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I. Introduction

Antiviral therapy and prophylaxis can contribute to achieving the goals of decreasing morbidity and mortality during a pandemic, as well as decreasing social and economic disruption. While these impacts may be greatest during the period before vaccines for a pandemic influenza strain are available, antiviral use also may have substantial impact during the period when vaccine supplies are available. Limitations of vaccination include imperfect effectiveness – particularly among the elderly and those with underlying immunosuppressive disease; the possible need for two vaccine doses to achieve optimal protection; and the inability to vaccinate certain persons with contraindications, such as anaphylactic hypersensitivity to eggs or other vaccine components.

There are a number of uncertainties that make planning antiviral strategies difficult. Most importantly, it is unclear how much antiviral drug supply will be available either in the public or private sector. In 2003, an initial acquisition of antiviral drugs approved for influenza was added to the Strategic National Stockpile (SNS). Analysis is ongoing to define optimal use strategies, potential health impacts, and the cost-benefits and cost-effectiveness of antiviral therapies. These analyses should contribute to decisions regarding the optimal use of an antiviral drug and the size of the stockpile. Public sector supply of antiviral drugs could also be increased by establishing stockpiles at State health department levels or, possibly, by additional purchase at the time a pandemic is imminent. Because of uncertainty regarding the quantity of antiviral drugs that will be distributed by the public sector, antiviral drug use strategies and priorities should be flexible and tailored to various potential levels of supply. Also, as a quantity of antiviral drug is likely to remain in the private sector, it is important to educate health care provider regarding appropriate use and to effectively communicate the strategies and priorities.

A second key uncertainty relates to the influenza pandemic strain and the characteristics of the pandemic it causes. The epidemiology of pandemic disease, as defined by surveillance for influenza hospitalizations and deaths may lead to revisions of priorities for treatment and prophylaxis. Data on resistance of the pandemic strain or the development and spread of antiviral resistance as the pandemic progresses also may result in changes in strategy. Finally, although antiviral drug use is unlikely to substantially modify the course of a pandemic caused by a influenza strain that is well adapted for person-to-person transmission (as in the pandemics of 1918, 1957, or 1968, or annual influenza outbreaks), it may be more effective in containing or delaying the spread of a novel influenza strain that may be less efficiently transmitted between people. In this setting, intensive antiviral use might control disease spread in a community or delay spread and introduction into new areas while other preventive interventions such as vaccination are implemented. Results from surveillance and epidemiological investigations are likely to help to indicate whether such a strategy might be effective.

II. Characteristics of Available Antiviral Agents

Antiviral agents for influenza consist of two classes of drugs: adamantanes or M2 ion-channel inhibitors (amantadine and rimantadine) and neuraminidase inhibitors (zanamivir and oseltamivir). Adamantanes have activity against influenza A and neuraminidase inhibitors are active against influenza A and B. Because pandemics are caused by novel influenza A strains, this difference has no impact for pandemic planning. The antiviral activity of both classes of drugs is specific to influenza; their stockpile for use would have no value for other viruses that may cause other outbreaks. Similarly, antiviral agents currently in use for other viruses are unlikely to make any meaningful contribution to control of influenza infection. Additional details regarding influenza antivirals are available at http://www.fda.gov/cder/drug/antivirals/influenza/default.htm

A. Adamantane Derivatives.

The adamantane derivatives, amantadine and rimantadine, are chemically related, orally administered drugs that are approved for treatment and prophylaxis of influenza A. Amantadine and rimantadine inhibit replication of influenza A viruses.

Clinical uses

Amantadine is approved for the treatment of influenza A infections in persons aged one year and older. Rimantadine is approved for treatment of influenza A infections in adults. The usual recommended duration of treatment is 5 days. Both drugs are approved for prophylaxis to prevent influenza A infections in persons one year old and older (*see Table 1*). Prophylaxis may be recommended for the duration of the influenza season, during the period when influenza is present in a community, or for a shorter period following exposure in a household or institutional setting, or following vaccination until the development of protective immunity.

Efficacy

When administered for treatment within 48 hours of illness onset, controlled studies have found that both drugs are effective in decreasing viral shedding and reducing the duration of illness of influenza A by approximately one day compared with placebo. No prospective trials have documented reductions in influenza complications such as pneumonia or in the need for hospitalization. When used for prophylaxis during annual influenza outbreaks, amantadine and rimantadine generally have been approximately 70 percent to 90 percent effective in preventing symptomatic illness caused by influenza A. Some studies, including those conducted during influenza pandemics have shown lower prophylactic efficacy. Although this difference may be due to a delay in starting prophylaxis, it may also be attributed to the immune status of a patient with no prior illness or vaccination with that influenza subtype.

Adverse events
Gastrointestinal and central nervous system (CNS) adverse effects have been reported during controlled prophylaxis studies of amantadine and rimantadine in healthy adults and elderly nursing home residents. Prophylactic use of both drugs has been associated with CNS toxicity such as lightheadedness, difficulty concentrating, nervousness, insomnia, and seizures in patients with pre-existing seizure disorders. Toxicity is more likely among persons with renal insufficiency, older persons, and those with seizure disorders or psychiatric illness. Doses administered should be decreased in persons with reduced creatinine clearance (less than 80 ml/min) and persons 65 years old and older. Rimantadine use has been associated with substantially fewer CNS side effects than amantadine; the rate of gastrointestinal adverse events, primarily nausea, is similar for both drugs. Amantadine has been shown to be teratogenic and embryo toxic in animals. The safety of amantadine and rimantadine in pregnant women has not been established.

Resistance
The therapeutic use of amantadine and rimantadine has been associated with the rapid selection and development of resistant viruses. Resistance results from point mutations that correspond with a single amino acid change in the target protein. Resistant variants may replace susceptible strains after two to four days of treatment. In some settings, resistance has been found in more than 30 percent of those treated. Drug-resistant viruses can be spread to contacts of treated individuals, including persons receiving prophylaxis. Drug resistant and drug susceptible strains spread equally well. Resistance renders both treatment and prophylaxis ineffective. Since the mechanism of resistance is the same for both adamantane derivatives, influenza A viruses resistant to one adamantane drug are also resistant to the other. Resistance to adamantanes does not affect susceptibility to neuraminidase inhibitors. The percentage of influenza viral isolates from the general population during the annual influenza outbreaks that exhibit resistance to amantadine or rimantadine has been low. The risk of resistance during a pandemic is likely to be higher because antiviral drug use would be more widespread in the U.S. and potentially in the countries from which the pandemic strain spread. The strains of the avian H5N1 influenza virus that infected persons in Vietnam and Thailand in 2004 were resistant to the adamantanes.

Production and supply
Both amantadine and rimantadine are available in proprietary and generic formulations, both as capsules/tablets and syrup. Amantadine also is used to treat symptoms of Parkinson's disease. Given the expected demand during a pandemic and a potential duration of prophylaxis of up to three months, supply shortages likely would occur soon after the onset of the pandemic.

Table: Characteristics of the adamantanes and neuraminidase inhibitors

	Adamantane Derivatives		Neuraminidase Inhibitors	
	Amantadine	Rimantadine	Oseltamivir	Zanamivir
Spectrum of activity	Influenza A	Influenza A	Influenza A & B	Influenza A & B
Administration	Oral	Oral	Oral	Inhalation
Prophylaxis licensure	≥ 1 year	>1 year	≥ 13 years	Not approved
Treatment licensure	≥ 1 year	Adults	≥ 1 year	≥ 7 years
Selected adverse events (see package insert for more complete list)	CNS (e.g. dizziness, insomnia), GI (e.g. nausea); some reports of cardiac toxicity, especially in overdose; CNS effects may be severe including suicide attempts, seizures	CNS (e.g. insomnia, dizziness), GI (e.g. nausea, vomiting)	GI (principally nausea, vomiting)	Some reports of bronchospasm and decrease in lung function, especially in patients with underlying airway disease (not generally recommended for such patients)
Adult treatment dose (see package insert for pediatric dosing and for dose adjustments in special populations)	200 milligrams once daily or 100 milligrams twice daily (reduce for elderly and persons with renal impairment or with intolerance to full dose; same dose for prophylaxis)	100 milligrams twice daily (reduce for severe hepatic or renal impairment and high-risk elderly; same dose for prophylaxis)	75 milligrams twice daily (reduce for persons with renal impairment; 75 milligrams/day for prophylaxis, also adjusted in renal impairment)	10 milligrams twice daily (not approved for prophylaxis)
Generic production	Yes	Yes	No	No

B. Neuraminidase Inhibitors

The neuraminidase inhibitors, zanamivir and oseltamivir, are chemically related members of a new class of antiviral drugs for influenza that have activity against both influenza A and B viruses.

Clinical uses

Oseltamivir is approved for treatment of influenza in persons one year of age and older. Zanamivir is approved for treatment of influenza in persons seven years and older. Oseltamivir is also approved for prophylaxis of influenza in persons aged 13 years and older while zanamivir is not approved for prophylaxis (*see Table 1*). For both drugs, the recommended duration of treatment is five days. The duration of prophylaxis may vary as described for the adamantanes.

Efficacy

When treatment is initiated within 48 hours of illness onset, both drugs are effective in decreasing shedding and reducing the duration of symptoms of influenza by approximately one to two days compared with placebo. Recent studies have also suggested efficacy of the neuraminidase inhibitors in reducing complications of influenza. The impacts of oseltamivir therapy on lower respiratory tract complications (LRTCs) of influenza and on influenza hospitalizations were calculated in a pooled analysis of 10 randomized placebo-controlled studies that included 3,591 adults and adolescents. Overall, 4.6 percent of oseltamivir treated persons had an LRTC of influenza infection compared with 10.3 percent of persons who received placebo – a 55 percent reduction ($P<0.001$). Significant reductions were documented both for healthy persons 13 to 65 years old and those who were at increased risk for influenza complications. Pneumonia, the most severe LRTC of influenza occurred in 0.7 percent of oseltamivir recipients compared with 1.8 percent of placebo recipients ($p<0.02$). In a separate analysis, zanamivir was shown to reduce influenza associated LRTCs by 40 percent; no impact was shown on hospitalization rate, which was low in the predominantly healthy study population. These studies were unable to directly assess the impact on mortality due to the infrequency of this outcome in the study population. However, given their impact on pneumonia and hospitalizations, such an effect is likely. Several cautions should be emphasized in generalizing from these data. The large majority of persons studied were not at high risk of influenza complications and those at increased risk were not severely immunocompromised. Also, therapy generally was started early (at ~24 hours after symptom onset); the impact would likely be less for persons who start therapy later. Finally, these most study participants were treated as outpatients and the impacts of therapy could be different for persons who were more severely ill at the time treatment was begun.

Adverse events

Oseltamivir use has been associated with nausea and vomiting during controlled treatment studies compared with placebo. In the combined analysis of randomized trials, 1.8 percent in both the oseltamivir and placebo groups withdrew because of adverse events. This proportion may be less during a pandemic when the increased risk of influenza infection and severe illness

is weighed against the treatment-associated adverse events. Nausea, diarrhea, dizziness, headache, and cough have been reported during zanamivir treatment, but the frequencies of adverse events were similar to inhaled powered placebo drug. Few serious CNS adverse effects have been reported for the neuraminidase inhibitor drugs when compared to placebo.

Safety concerns have been raised for use of oseltamivir among infants under one year of age based on results of a study in seven day old rats in which deaths associated with high central nervous system drug levels were observed following administration of a very high dose of oseltamivir.

Zanamivir generally is not recommended for use in persons with underlying respiratory disease because of the risk of precipitating bronchospasm. Serious adverse respiratory events resulting from zanamivir use have been reported in persons with chronic pulmonary disease and in healthy adults. There are limited data about the potential to use neuraminidase inhibitors for treatment influenza during pregnancy.

Resistance
Primary resistance of clinical influenza isolates to the neuraminidase inhibitors has not been demonstrated and treatment is associated with a low incidence of resistance emergence due to neuraminidase mutations. Resistant variants have been detected late during therapy and have not been associated with clinical deterioration. Limited nonclinical data suggest neuraminidase inhibitor resistance might reduce the fitness of influenza strains decreasing their transmissibility. Because these drugs have been available only for a few years and their use has not been widespread, there has been limited selective pressure for resistance. As these drugs are used for a longer time – especially if they are used more often – increased rates of resistance could occur, highlighting the importance of on-going viral monitoring. *In vitro* studies have found that cross-resistance occurs between the neuraminidase inhibitor drugs, but does not affect susceptibility to adamantane drugs.

Supply
Oseltamivir is made by a single manufacturer. Production occurs in a series of steps and takes about 12 months from raw material to finished product. Because of limited demand, very little zanamivir is available in the U.S

C. Comparison of antiviral agents

Controlled studies have not been done to directly compare the adamantanes (amantadine, rimantadine) with the neuraminidase inhibitors (zanamivir, oseltamivir) for treatment or prophylaxis of influenza A. Both classes of drugs have had similar impacts in reducing the duration of uncomplicated influenza illness when started within two days of illness onset. The costs, routes of administration, adverse events, contraindications, and potential for antiviral

resistance differ between the four drugs. Several issues have implications on their use during a pandemic:

- The adamantanes often induce clinically significant resistance when used for therapy; because of this, adamantane use should be reserved for prophylaxis.
- Both classes of influenza antiviral drugs have been shown to be equally effective in preventing influenza A infections when used as prophylaxis. Because of their greater availability and substantially lower cost, adamantanes may be the preferred choice for prophylaxis if the pandemic strain is susceptible.
- Limited data suggest that the neuraminidase inhibitors reduce lower respiratory tract complications of influenza and hospitalizations when used as therapy for acute infection. Because of this and because adamantanes are more likely to induce antiviral resistance when used for therapy, neuraminidase inhibitors may be the preferred choice for treatment.
- Amantadine is inexpensive and produced in the U.S. and internationally by multiple generic drug manufacturers. Several manufacturers also produce rimantadine. By contrast, the neuraminidase inhibitors each are produced by a single manufacturer at facilities outside the U.S.
- Neurological adverse events occur more often with amantadine use, particularly among the elderly, those with reduced renal function, and those with preexisting neurological illness. Dosage modifications may be needed when amantadine is used in these groups.

III. Goals of Antiviral Use during an Influenza Pandemic

During an influenza pandemic, the primary goal of antiviral prophylaxis and therapy would be to decrease adverse health impact (morbidity and mortality) and reduce social and economic disruption, supporting overall pandemic response goals. The relative importance of antiviral drug use is likely to be greatest early in the pandemic when vaccines are not available or their supply is limited. However, benefit is likely to accrue throughout the course of the pandemic as illness will still occur among some vaccinated persons and, even when vaccine supply is sufficient, some will remain unvaccinated because of access, choice, or contraindications to vaccination. Because of the limited supply of antiviral drugs and because clinically significant resistance to the adamantanes is likely to develop if these agents are not used appropriately, another goal for antiviral use is to assure the judicious and appropriate use of these agents in both the public and private sectors.

Antiviral drug use should not be considered as a strategy for altering the overall course of a pandemic. Modeling suggests that the amount of drug needed for this effect would be far greater than available supply. Prophylaxis and therapy can decrease the transmission of infection in specific settings (such as long term care facilities, workplaces, or families). In addition, there is a theoretical ability of intensive prophylaxis and therapy, in conjunction with quarantine and

isolation, to decrease the spread of a novel influenza strain that is less efficiently transmitted between people than are influenza viruses that cause annual outbreaks. However, each of the 20th century influenza pandemics was caused by a strain that was transmitted effectively between people. Possible impacts of antiviral drug use during the initial phases of a pandemic would need to be assessed at the time the pandemic occurs.

IV. Strategies for Antiviral Drug Use

Four overarching principles guide antiviral drug use strategies for an influenza pandemic:

1. Target antiviral drug use to defined priority groups: Because antiviral drug supply is limited, planning for the use of antiviral drugs should be based on defined goals and identify priority groups that should be targeted to achieve those goals.

2. Maintain flexibility and responsiveness to local conditions: Planners should be flexible in deciding optimal use of antiviral drug supply based on the available supply, and the local impacts and epidemiology of the pandemic.

3. Consider efficiency: The duration of prophylaxis is estimated to be six to eight weeks if used while influenza is circulating in a community or may be longer if used during the entire influenza season. Because prophylaxis would be provided to a group of people who were at risk of exposure to the pandemic virus and its consequences, many of those who receive prophylaxis may not become infected and may not have become ill even in its absence. Therefore, for a given quantity of antiviral drugs, treatment is a more efficient strategy to reduce the health impacts of a pandemic than is prophylaxis, assuming adequate delivery systems and similar therapeutic and prophylactic efficacy as documented previously (note: this applies to the neuraminidase inhibitors; because of the risk of antiviral resistance, use of adamantanes for therapy should be limited).

4. Use antiviral drugs appropriately: Use of adamantanes for therapy can lead to the development and subsequent spread of resistant influenza viruses. Administering antiviral drug therapy more than 48 hours after onset of influenza symptoms is likely to be much less effective than earlier treatment and generally should be avoided.

A. Prophylaxis

Long-term prophylaxis, generally lasting for six to eight weeks and is designed to protect against influenza throughout the course of an outbreak in a community. Given the amount of drug needed for long-term prophylaxis and its cost, amantadine or rimantadine are the preferred agents for this indication during the inter-pandemic period, provided adequate amounts are available.

The trigger for starting seasonal prophylaxis would be the initial identification of influenza activity within a community based on isolation of the pandemic strain or an increase in influenza-like activity. Prophylaxis should end after influenza activity in the community has ceased – generally after six to eight weeks. If a person is vaccinated while receiving seasonal prophylaxis, the antiviral can be stopped 14 days after vaccination or if two vaccine doses are needed for protection, 14 days after the second dose. Prophylaxis should not be used in conjunction with live-virus vaccination as it may blunt replication and decrease immune response.

Short-term prophylaxis, lasting for 10 to 14 days, may be used to prevent infection in families or institutions following exposure to influenza. While the adamantanes should be the primary choice for short-term prophylaxis, their use in a family or institutional outbreak may be of limited by the development of resistance. In these settings, the neuraminidase inhibitors could be considered as an alternative. Decisions about the initiation of short-term prophylaxis and the agent to use should be based on the epidemiological situation and what is known about antiviral resistance.

A primary goal of prophylaxis is to maintain essential healthcare and public safety services. Prophylaxis of individuals carrying out these services may be desired to minimize disruption of critical public safety activities. A secondary goal will be the prophylaxis of individuals at high risk for severe complications, but limited supplies may restrict antiviral use in these groups.

State and local health departments, as part of their pandemic planning activities, should work with health care organizations and communities to identify who should be included in defined priority groups and to develop plans for acquiring and distributing antiviral prophylaxis. Plans should consider who will distribute antiviral drugs, what sites will be used, how recipients will document that they are in a priority group and designated to receive the drug, what education and materials will be provided, and how drug supply and use will be monitored. If prophylaxis throughout the course of an outbreak in a community is being provided, health departments should consider providing only a limited supply with additional drug given when needed. This approach will allow the most flexibility if the situation changes. Communications plans must be able to clearly describe the rationale for defining certain groups as higher priority for prophylaxis and eligibility to avoid confusion. Health departments also should work with private sector health care organizations and health care providers to develop pandemic response plans and provide education regarding target groups and optimal drug use strategies; these efforts will increase the likelihood that private sector antiviral drug supply will be used to meet pandemic response goals.

B. Therapy

Antiviral therapy of persons with influenza infection during a pandemic has the potential to significantly reduce pneumonia, hospitalization and, by extrapolation of data from randomized

trials, death. Neuraminidase inhibitors should be used for therapy, when feasible, because of the risk of resistance developing to adamantanes and the study data suggesting effectiveness of the neuraminidase inhibitors in reducing influenza complications. Therapy generally should be offered only to those who have been symptomatic for two days or less. Exceptions may include persons with illness requiring inpatient care or persons who are immunosuppressed and may have a prolonged period of active viral replication. Because the impacts of therapy are greater with a shorter interval between onset of symptoms and treatment, emphasis should be placed on early care seeking and rapid diagnosis. Use of influenza rapid diagnostic tests may be of benefit to confirm an influenza infection. Alternately, therapy could be started without etiological confirmation in someone with a compatible clinical illness in a community with known influenza activity; however, given likely supply shortages, confirming influenza infection could help assure that therapy is reserved for persons who may accrue a known benefit.

Antiviral therapy is likely to have the greatest impact during a pandemic if it is targeted to those who, in the absence of treatment, would go on to adverse health outcomes, either hospitalization or death. In annual influenza outbreaks, rates of lower respiratory tract complications, hospitalization, and death are higher among persons in defined risk groups compared with healthy adolescents and adults. These risk groups include young children (note that no antiviral drug is approved for use in children <1 year old and adverse outcomes occurred in infant rats exposed to high doses of oseltamivir); persons 65 years old or older; and persons of any age with chronic medical conditions such as heart or lung disease including asthma, diabetes mellitus, metabolic disease, or immunosuppressive conditions. During past influenza pandemics, however, risk group differed from those seen during annual disease outbreaks. For example, during the 1918 pandemic, a much greater proportion of overall mortality occurred among young adults. Thus, the definition of risk groups should be reassessed during a pandemic based on surveillance data and epidemiological investigations. The need for hospitalization can be used to define, *de facto*, those who are most likely to suffer an adverse outcome and who may benefit from therapy.

In addition to decreasing the risk of severe complications, antiviral therapy also may decrease influenza transmission and shorten the time to recovery and return to work. To achieve this public health objective, target groups may be similar to those recommended for prophylaxis. Because the amount of antiviral drug needed per-person for treatment is much less than for prophylaxis, assuring the availability of treatment or post-exposure prophylaxis for these groups may be preferable to providing seasonal prophylaxis, particularly if antiviral drug supplies are limited. Optimal strategies will depend on the amount and types of antiviral drugs available, the severity and drug responsiveness of pandemic disease, the ability to deliver drugs for therapy soon after symptom onset, and the ability to tolerate some absences from work due to illness.

As with antiviral prophylaxis, distributing antiviral therapy will be a challenge and will require planning in advance of a pandemic. Because of the need to implement therapy early in the course of illness, strategies that make drugs available at the point-of-care are most likely to be

successful. For example, antiviral drugs could be distributed to hospitals in relative quantities that reflect number of acute care beds and emergency room visits.

C. Monitoring for Adverse Events:

Adverse events temporally or causally associated with antiviral drug use inevitably will occur underscoring the need to anticipate the data and epidemiologic studies that will help to define those that are indeed caused by the drug. Information sheets should be available listing contraindications, precautions, drug-drug interactions, and potential adverse events with therapy and prophylaxis. Persons who take antiviral prophylaxis because of their employment (such as health care workers or those who provide other essential community services) may be eligible for workers' compensation if they experience significant adverse events.

State-level systems to monitor who receives influenza antiviral drugs from public sector stockpiles, their compliance with recommendations for prophylaxis and therapy, and adverse events should be considered. Studies implemented following the 2001 anthrax attacks indicated that many persons who received long-term antibiotics to prevent anthrax disease did not comply with therapy. Assessing compliance to influenza antiviral drug prophylaxis in a pandemic may help guide the use of this intervention and identify potential problems that would need to be addressed. Adverse events following use of antiviral medications currently are monitored nationally by FDA's MedWatch system (http://www.fda.gov/medwatch). Reports may be submitted electronically, or by fax or telephone. More active programs to monitor adverse events in subsets of recipients may provide additional useful data on adverse events and acceptability.

Because antiviral drug resistance would reduce or eliminate the benefits of prophylaxis or therapy, ongoing monitoring should occur for drug resistance among influenza strains causing annual outbreaks and of novel influenza strains identified from people. Improving laboratory assays to test for resistance and disseminating them more broadly within the U.S. and to other countries would be beneficial.