28, 29).

##### *Oseltamivir*

The efficacy of oseltamivir in preventing influenza illness has been evaluated in a postexposure prophylaxis study in households ( $n = 962$ ) (30) and in 3 seasonal prophylaxis studies ( $n = 2134$ ) (31, 32). In these placebo-controlled trials only adults and adolescents aged above 12 y were recruited. The primary efficacy parameter for all of these studies was the incidence of symptomatic laboratory-confirmed influenza.

The protective efficacy of prophylaxis with oseltamivir 75 mg once daily for 7 d, started within 48 h after exposure to influenza in the family, was 92% (95% CI 72–98%) when the index case had a verified influenza infection and 89% (95% CI 72–96%) in the ITT analysis (30). The incidence of influenza in the PP population was 12% (24/200) in the

placebo group and 1% (2/205) in the oseltamivir group. Corresponding figures in the ITT population were 7% (34/462) and 1% (4/493), respectively. Thus, the number needed to treat (NNT) for prevention of 1 case of influenza was 9 and 16 in the PP and ITT analyses, respectively.

The 2 community-based trials enrolled unvaccinated, otherwise healthy adults and, since the study designs were identical, their results were pooled (31). In the third trial, elderly residents of nursing homes aged > 65 y were included, of whom 80% had received vaccine in the season of the study (32). In all studies the subjects received oseltamivir or placebo for 6 weeks during a community outbreak of influenza. In the pooled analysis of the 2 trials in healthy adults, the incidence of clinical influenza illness was reduced by 76% (95% CI 42–90%), from 4.8% (25/519) in the placebo group to 1.2% (6/520) in the oseltamivir group. The corresponding reduction in the study including the elderly was 92% (95% CI 37–99%), from 4.4% (12/272) in the placebo group to 0.4% (1/276) in the oseltamivir group. NNT was 28 in the adult study and 25 in the elderly study.

The protective efficacy against influenza B was calculated as 78% in the family study; the other studies included too few subjects with influenza B to allow any conclusions to be drawn.

Oseltamivir was generally well tolerated in these studies. Nausea was more common in those receiving active treatment compared with placebo. Headache was the most commonly reported adverse event, but occurred with similar frequencies in the placebo and oseltamivir groups.

##### *Amantadin*

Studies of amantadin have shown a 70–90% protective efficacy against influenza A infections (33, 34). For influenza A prophylaxis, amantadin can be used in individuals aged > 10 y. The recommended dose is 2.5 mg/kg twice daily up to 100 mg twice daily. Elderly people aged > 65 y should be given 50 mg twice daily.

##### *Recommendations*

Oseltamivir is recommended as the main prophylactic agent, since amantadin lacks activity against influenza B virus and is associated with a high incidence of adverse effects. Moreover, it has been demonstrated that amantadin prophylaxis becomes ineffective if the drug is concurrently used for the treatment of index patients, owing to the rapid emergence and transmission of drug-resistant influenza A variants (35). Such resistance has not been observed with the prophylactic use of neuraminidase inhibitors.

The target group for prophylaxis against influenza comprises individuals who are at high risk of serious complications. Vaccination remains the cornerstone for the control of influenza in the high-risk groups. The indication for antiviral drug prophylaxis is to be determined on a case-by-case basis by the circumstances and the population requir-

ing protection. In special situations, e.g. in the case of a poor match between the circulating and vaccine virus strains and in a pandemic situation, broader use of antiviral prophylaxis in the at-risk groups could be indicated. Antiviral drug prophylaxis could be considered in the following situations:

- For individuals belonging to the at-risk groups, vaccination is the primary prophylactic choice. However, in conjunction with late-season immunization before the vaccine has induced an immune response, antiviral drug prophylaxis for 10–14 d may be considered.
- People in at-risk groups who are unable to be vaccinated (e.g. due to egg allergy) and individuals with immunodeficiencies who are unlikely to respond to vaccination are, in the first place, advised to avoid gatherings of people and to increase hygienic measures such as hand washing. However, in exceptional circumstances long-course antiviral prophylaxis for up to 6 weeks, during the influenza epidemic season, could be considered.
- General prophylaxis for at-risk groups may be considered when there is a poor match between the vaccine strains and the epidemic strains or if supplies of vaccine are insufficient.
- In the case of influenza in a household including an at-risk individual, antiviral prophylaxis is recommended for 7 d for all family members, starting as soon as possible and not later than 48 h after onset of symptoms in the index case.
- When influenza occurs in institutions and in long-term facilities for the elderly, samples from the index case for confirmation of diagnosis and for typing of the viral strain should be collected. Amantadin prophylaxis has been shown to provide 60–90% protection in nosocomial influenza A outbreaks (33). Such data are still lacking for oseltamivir, but in the above-mentioned studies of postexposure prophylaxis the preventive efficacy was at least as good. In addition, uncontrolled studies have indicated that neuraminidase inhibitors can terminate institutional influenza outbreaks (36). Prophylaxis with oseltamivir can therefore be considered in these situations. In the case of a confirmed influenza outbreak in institutions that house people at high risk, oseltamivir or amantadin can be used when influenza A is the causative agent and oseltamivir when the aetiology is influenza B. Antiviral drug prophylaxis should be combined with vaccination and continue for up to 14 d, or until 7 d after the onset of the last confirmed case of influenza. Other measures to limit the transmission of influenza, such as isolating ill patients, restricting the number of visitors and requiring sick staff members to stay at home, are also recommended.
- Hospitalized patients who are exposed to influenza by a fellow patient or hospital staff should be offered chemoprophylaxis. When this situation occurs in a hospital ward for high-risk patients, e.g. a transplantation unit, antiviral drug prophylaxis should be given to all patients in the unit.
- It is desirable to be able to offer antiviral drug prophylaxis to children belonging to the at-risk groups. However, data are lacking and until studies have been performed and published, prophylactic use of oseltamivir must be at the discretion of the responsible physician.
- Antiviral drug prophylaxis may be valuable in a pandemic situation, but this has not been tested.

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