

REVIEW ARTICLE

DRUG THERAPY

Neuraminidase Inhibitors for Influenza

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THE IMPACT OF INFLUENZA INFECTION IS FELT GLOBALLY EACH YEAR when the disease develops in approximately 20 percent of the world's population. In the United States, influenza infections occur in epidemics each winter, generally between late December and early March. Recent events, including human cases of avian influenza, have heightened awareness of the threat of a pandemic and have spurred efforts to develop plans for its control.

Although vaccination is the primary strategy for the prevention of influenza, there are a number of likely scenarios for which vaccination is inadequate and effective antiviral agents would be of the utmost importance. During any influenza season, antigenic drift in the virus may occur after formulation of the year's vaccine has taken place, rendering the vaccine less protective, and outbreaks can more easily occur among high-risk populations. In the course of a pandemic, vaccine supplies would be inadequate. Vaccine production by current methods cannot be carried out with the speed required to halt the progress of a new strain of influenza virus; therefore, it is likely that vaccine would not be available for the first wave of spread of virus.¹ Antiviral agents thus form an important part of a rational approach to epidemic influenza and are critical to planning for a pandemic.

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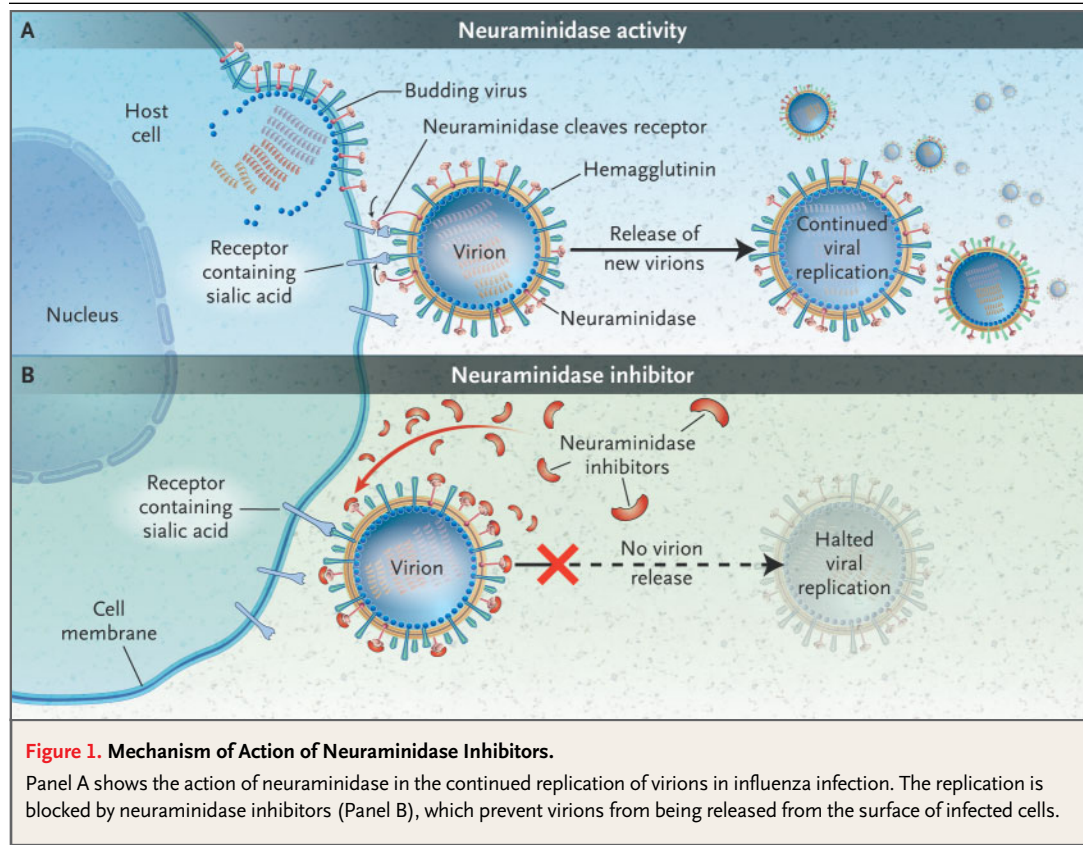
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ADAMANTANES AND NEURAMINIDASE INHIBITORS

Four drugs are currently available for the treatment or prophylaxis of influenza infections: the adamantanes (amantadine and rimantadine) and the newer class of neuraminidase inhibitors (zanamivir [Relenza] and oseltamivir [Tamiflu]). The adamantanes interfere with viral uncoating inside the cell. They are effective only against influenza A and are associated with several toxic effects and with rapid emergence of drug-resistant variants. Adamantane-resistant isolates of influenza A are genetically stable, can be transmitted to susceptible contacts, are as pathogenic as wild-type virus isolates, and can be shed for prolonged periods in immunocompromised patients taking the drug. This potential for the development of resistance especially limits the use of the adamantanes for the treatment of influenza, although the drugs still have a place in planning for prophylaxis during an epidemic.

The neuraminidase inhibitors zanamivir and oseltamivir interfere with the release of progeny influenza virus from infected host cells, a process that prevents infection of new host cells and thereby halts the spread of infection in the respiratory tract (Fig. 1). Since replication of influenza virus in the respiratory tract reaches its peak between 24 and 72 hours after the onset of the illness, drugs such as the neuraminidase inhibitors that act at the stage of viral replication must be administered as early as possible. In contrast to the adamantanes, the neuraminidase inhibitors are associated with very little toxicity and are far less likely to promote the development of drug-resistant influenza. As a class, the neuraminidase inhibitors are effective against all neuraminidase subtypes



and, therefore, against all strains of influenza, a key point in epidemic and pandemic preparedness and an important advantage over the adamantanes, which are effective only against sensitive strains of influenza A. These new drugs, if used properly, have great potential for diminishing the effects of influenza infection.

DEVELOPMENT OF NEURAMINIDASE INHIBITOR MOLECULES

All influenza viruses bear two surface glycoproteins, a hemagglutinin and a neuraminidase, which are the antigens that define the particular strain of influenza. The variation of these molecules over time permits the virus to evade human immune responses and therefore necessitates the formulation of a new vaccine each year. The hemagglutinin is a sialic acid receptor-binding molecule and mediates entry of the virus into the target cell. The neuraminidase—the target molecule of the neuraminidase inhibitor compounds—cleaves the cellular-receptor sialic acid residues to which the newly formed particles are attached (Fig. 1). This cleavage releases the viruses,

which can now invade new cells. Without neuraminidase, infection would be limited to one round of replication, rarely enough to cause disease. Neuraminidase may also facilitate viral invasion of the upper airways, possibly by cleaving the sialic acid moieties on the mucin that bathes the airway epithelial cells.²

The ability of transition-state analogues of sialic acid to inhibit the influenza neuraminidase was first recognized in the 1970s,³⁻⁵ but the design of highly effective inhibitors became feasible when analysis of the three-dimensional structure of influenza neuraminidase⁶ disclosed the location and structure of the catalytic site. Potent inhibitors such as zanamivir closely mimic the natural substrate, fitting into the active site pocket and engaging the protein in the most energetically favorable interaction.⁷⁻⁹ Zanamivir is administered by oral inhalation, which delivers the drug directly to the respiratory tract. Oseltamivir was developed through modifications to the sialic acid analogue framework (including the addition of a lipophilic side chain) that allow the drug to be used orally.¹⁰

PHARMACOKINETICS

Zanamivir is not bioavailable orally and is marketed as a dry powder for inhalation. It is delivered directly to the respiratory tract through an inhaler (Diskhaler, Glaxo Wellcome) that holds small pouches of the drug. Zanamivir is highly concentrated in the respiratory tract; 10 to 20 percent of the active compound reaches the lungs, and the rest is deposited in the oropharynx. Five to 15 percent of the total dose is absorbed and excreted in the urine,¹¹ resulting in a bioavailability of 2 percent, a feature that is potentially advantageous in situations in which a systemic drug is undesirable. The concentration of the drug in the respiratory tract has been estimated to be more than 1000 times as high as the 50 percent inhibitory concentration (IC₅₀) for neuraminidase; in addition, the inhibitory effect starts within 10 seconds — two favorable features in terms of reducing the likelihood of emergence of drug-resistant variant viruses.

Oseltamivir is available as a capsule or powder for liquid suspension with good oral bioavailability. It is readily absorbed from the gastrointestinal tract, is converted by hepatic esterases to the active form of the compound (oseltamivir carboxylate), and is widely distributed in the body. The half-life is 6 to 10 hours. The drug is excreted primarily through the kidneys; thus, dosing must be modified in patients with renal insufficiency (Table 1). Oseltamivir achieves high plasma levels and thus can act outside the respiratory tract.

CLINICAL TRIALS OF ZANAMIVIR AND OSELTAMIVIR

TREATMENT OF HEALTHY ADULTS

An initial 1997 study¹² indicated that confirmed cases of influenza could be treated with zanamivir, demonstrating an approximately one-day reduction in the time to alleviation of symptoms. Subsequent studies¹²⁻²³ in widely diverse geographic locations showed that when otherwise healthy adults with influenza received zanamivir or oseltamivir within 36 to 48 hours after the onset of illness, a decrease in symptomatic illness of one to two days occurred (Table 2). One large study in the United States evaluated the efficacy of oseltamivir treatment¹⁸ in 629 healthy, nonimmunized adults 18 to 65 years of age who presented with a febrile respiratory illness of no more than 36 hours' duration, along with one respiratory and one constitutional symptom. Influenza

Table 1. Dosing Schedule of Neuraminidase Inhibitors for the Treatment and Prevention of Influenza, According to Patient's Age and Coexisting Illnesses.*

Antiviral Drug	Recommended Dose According to Age			Coexisting Illness		
	1-6 yr	7-12 yr	13-64 yr	≥65 yr	Renal Disease	Hepatic Disease
Treatment						
Zanamivir	NA	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	—
Oseltamivir	Weight <15 kg: 30 mg twice daily for 5 days; 15-23 kg: 45 mg twice daily for 5 days; >23-40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	Weight <15 kg: 30 mg twice daily for 5 days; 15-23 kg: 45 mg twice daily for 5 days; >23-40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	75 mg twice daily for 5 days	75 mg twice daily for 5 days	For adults, reduce dose if creatinine clearance is ≤30 ml/min; if creatinine clearance is 10-30 ml/min, 75 mg once daily†	Not evaluated
Prevention						
Oseltamivir	NA	NA	75 mg once daily for >7 days (up to 6 wk)	75 mg once daily for >7 days (up to 6 wk)	If creatinine clearance is 10-30 ml/min, 75 mg every other day†	Not evaluated

* The doses listed are those currently approved in the United States. NA denotes not applicable.

† No regimen is available for patients with end-stage renal disease.

Table 2. Selected Treatment Trials of Neuraminidase Inhibitors.

Study	No. of Patients	Characteristics of Patients*	Time from Onset of Symptoms to Start of Therapy	Reduction in Length of Illness†
Zanamivir				
Hayden et al., ¹² Cooper et al., ¹³ Monto et al., ¹⁴ Makela et al., ¹⁵ MIST Study Group, ¹⁶ Matsumoto et al. ¹⁷	2600 (pooled number)	Healthy adults	36–48 hr	1.0–2.0 days
Cooper et al. ¹³	Pooled number (meta-analysis)	Elderly and high-risk patients	36–48 hr	2.0 days
Hedrick et al. ²¹	471	Children 5–12 yr	36–48 hr	1.0 day
Oseltamivir				
Cooper et al. ¹³	Pooled number	Healthy adults with laboratory-confirmed influenza	<48 hr	1.4 days
Treanor et al. ¹⁸	629	Healthy adults with laboratory-confirmed influenza	<36 hr	1.3 days
Nicholson et al. ¹⁹	726	Healthy adults with laboratory-confirmed influenza	24–36 hr	1.0–2.0 days
Aoki et al. ²³	1426 (total)	Healthy adults (12–70 yr) with laboratory-confirmed influenza	0–6 hr	4.1 days‡
Aoki et al. ²³	1426 (total)	Healthy adults (12–70 yr) with laboratory-confirmed influenza	6–12 hr	3.1 days‡
Cooper et al., ¹³ Kaiser et al. ²⁴	Pooled number from compiled studies	Elderly and high-risk patients with laboratory-confirmed influenza	36–48 hr	0.5 day§
Whitley et al. ²²	695	Children (1–12 yr) with influenza-like illness (65% with laboratory-confirmed influenza)	<48 hr	1.5 days¶

* In cases in which results were collected for both influenza-like illness and laboratory-confirmed influenza, data are given for laboratory-confirmed influenza.

† Comparisons were between a neuraminidase inhibitor and no therapy, unless otherwise noted.

‡ Comparisons were between a neuraminidase inhibitor at the designated time and at 48 hours after the onset of symptoms, rather than no treatment.

§ Patients also had a 34 percent reduction in the use of antibiotic therapy for infections of the lower respiratory tract.

¶ Patients also had a 44 percent reduction in the incidence of otitis media.

enza was confirmed in 374 of the subjects, and oseltamivir treatment reduced the median duration of illness by more than 30 percent (from 4.3 days to 3 days) and the severity of illness by about 40 percent. There was a reduction in fever and a resolution of symptoms as soon as 24 hours after the initiation of treatment. Furthermore, treated patients had a lower frequency of secondary complications than did untreated patients.

Early initiation of treatment appears to be the most important determinant of treatment efficacy, as demonstrated in the 2003 Immediate Possibility to Access Treatment (IMPACT) study, which directly investigated the relationship between the time

to the initiation of oseltamivir therapy and the duration of illness and other efficacy measures in 1426 patients ranging in age from 12 to 70 years.²³ Treatment that started within the first 12 hours after the onset of fever shortened the illness by more than three days, as compared with treatment that was started at 48 hours. The initiation of treatment at intermediate times shortened the illness proportionately. The duration of fever, severity of symptoms, and time to return to normal activity also correlated with the time of antiviral intervention, leading to the clear conclusion that treatment initiated at 36 to 48 hours after the onset of symptoms does not fairly reflect the excellent outcomes obtainable

with earlier treatment. A large multicenter trial in Japan extended the IMPACT results to treatment of influenza B.²⁵ Early administration of the drug (within 12 hours after the onset of symptoms) appreciably increased the effectiveness of oseltamivir therapy for both influenza A and B, suggesting that prompt identification of illness and initiation of treatment as early as possible should be the goal for the proper use of neuraminidase inhibitors.

THErapy IN THE ELDERLY

Do neuraminidase inhibitors reduce morbidity or mortality in the groups considered to be at high risk, including the elderly? A meta-analysis of trials that were conducted before 2002¹³ involving influenza-positive high-risk patients older than 65 years of age or with chronic medical conditions reported that zanamivir reduced the time to the alleviation of symptoms by 2.0 days and that oseltamivir did so by about 0.5 day. A study in Canadian long-term care facilities²⁶ demonstrated that elderly residents—even those who had been immunized against influenza—who were given oseltamivir within 48 hours after the onset of symptoms were considerably less likely to be prescribed antibiotics, to be hospitalized, or to die.

Experiments in animals suggest that the influenza neuraminidase plays a role in the synergism between influenza virus infection and *Streptococcus pneumoniae*, thus providing a mechanism whereby neuraminidase inhibitors might reduce the incidence of secondary bacterial pneumonia.²⁷ A recent analysis of 10 trials of treatment with oseltamivir (Table 2) revealed that treatment of documented influenza lowered the incidence of related complications involving the lower respiratory tract that required antibiotic therapy and lowered the hospitalization rate from influenza.²⁴

THErapy IN CHILDREN

In the first trial of neuraminidase inhibitors in children, zanamivir appeared to be effective in shortening the duration and severity of clinically diagnosed influenza symptoms in children between the ages of 5 and 12 years (Table 2).²¹ A large trial of oseltamivir treatment in children from 1 to 12 years of age with clinically diagnosed influenza of a duration of no more than 48 hours (65 percent with proven influenza²²) indicated that treatment reduced the length of illness by 36 hours. The incidence of otitis media, a frequent complication, was reduced by 44 percent. Oseltamivir is currently ap-

proved for therapy in children as young as one year of age (Table 1).

PROPHYLACTIC EFFICACY OF ZANAMIVIR AND OSELTAMIVIR

PROPHYLAXIS IN HEALTHY ADULTS

Several large, controlled studies of prophylaxis²⁸⁻³³ have demonstrated that zanamivir and oseltamivir are effective in preventing clinical influenza in healthy adults when the drugs are used either as prophylaxis after exposure for close contacts, such as household members,^{28-30,33} or as seasonal prophylaxis in the community.^{31,32} Overall, both oseltamivir and zanamivir were 70 to 90 percent effective in preventing disease when used for prophylaxis either before or after exposure for both influenza A and influenza B^{13,28-32,34,35} (Table 3). However, only oseltamivir is currently approved for use as prophylaxis in the United States.

PROPHYLAXIS IN HIGH-RISK ELDERLY OR CHRONICALLY ILL POPULATIONS

There are fewer data on the use of these drugs to prevent disease in the most vulnerable patients, including the elderly.^{36,37} One important double-blind, placebo-controlled, randomized study³⁶ demonstrated that the use of oseltamivir for seasonal prophylaxis in residential homes for elderly persons led to a 92 percent reduction in the incidence of laboratory-confirmed influenza, even though the great majority of the elderly residents had received the appropriate vaccine for the season. Thus, antiviral prophylaxis provided important additional protection to that conferred by vaccination.³⁶ Efforts to improve early recognition of influenza symptoms in the elderly and rapid response by staff members will enhance the effectiveness of oseltamivir prophylaxis for control of outbreaks in institutions.^{26,37}

PROPHYLAXIS IN CHILDREN AFTER EXPOSURE

Although currently approved only for prophylaxis in children over the age of 13 years, oseltamivir appears to be very effective for postexposure prophylaxis in children as young as 1 year of age. In a prospective, randomized study that assessed the efficacy of postexposure prophylaxis together with treatment of index cases with oseltamivir²⁹ (Table 3), most illness in contacts began very early (1 to 2 days) after index cases became ill. If patients with known influenza or positive viral cultures at baseline were excluded, the protective efficacy was 80 percent for

Table 3. Selected Trials of Prophylaxis with the Use of Neuraminidase Inhibitors.

Study and Drug	No. of Patients	Characteristics of Patients	Setting of Prophylaxis	Reduction in Incidence of Influenza*
Zanamivir				
Monto et al. ³¹	1107	Healthy adults	Seasonal prophylaxis in the community	69% (laboratory-confirmed influenza)
Cooper et al. ¹³	Pooled number	Healthy adults	Prophylaxis after exposure in household	81%
Oseltamivir				
Hayden et al. ³²	1559	Healthy adults	Seasonal prophylaxis in the community	87% (laboratory-confirmed influenza); 74% (influenza-like illness)
Welliver et al. ³⁰	955	Teenagers and adults (>12 yr)	Prophylaxis after exposure in household	89% (laboratory-confirmed influenza); 84% (disease in the household)
Hayden et al. ²⁹	812	All ages (including children >1 yr)	Prophylaxis after exposure in household	68% (laboratory-confirmed influenza) (85%, excluding patients who tested positive at start of prophylaxis); children, 55% (80%, excluding patients who tested positive at start of prophylaxis)†
Peters et al. ³⁶	548	Elderly persons (>80% vaccinated against influenza)	Seasonal prophylaxis in institutional setting	92% (laboratory-confirmed influenza)

* Influenza was defined as both laboratory-confirmed influenza and influenza-like illness, unless otherwise indicated.

† Results were compared with the treatment of index cases.

children one year old or older when compared with treating only index cases. These data highlight the importance of recognizing an exposure before viral replication has begun.

SAFETY AND DOSAGE OF NEURAMINIDASE INHIBITORS

In general, zanamivir is well tolerated; studies to date suggest that adverse effects, primarily minor transient upper respiratory and gastrointestinal symptoms, develop in equal numbers of patients in drug and placebo groups (Table 4). However, post-licensure reports indicated that zanamivir may cause cough, bronchospasm, and a reversible decrease in pulmonary function in some patients.⁴² On the other hand, a well-controlled trial demonstrated that the recommended dosages of zanamivir did not adversely affect pulmonary function in patients with respiratory disorders.²⁰ If patients with pulmonary dysfunction do receive zanamivir, it is recommended that they have a fast-acting bronchodilator available and discontinue zanamivir if respiratory difficulty develops. Oseltamivir has few adverse effects when administered for either treatment or prophylaxis.²⁹ The most frequent side ef-

fects are transient nausea, vomiting, and abdominal pain, which occur in approximately 5 to 10 percent of patients. Most adverse events occur only once, close to the initiation of therapy, and resolve spontaneously within one to two days.¹⁹ The consumption of food does not interfere with the absorption of oseltamivir and may reduce nausea and vomiting. The safety profile among elderly persons is similar to that in persons younger than 65. Dosage recommendations for both medications are presented in Table 1. Although zanamivir currently is available only on a limited basis, future public health planning may change the availability of the drug.

RESISTANCE TO THE NEURAMINIDASE INHIBITORS

A key advantage of the neuraminidase inhibitors, and a major difference from the adamantanes, is that development of resistance is very rare. The global neuraminidase inhibitor susceptibility network (NISN), which coordinates the analysis of clinical isolates collected through the World Health Organization's surveillance network,⁴³ found no influenza isolates with spontaneous resistance to neuraminidase inhibitors.⁴⁴ Until recently, there

Table 4. Percentage of Patients with Serious or Minor Adverse Effects Associated with the Administration of Neuraminidase Inhibitors.

Drug and Use	Adverse Effects
Zanamivir treatment*	<p>Serious or life-threatening: Allergic or allergic-like reaction, arrhythmia, bronchospasm, dyspnea, facial edema, rash, seizure, syncope, urticaria (<1.5%)</p> <p>Minor: Central nervous system: headache (2%), dizziness (2%) Gastrointestinal system: nausea (3%), diarrhea (adults, 3%; children, 2%), vomiting (adults, 1%; children, 2%) Respiratory system: sinusitis (3%), bronchitis (2%), cough (2%), other nasal signs and symptoms (2%), infection (ear, nose, and throat: adults, 2%; children, 5%)</p>
Oseltamivir treatment†	<p>Serious or life-threatening: Aggravation of diabetes, arrhythmia, confusion, hepatitis, pseudomembranous colitis, pyrexia, rash, seizure, swelling of face or tongue, toxic epidermal necrolysis, unstable angina (<1%)</p> <p>Minor: Central nervous system: insomnia (adults, 1%), vertigo (1%) Gastrointestinal system: nausea (10%), vomiting (9%)</p>
Oseltamivir prophylaxis‡	<p>Similar to those reported during treatment, but generally with lower incidence</p> <p>More common with prophylactic use: headache (20%), fatigue (8%), cough (6%), diarrhea (3%)</p>

* Data are from Hayden et al.,¹² Monto et al.,¹⁴ Makela et al.,¹⁵ the MIST Study Group,¹⁶ Matsumoto et al.,¹⁷ Hedrick et al.,²¹ Harper et al.,³⁸ and Glaxo Wellcome.³⁹ The frequencies of most adverse effects were similar among patients who received a study drug and among controls who received a lactose placebo. Adverse effects are listed if they were reported by more than 1.5 percent of patients, except for serious, life-threatening symptoms, which were reported by less than 1.5 percent of patients.

† Data are from Treanor et al.,¹⁸ Nicholson et al.,¹⁹ Whitley et al.,²² Hayden et al.,⁴⁰ and Roche Laboratories.⁴¹ Adverse effects are listed if they were reported by more than 1 percent of patients, except for serious, life-threatening symptoms, which were reported by less than 1 percent of patients.

‡ Data are from Hayden et al.⁴⁰

was little emergence of resistance during treatment and no resistant viruses isolated from immunocompetent persons who received zanamivir. For oseltamivir, the published frequency of viruses that were isolated after treatment and were resistant to the drug is somewhat higher. About 0.4 percent of treated adults harbored viruses with resistant neuraminidases.

However, more resistant isolates emerged during treatment of children. One study identified resistant isolates in 4 percent of treated children,²² and in a recent study of children treated with oseltamivir in Japan, 9 of 50 treated children harbored viruses with mutations in the neuraminidase gene that encoded drug-resistant neuraminidase proteins.⁴⁵ If this frequent emergence of resistant mutants is found to be a general occurrence in children, it is a serious concern, especially since children are an important source of the spread of influenza in the community.⁴⁶ The most clinically relevant

question is whether the oseltamivir-resistant viruses are transmissible and pathogenic. To date, no documented transmission of an oseltamivir-resistant virus has occurred between people. Generally, neuraminidase mutations lead to a functionally defective enzyme, which reduces the fitness of the virus and causes decreased pathogenicity, at least in animal models.^{46,47} However, in the ferret model, resistant variants with the same mutation that is found in some children grew well in both the index ferret and in contact animals and were readily transmitted,⁴⁷ raising concern that some oseltamivir-resistant mutant viruses might be transmissible during an epidemic.

STRATEGIES FOR TREATMENT

Either zanamivir or oseltamivir may be used for treatment of infection with influenza A or influenza B. Current policy issues will inform recommen-

dations for the future use of neuraminidase inhibitors (and the availability of zanamivir, currently in short supply). When surveillance data indicate the presence of an epidemic in the community, either rapid laboratory confirmation of influenza infection or the typical constellation of influenza symptoms can signal the need for the initiation of treatment in adults; of clinical symptoms, the combination of fever and cough had the highest predictive value.⁴⁸ Rapid diagnostic tests, only recently readily available for use in physicians' offices, use antigen, enzyme, or nucleic acid detection methods.⁴⁹ Some assays detect only influenza A, whereas others detect both influenza A and influenza B. Results are often available in less than an hour, though the sensitivities vary considerably depending on the specific test.⁵⁰ Improved diagnostic tests are needed, particularly for elderly people with atypical presentations who may shed little virus in their secretions. Meanwhile, the results from rapid assays should be interpreted in light of the sensitivity of the particular test along with influenza surveillance data from the community.

The neuraminidase inhibitors should be used only when symptoms have occurred within the previous 48 hours and, as discussed above, should ideally be initiated within 12 hours after the start of illness. An exception may be made for critically ill, hospitalized patients with influenza, in whom therapy can be considered even when more time has elapsed, though no controlled data are available to support this practice. Treatment that is based on clinical grounds alone, even in the absence of diagnostic tests, is particularly valuable for high-risk patients. Limiting the use of antiviral treatment to severely ill patients is illogical, since at the earliest stages, when therapy should be started, it cannot be predicted whether influenza in a patient will progress to severe illness. In the case of children, fever, cough, and other respiratory symptoms have little predictive value, since the important pediatric respiratory viral pathogens can cocirculate with influenza; thus, the focus needs to be on rapid access to laboratory diagnosis and initiation of therapy.

STRATEGIES FOR PROPHYLAXIS

Vaccination remains the primary strategy for the prevention of influenza, and the broadened recommendations should lead to protection of a larger portion of the population. However, although the

neuraminidase inhibitors clearly cannot substitute for vaccination, they can be valuable adjuncts. Currently, only oseltamivir is approved for use as prophylaxis in the United States. During community epidemics, household postexposure prophylaxis with oseltamivir is suggested for unvaccinated persons, starting as early as possible but no more than two days after exposure. Wider prophylaxis in the community for up to six weeks during an epidemic (seasonal prophylaxis) is a consideration if the epidemic strain is different from that of the vaccine that was administered. The adamantanes may also be considered for this purpose if the circulating strain is influenza A. Nursing homes and other institutions should initiate institution-wide prophylaxis as soon as possible after influenza is found in the community and should provide prophylaxis to vaccinated as well as unvaccinated residents.^{26,36,37} Obviously, the feasibility of most of the suggestions made here will depend on the availability of stockpiles of the neuraminidase inhibitors and on future public health decisions.

Exposure to influenza or illness in an infant younger than one year of age presents a quandary. The safety of oseltamivir in infants has not been established, and serious concerns have been raised by the observation that juvenile rats accumulate extremely high levels of oseltamivir in the central nervous system.⁵¹ The immature blood-brain barrier of the human infant is permeable and might similarly allow access of the drug to the central nervous system in an unpredictable fashion. Thus, infants less than one year of age cannot be offered oseltamivir for either chemoprophylaxis or therapy unless further studies are done in the appropriate age group. Similar concerns about potential toxicity to the fetus or infant arise in the case of pregnant women or breast-feeding mothers who are exposed to influenza, though it should be feasible to target public health efforts toward vaccination of pregnant women in order to avoid this scenario.

AVIAN INFLUENZA AND PANDEMIC PLANNING

Pandemics result from the emergence of an influenza strain to which large numbers of the population have not been exposed. A new virus that can be transmitted readily from person to person and that can cause human disease can potentially lead to an

influenza pandemic. Highly pathogenic avian influenza A (H5N1) has now fulfilled two of these three criteria. Although a probable transmission of H5N1 avian influenza from an infected child to two close contacts has been reported,⁵² sustained human-to-human transmission has not been documented. However, the H5N1 viruses that have now become endemic in Asian domestic fowl are being spread by wild birds and appear unlikely to be eradicable.⁵³ H5N1 viruses are expanding their mammalian host range,⁵⁴ and sporadic human infections with high fatality rates continue to occur in Vietnam, Thailand, and Cambodia.⁵⁵ These events increase the alarming likelihood that there will be ample opportunity for further adaptation of H5N1 to human hosts.^{54,56}

Antiviral drugs form an important part of a strategy for dealing with an influenza pandemic with a new influenza virus of any origin, including avian influenza. Vaccines that are specific for newly arising strains require several months of preparation, and although the development of a vaccine against H5N1 influenza is under way, none is yet available. In the 1968 and 1977 pandemics, adamantanes were found to have a protective efficacy of around 70 percent, only slightly lower than the efficacy reported during the interpandemic period.⁵⁷ The protective efficacy of the neuraminidase inhibitors during a pandemic would be expected to be at least as high as that of the adamantanes. The markedly lower rate of emergent resistance and lack of spontaneous resistance to the neuraminidase inhibitors make them the drugs of choice. The 2004 avian H5N1 viruses are resistant to the adamantanes⁵⁸ but are sensitive to the neuraminidase inhibitors zanamivir and oseltamivir.^{59,60} Thus, neuraminidase inhibitors are currently the only options for treatment or prophylaxis in humans infected with these strains. Many countries have reportedly stockpiled oseltamivir as part of their pandemic planning. However, there has been a recent report of the isolation of drug-resistant H5N1 virus from a patient treated with oseltamivir in Vietnam.⁶¹ This observation suggests that in addition to oseltamivir, zanamivir should be included as part of pandemic preparedness. The neuraminidase inhibitors are also effective against the neuraminidase from the virus that caused the 1918 pandemic⁶² and the avian viruses that caused outbreaks from 1997 to 1999.^{63,64}

The fact that influenza virus is frequently transmitted from person to person during epidemics before the onset of recognizable symptoms would obviously complicate efforts to control spread during a pandemic.⁶⁵ However, several strategies are worthy of consideration.⁵⁴ Although several countries have developed policies that entail treatment of index cases (and possibly prophylaxis of health care workers and other essential workers) as the most efficient use of a limited drug supply, this strategy would not prevent spread. Surveillance might provide advance warning of a new transmissible strain, which could render it feasible to interrupt transmission at the source, delay global spread, and diminish the severity of the initial phase of a pandemic.^{54,56} Prophylaxis around a localized outbreak to limit the pandemic would require rings of prophylaxis around the contacts of index cases.^{1,66} Drug stockpiles that can be made rapidly available at the site of an outbreak are essential, and one approach may be to develop an international stockpile managed by the World Health Organization.⁶⁷ Seasonal prophylaxis and postexposure prophylaxis are other feasible strategies. Targeting high-risk groups may also be considered, although previous pandemic strains have not shown a predilection for the groups most affected during interpandemic periods. Vigilant surveillance, together with clinical and epidemiologic data rapidly applied, as with the recent case of human transmission of avian influenza,⁵² should guide critical public health decisions.

Current supplies of neuraminidase inhibitors are inadequate for any proposed strategy for pandemic response,¹ even for the least satisfactory option of treating only the ill. There is little capacity to increase production in the time of need, and therefore anticipatory stockpiling of drugs and the development of efficient distribution methods in case of need are high priorities. In 2005, we have in hand greatly improved tools for surveillance and diagnosis, as well as highly effective drugs, which is a better state of affairs than that during previous influenza pandemics. Identifying feasible strategies for mass production and distribution of these antiviral agents, combined with research into the incidence and mechanisms of drug resistance, may hold the key to our ability to lessen considerably the impact of the next pandemic.

REFERENCES

1. Hayden FG. Pandemic influenza: is an antiviral response realistic? *Pediatr Infect Dis J* 2004;23:Suppl:S262-S269.
2. Matrosovich MN, Matrosovich TY, Gray T, Roberts NA, Klenk HD. Neuraminidase is important for the initiation of influenza virus infection in human airway epithelium. *J Virol* 2004;78:12665-7.
3. Meindl P, Bodo G, Palese P, Schulman J, Tuppy H. Inhibition of neuraminidase activity by derivatives of 2-deoxy-2,3-dehydro-N-acetylneuraminic acid. *Virology* 1974;58:457-63.
4. Palese P, Compans RW. Inhibition of influenza virus replication in tissue culture by 2-deoxy-2,3-dehydro-N-trifluoroacetylneuraminic acid (FANA): mechanism of action. *J Gen Virol* 1976;33:159-63.
5. Palese P, Schulman JL, Bodo G, Meindl P. Inhibition of influenza and parainfluenza virus replication in tissue culture by 2-deoxy-2,3-dehydro-N-trifluoroacetylneuraminic acid (FANA). *Virology* 1974;59:490-8.
6. Colman PM, Varghese JN, Laver WG. Structure of the catalytic and antigenic sites in influenza virus neuraminidase. *Nature* 1983;303:41-4.
7. Varghese JN, McKimm-Breschkin JL, Caldwell JB, Kortt AA, Colman PM. The structure of the complex between influenza virus neuraminidase and sialic acid, the viral receptor. *Proteins* 1992;14:327-32.
8. von Itzstein M, Wu W-Y, Kok GB, et al. Rational design of potent sialidase-based inhibitors of influenza virus replication. *Nature* 1993;363:418-23.
9. Varghese JN, Epa VC, Colman PM. Three-dimensional structure of the complex of 4-guanidino-Neu5Ac2en and influenza virus neuraminidase. *Protein Sci* 1995;4:1081-7.
10. Kim CU, Lew W, Williams MA, et al. Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: design, synthesis, and structural analysis of carbocyclic sialic acid analogues with potent anti-influenza activity. *J Am Chem Soc* 1997;119:681-90.
11. Cass LM, Brown J, Pickford M, et al. Pharmacoscintigraphic evaluation of lung deposition of inhaled zanamivir in healthy volunteers. *Clin Pharmacokinet* 1999;36:Suppl 1:21-31.
12. Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Engl J Med* 1997;337:874-80.
13. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003;326:1235.
14. Monto AS, Fleming DM, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis* 1999;180:254-61.
15. Makela MJ, Pauksens K, Rostila T, et al. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. *J Infect* 2000;40:42-8.
16. The MIST (Management of Influenza in the Southern Hemisphere Trialist) Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet* 1998;352:1877-81. [Errata, *Lancet* 1999;353:504, 1104.]
17. Matsumoto K, Ogawa N, Nerome K, et al. Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: results from Japan. *Antivir Ther* 1999;4:61-8.
18. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *JAMA* 2000;283:1016-24.
19. Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. *Lancet* 2000;355:1845-50. [Erratum, *Lancet* 2000;356:1856.]
20. Murphy KR, Eivindson A, Pauksens K, et al. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: a double-blind, randomised, placebo-controlled, multicentre study. *Clin Drug Investig* 2000;20:337-49.
21. Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. *Pediatr Infect Dis J* 2000;19:410-7.
22. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J* 2001;20:127-33. [Erratum, *Pediatr Infect Dis J* 2001;20:421.]
23. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother* 2003;51:123-9.
24. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 2003;163:1667-72.
25. Kawai N, Ikematsu H, Iwaki N, et al. Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from Japan of the 2002-2003 influenza season. *Clin Infect Dis* 2005;40:1309-16.
26. Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999-2000. *J Am Geriatr Soc* 2002;50:608-16.
27. McCullers JA, Bartmess KC. Role of neuraminidase in lethal synergism between influenza virus and *Streptococcus pneumoniae*. *J Infect Dis* 2003;187:1000-9.
28. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. *N Engl J Med* 2000;343:1282-9.
29. Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without post-exposure prophylaxis. *J Infect Dis* 2004;189:440-9.
30. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 2001;285:748-54.
31. Monto AS, Robinson DP, Herlocher ML, Hinson JM Jr, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 1999;282:31-5.
32. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999;341:1336-43.
33. Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis* 2002;186:1582-8.
34. Oxford J, Balasingam S, Lambkin R. A new millennium conundrum: how to use a powerful class of influenza anti-neuraminidase drugs (NAIs) in the community. *J Antimicrob Chemother* 2004;53:133-6.
35. Langley JM, Faughnan ME. Prevention of influenza in the general population. *CMAJ* 2004;171:1213-22.
36. Peters PH Jr, Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc* 2001;49:1025-31.
37. Monto AS, Rotthoff J, Teich E, et al. Detection and control of influenza outbreaks in well-vaccinated nursing home populations. *Clin Infect Dis* 2004;39:459-64.
38. Harper SA, Fukuda K, Uyeki TM, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2004;53(RR-6):1-40.
39. Relenza (zanamivir for inhalation). Research Triangle Park, N.C.: Glaxo Wellcome, 2001.
40. Hayden FG, Treanor JJ, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA* 1999;282:1240-6.
41. Tamiflu (oseltamivir phosphate) capsules. Nutley, N.J.: Roche Laboratories, 2000 (package insert).

42. Freund B, Gravenstein S, Elliott M, Miller I. Zanamivir: a review of clinical safety. *Drug Saf* 1999;21:267-81.
43. Zambon M, Hayden FG. Position statement: global neuraminidase inhibitor susceptibility network. *Antiviral Res* 2001;49:147-56.
44. McKimm-Breschkin J, Trivedi T, Hampson A, et al. Neuraminidase sequence analysis and susceptibilities of influenza virus clinical isolates to zanamivir and oseltamivir. *Antimicrob Agents Chemother* 2003;47:2264-72.
45. Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 2004;364:759-65.
46. Moscona A. Oseltamivir-resistant influenza? *Lancet* 2004;364:733-4.
47. Herlocher ML, Truscon R, Elias S, et al. Influenza viruses resistant to the antiviral drug oseltamivir: transmission studies in ferrets. *J Infect Dis* 2004;190:1627-30.
48. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000;160:3243-7.
49. Cox NJ, Subbarao K. Influenza. *Lancet* 1999;354:1277-82.
50. Storch GA. Rapid diagnostic tests for influenza. *Curr Opin Pediatr* 2003;15:77-84.
51. Health Sciences Authority. Product safety alert: new preclinical findings on oseltamivir. March 2004. (Accessed September 2, 2005, at: http://www.hsa.gov.sg/docs/safetyalert_oseltamivir_Mar04.pdf.)
52. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). *N Engl J Med* 2005;352:333-40.
53. Li KS, Guan Y, Wang J, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature* 2004;430:209-13.
54. Stöhr K. Avian influenza and pandemics — research needs and opportunities. *N Engl J Med* 2005;352:405-7.
55. World Health Organization. Cumulative number of confirmed human cases of avian Influenza A(H5N1) reported to WHO. 2005. (Accessed September 2, 2005, at http://www.who.int/csr/disease/avian_influenza/country/case_table_2005_08_05/en/index.html.)
56. Monto AS. The threat of an avian influenza pandemic. *N Engl J Med* 2005;352:323-5. [Erratum, *N Engl J Med* 2005;352:1056.]
57. Hayden FG. Perspectives on antiviral use during pandemic influenza. *Philos Trans R Soc Lond B Biol Sci* 2001;356:1877-84.
58. Centers for Disease Control and Prevention. Update on influenza A(H5N1) and SARS: interim recommendations for enhanced U.S. surveillance, testing, and infection controls. February 3, 2004. (Accessed September 2, 2005, at <http://www.cdc.gov/flu/avian/professional/han020302.htm>.)
59. Commonwealth Scientific and Industrial Research Organization. CSIRO based drug effective against bird flu. (Accessed September 2, 2005, at <http://www.csiro.au/index.asp?type=mediaRelease&id=PrBirdFlu5&stylesheet=mediaRelease>.)
60. Trampuz A, Prabhu RM, Smith TF, Badour LM. Avian influenza: a new pandemic threat? *Mayo Clin Proc* 2004;79:523-30. [Erratum, *Mayo Clin Proc* 2004;79:833.]
61. World Health Organization. WHO inter-country consultation: influenza A/H5N1 in humans in Asia, Manila May 6th-7th 2005. (Accessed September 2, 2005, at http://www.who.int/csr/disease/avian_influenza/H5N1InterCountryAssessment.pdf.)
62. Tumpey TM, Garcia-Sastre A, Mikulasova A, et al. Existing antivirals are effective against influenza viruses with genes from the 1918 pandemic virus. *Proc Natl Acad Sci U S A* 2002;99:13849-54.
63. Leneva IA, Goloubeva O, Fenton RJ, Tisdale M, Webster RG. Efficacy of zanamivir against avian influenza A viruses that possess genes encoding H5N1 internal proteins and are pathogenic in mammals. *Antimicrob Agents Chemother* 2001;45:1216-24.
64. Leneva IA, Roberts N, Govorkova EA, Goloubeva OG, Webster RG. The neuraminidase inhibitor GS4104 (oseltamivir phosphate) is efficacious against A/Hong Kong/156/97 (H5N1) and A/Hong Kong/1074/99 (H9N2) influenza viruses. *Antiviral Res* 2000;48:101-15.
65. Mills CE, Robins JM, Lipsitch M. Transmissibility of 1918 pandemic influenza. *Nature* 2004;432:904-6.
66. Balicer RD, Huerta M, Grotto I. Tackling the next influenza pandemic. *BMJ* 2004;328:1391-2.
67. World Health Organization. WHO consultation on priority public health interventions before and during an influenza pandemic. April 2004. (Accessed September 2, 2005 at: http://www.who.int/csr/disease/avian_influenza/consultation/en/.)

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