supplement 7
antiviral drug distribution and use

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SUMMARY OF PUBLIC HEALTH ROLES AND RESPONSIBILITIES FOR ANTIVIRAL DISTRIBUTION AND USE

INTERPANDEMIC AND PANDEMIC ALERT PERIODS

State and local health departments will work with healthcare partners to:

- Use antivirals in medical management of cases of novel strains of influenza
- Procure and maintain local stockpiles of antiviral drugs
- Develop state-based plans for distribution and use of antiviral drugs during a pandemic

HHS responsibilities:

- In advance of an influenza pandemic, HHS, in concert with the Congress and in collaboration with the States, will acquire sufficient quantities of antiviral drugs to treat 25% of the U.S. population and, in so doing, stimulate development of expanded domestic production capacity sufficient to accommodate subsequent needs through normal commercial transactions.
- Develop national guidance on use of antivirals during a pandemic, including identification of priority groups for antiviral drug treatment and prophylaxis.
- Continue procurement and maintenance of national supplies of antivirals in the Strategic National Stockpile.
- Maintain a program to test and extend dating of stockpiled antivirals, as needed, based on demonstration of continued potency.
- Develop protocols for monitoring antiviral effectiveness, safety, and resistance during a pandemic.
- Develop and distribute communication and education materials about antivirals for use by states and other stakeholders.

PANDEMIC PERIOD

State and local health departments will work with healthcare partners to:

- Prepare to activate state-based plans for distributing and administering antivirals to persons in priority groups.
- Review modifications, if any, to interim recommendations on antiviral prophylaxis in selected groups or circumstances.
- Accelerate training on appropriate use of antiviral drugs among public health staff and healthcare partners.
- Work with other governmental agencies and non-governmental organizations to ensure effective public health communications.

HHS responsibilities:

- Revise recommendations for treatment and prophylaxis with antivirals for priority groups, if necessary, guided by accumulating data about the pandemic virus (e.g., susceptibility, virulence, transmissibility, geographic spread, and age-specific attack rates).
- Provide state, territorial and local health departments, and healthcare partners with guidance on reporting specifications for tracking distribution, effectiveness, and safety of antivirals.

PANDEMIC PERIOD (CONT.)

- Work with WHO and global partners to determine the drug susceptibilities of the pandemic strain and monitor changes over time.
- Provide state, territorial and local health departments, and healthcare partners with guidance on reporting specifications for tracking distribution, effectiveness, and safety of antivirals.
- Provide information to health professionals and the public on issues related to availability and use of antiviral drugs during an influenza pandemic.

If pandemic influenza is detected in the United States:

State and local health departments will work with healthcare partners to:

- Distribute and deliver stockpiled supplies of antivirals, as appropriate, to healthcare facilities that will administer them to priority groups.
- Work with HHS to monitor antiviral drug use and effectiveness.
- Work with HHS to monitor and investigate adverse events.
- Provide updated information to the public via the news media.

Federal responsibilities:

- Establish and maintain stockpiles of influenza antiviral drugs at the SNS.
- Distribute antiviral drugs from the SNS to state and large city health departments and federal agencies with direct patient care responsibilities, as appropriate.
- Work with state and local health departments and healthcare partners to:
  - Evaluate the effectiveness of antivirals for treatment and prophylaxis.
  - Monitor the incidence of adverse events associated with antiviral use.
  - Monitor the emergence of antiviral resistance.
- Issue updated national guidelines for appropriate use of antivirals as the pandemic continues.
- Continue to provide information to health professionals and the public, as the situation changes, on drug availability, distribution, administration, side effects, and the rationale for targeted drug use.

S7-I. RATIONALE

Drugs with activity against influenza viruses ("antivirals") include the adamantanes *amantadine* and *rimantadine* and the neuraminidase inhibitors *oseltamivir* and *zanamivir* (see Table 1 and Appendix). Appropriate use of these agents during an influenza pandemic may reduce morbidity and mortality and diminish the overwhelming demands that will be placed on the healthcare system. Antivirals might also be used during the Pandemic Alert Period in limited attempts to contain small disease clusters and potentially slow the spread of novel influenza viruses. A huge and uncoordinated demand for antivirals early in a pandemic could rapidly deplete national and local supplies. Preparedness planning for optimal use of antiviral stocks is therefore essential.

S7-II. OVERVIEW

Supplement 7 provides recommendations to state and local partners on the distribution and use of antiviral drugs for treatment and prophylaxis during an influenza pandemic. The Interpandemic and Pandemic Alert Period recommendations focus on preparedness planning for the rapid distribution and use of antiviral drugs (e.g., procurement, distribution to priority groups, legal preparedness, training, and data collection on use, effectiveness, safety, and the development of drug resistance). These recommendations also cover the use of antiviral drugs in the management and containment of cases and clusters of infection with novel strains of influenza, including avian influenza A (H5N1) and human strains with pandemic potential.

The Pandemic Period recommendations focus on the local use of antiviral drugs in three situations: 1) when pandemic influenza is sporadically reported in the United States (without evidence of spread in the United States), 2) when there is limited transmission of pandemic influenza in the United States, and 3) when there is widespread transmission in the United States. National recommendations for optimal use of limited stocks of antivirals will be updated throughout the course of an influenza pandemic to reflect new epidemiologic and laboratory data. Interim recommendations will also be updated as an effective influenza vaccine becomes available.

The activities described below are primarily the responsibility of government health authorities at the state, federal, and local levels. Additional issues that may be of interest to healthcare partners who administer antiviral drugs are outlined in **Supplement 3**.

S7-III. RECOMMENDATIONS FOR THE INTERPANDEMIC AND PANDEMIC ALERT PERIODS

A. Use of antivirals in management of cases of novel influenza

Influenza infections may be due to:

1) Interpandemic (i.e., 'normal') seasonal strains of influenza[1]
2) Novel strains of influenza that do not appear to be easily transmissible but could be precursors to human pandemic strains (e.g., avian influenza A [H5N1] viruses)
3) Novel strains of influenza that demonstrate person-to-person transmission and therefore have pandemic potential (e.g., a new human pandemic strain)

In this document the term "novel strains of influenza" is used to refer to avian or animal influenza strains that can infect humans (like avian influenza A [H5N1]) and new or re-emergent human influenza viruses that cause cases or clusters of human disease. Criteria for early detection and identification of novel strains of influenza are discussed in **Supplement 1**.

1. Use of antivirals for treatment

A patient with a suspected case of avian influenza A (H5N1) or another novel strain of influenza should be isolated as described in **Supplement 4** and treated in accordance with the clinical algorithm for the Pandemic Alert Period provided in **Supplement 5**. As of fall 2005, the recommendation for treatment includes the use of oseltamivir or zanamivir, administered as early as possible and ideally within 48 hours after onset of symptoms. These neuraminidase inhibitors are preferred because the majority of avian influenza A (H5N1) viruses currently affecting humans are resistant to amantadine and rimantadine, and resistance to these drugs typically develops rapidly when they are used for treatment of influenza. Although resistance to

[1] Information on seasonal outbreaks of interpandemic influenza, including public health measures to contain outbreaks, can be found at http://www.cdc.gov/flu/.

zanamivir and oseltamivir can be induced in influenza A and B viruses *in vitro*, multiple passages in cell culture are usually required to produce neuraminidase inhibitor resistance, in contrast with adamantane resistance, which can develop after a single passage.[2,3] Because the neuraminidase inhibitors have different binding sites for the enzyme, cross-resistance between zanamivir- and oseltamivir-resistant viruses is variable. Current U.S. recommended doses for antiviral treatment are provided in Table 2.

2. Use of antivirals for prophylaxis of contacts

State and local health departments, in consultation with CDC, will consider whether it is necessary and feasible to trace a patient's close contacts and provide them with postexposure antiviral prophylaxis.

Close contacts may include family, schoolmates, workmates, healthcare providers, and fellow passengers if the patient has been traveling. If deemed necessary by public health authorities, these persons may receive post-exposure prophylaxis with oseltamivir, as zanamivir is not currently indicated for prophylaxis. If the exposure to the novel influenza virus strain occurs during the regular influenza season, the patient's healthcare contacts (who may also care for persons with seasonal influenza) should be vaccinated against seasonal influenza to reduce the possible risk of co-infection and reassortment of seasonal and novel strains.

3. Use of antivirals for containment of disease clusters

In special circumstances, state and local health departments could consider "targeted antiviral prophylaxis" as a community-based measure for containing small clusters of infection with novel strains of influenza (see **Supplement 8**). This measure could be implemented in small, well-defined settings such as the initial introduction of a virus with pandemic potential into a small community or a military base. However, once a pandemic is underway, such a strategy would not represent an efficient use of limited antiviral supplies.

Because targeted antiviral prophylaxis would require rapid delivery and administration of substantial stocks of antiviral drugs, its feasibility should be evaluated in light of antiviral drug supply and interim recommendations on antiviral drug use during a pandemic (see S7-III.B). Targeted antiviral prophylaxis would involve investigation of disease clusters, administration of antiviral treatment to persons with confirmed or suspected cases of pandemic influenza, and provision of drug prophylaxis to all persons in the affected community. Targeted antiviral prophylaxis would also require intensive case-finding in the affected area as well as effective communication with the affected community.

B. Preparedness planning for use of antivirals during a pandemic

1. National recommendations on use of antivirals during a pandemic

HHS is working with private-sector partners to increase production of antivirals and to procure additional stocks of antivirals for the Strategic National Stockpile (SNS) (http://www.HHS.gov/nvpo/pandemicplan/). Despite these efforts, demand for antivirals during an influenza pandemic is likely to far outstrip supplies available in stockpiles or through usual channels of distribution.

- A list of priority groups for receiving antiviral treatment or prophylaxis and the rationale for prioritization are provided in Part 1 Appendix D. During an actual pandemic, these recommendations could be modified, based on the characteristics of the causative virus (e.g., drug susceptibilities, initial geographic distribution, fatality rate, age-specific morbidity and mortality rates) and the effectiveness of implemented strategies.

2 McKimm-Breschkin JL. Resistance of influenza viruses to neuraminidase inhibitors — a review. Antiviral Res. 2000, 47:1-17.

[3] Tisdale M. Monitoring of viral susceptibility: new challenges with the development of influenza NA inhibitors. Rev Med Virol, 2000, 10:45-55.

2. State-level planning

State and local health departments should work with healthcare partners to develop state-based plans for antiviral need, procurement, distribution, and targeted use. Materials of potential benefit in these efforts include:

- Strategies outlined in Box 1 for optimizing antiviral use in treatment and prophylaxis. These strategies are based on scientific findings summarized in the July 2005 recommendations of the Advisory Committee on Immunization Practices (ACIP). http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf
- Clinical treatment algorithms provided in **Supplement 5**
- Interim recommendations developed by NVAC on priority groups for prophylaxis and treatment (see Part 1, Appendix D)
- Existing plans for emergency distribution of medical supplies (e.g., bioterrorism plans or SARS plans)

State-based planning for antiviral use should include obtaining antiviral drugs from national, state, and local stockpiles, and their distribution to priority groups by healthcare providers; data collection on drug use, drug-related adverse events, and drug resistance; coordination with bordering jurisdictions; legal preparedness; training; and dissemination of public health information.

These planning efforts require coordination and collaboration with healthcare providers who will administer antivirals during a pandemic. Examples of collaborative planning activities include:

- Convening local or state-wide pandemic influenza strategy meetings on the use of antivirals to facilitate local planning and define public- and private-sector roles (e.g., related to rapid administration to priority groups and medical surge capacity)
- Involving the local medical community (critical care, infectious disease, emergency medicine, and other specialties) in refining national guidelines for treatment and prophylaxis and providing information to the media and local populations on the appropriate use of antivirals
- Identifying contacts in tribal authorities and bordering states for coordinating distribution of antivirals (see below)

a) Procurement

Examples of planning steps for state-level procurement of antivirals include:

- Estimating the quantities of antiviral drugs that will be needed for treatment and prophylaxis of priority groups (see below)
- Identifying sources of antiviral drugs (e.g., state stockpiles, private sector, and federal supplies from the SNS). Drug procurement strategies might include:
  - Creating state or local stockpiles
  - Encouraging healthcare facilities to create institutional stockpiles
  - Making arrangements with local private-sector distributors for emergency purchase of antiviral drugs, if available

The establishment of state, local, or institutional stockpiles should take into account the expiration dates of the purchased material. All drugs are marked with an expiration date, based on review of stability data, at the time of manufacture. However, when purchased, the drugs might have been stored for some time in warehouses so that the time to expiration might be shorter than the time from initial manufacture to expiration date. Moreover, one shipment might consist of several batches with different expiration dates. Antivirals maintained in the national stockpile may be tested for potency and dating extended under the FDA shelf life extension program. Currently, state stockpiles are not included in this program.

b) Establishing priority groups

Based on interim recommendations on priority groups for antiviral treatment and prophylaxis (see Part 1, Appendix D), state and local health authorities should determine how certain priority groups (e.g., public safety workers, essential service providers, key decision makers) will be defined in their jurisdictions.

The Department of Defense (DoD) has purchased a supply of antivirals for use during a pandemic. Should the pandemic occur before the stockpile is received, DoD may require a portion of the national stockpile to treat or protect personnel in order to continue current combat operations and to preserve critical components of the military medical system. Should the military stockpile be exhausted and additional antiviral medication required to ensure national defense or continued support to civil authorities, use of antiviral drugs from the national stockpile may also be required.

c) Distributing and dispensing antivirals to priority groups

Planning steps for distribution of antivirals to priority groups might include:

- Estimating the size and needs of priority groups in local jurisdictions, using interim recommendations
- Assessing antiviral stocks available at the state, local, and hospital levels
- Establishing a mechanism to request antivirals from the federal stockpile, if needed (see below)
- Activating pre-existing plans for the transport, receipt, storage, security, tracking, and delivery of:
  - Antiviral stocks for use in treatment to hospitals, clinics, nursing homes, alternative care facilities, and other healthcare institutions. Prompt dispensing to point-of-care locations is crucial, because clinical efficacy for these agents has been demonstrated when treatment begins within 48 hours of the onset of symptoms.
  - Antiviral stocks for use in post-exposure prophylaxis (e.g., for direct contacts of infected patients)
  - Antiviral stocks for use in prophylaxis (e.g., if recommended for healthcare workers, public safety workers, and essential service providers)
- Considering the use of standing orders for treatment of certain priority groups, such as hospitalized patients and healthcare workers
- Developing a communication plan to explain the rationale for establishing these target groups (see also **Supplement 10**)

The decision to deploy federal assets from the SNS during an influenza pandemic will be made by HHS officials, as it would be during any public health emergency. Each state and federal agency with direct patient care responsibilities should designate a representative (e.g., the state epidemiologist or public health director) to make emergency requests for federal assets in the SNS.

Federal supplies of antivirals will be delivered to a site designated by state planners in each state or large city (e.g., state health department; existing SNS receipt, storage, staging site). State SNS coordinators should provide logistical guidance on the receipt and distribution of federal assets to priority groups.

d) Monitoring and data collection

To ensure optimal use of antiviral drugs during an influenza pandemic, state and local health departments and healthcare partners should work with federal officials and collect data on:

- Distribution of state or federal supplies of antiviral drugs
- Occurrence of adverse events following administration of antiviral drugs

State and local departments could also participate in federal efforts to collect data on:

- Effectiveness of treatment and prophylaxis
- Development of drug resistance

(1) Distribution. Allocation and distribution of antiviral drugs from state and local health departments to drug delivery or dispensing sites will be established based on state and local pandemic plans. Health departments should develop strategies to monitor drug distribution and use, assessing whether drugs are being effectively targeted to priority groups and whether distribution is equitable within those groups (e.g., among racial and ethnic minorities and persons of different socioeconomic levels).

(2) Antiviral effectiveness. Studies to evaluate the effectiveness of antiviral drug use during a pandemic will be conducted by federal agencies in collaboration with state and local health departments and other healthcare and academic partners. The effectiveness of antiviral therapy and prophylaxis will be assessed by comparing rates of severe influenza-related illness and death among treated and untreated persons and among persons who did and did not receive prophylaxis. Analyses of antiviral drug effectiveness should take into account characteristics that will vary among individuals and those that may vary over time, such as diagnostic practices, length of time to initiate therapy, and changes in the pandemic virus.

(3) Adverse events. Serious adverse events associated with the use of antiviral drugs for prophylaxis and treatment of influenza should be reported to FDA, using the MedWatch monitoring program. During an influenza pandemic, state and local health departments can assist in this effort by providing protocols and information to healthcare providers and encouraging hospitals to download MedWatch forms (available at http://www.fda.gov/medwatch/) for distribution to patients. Adverse events reported to MedWatch are collated and analyzed by FDA's Adverse Events Reporting System (AERS).

Use of antivirals will be much greater during a pandemic than during a regular influenza season.. To help improve the detection of serious adverse effects (especially rare effects or effects in vulnerable populations), additional efforts to encourage recognition and reporting of adverse events will be needed. These efforts might include:

- Active monitoring for adverse events observed at emergency rooms, through the National Electronic Injury Surveillance System Cooperative Adverse Drug Event project (NEISS-CADE)
- Local campaigns to educate healthcare workers about the recognition and reporting of adverse events
- Distribution of MedWatch forms and descriptions of known adverse events to each end-user who receives antiviral drugs

In addition, CDC, FDA, and AHRQ will explore the use of existing drug-monitoring systems that have access to individual health utilization records that may allow active, population-based surveillance for adverse events following the use of antivirals for treatment or prophylaxis.

(4) Antiviral drug resistance. CDC will work with state and local partners to monitor the development of resistance to antivirals. Because resistance to M2 inhibitors may involve a single base pair change, resistance may develop rapidly if these drugs are used widely. Information about resistance to M2 inhibitors and neuraminidase inhibitors can be found in the July 2005 recommendations of the ACIP http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf .

Global surveillance for neuraminidase resistance during a pandemic will also be conducted by the Neuraminidase Inhibitor Susceptibility Network (NISN). The global NISN was established in 1999 to address public health and regulatory concerns regarding the potential emergence and consequences of drug resistance in influenza viruses following the introduction of the influenza neuraminidase inhibitor (NI) class of antiviral agents. The Network includes representatives of each of the four WHO global influenza reference laboratories and scientists from regions of the world where increasing use of these drugs is anticipated.

CDC will test the drug susceptibilities of viruses isolated from different age groups and geographic groups over the course of the pandemic (see Antiviral Effectiveness above). State and local health departments should encourage clinicians to obtain specimens from patients who develop severe disease while receiving treatment or prophylaxis. State health departments should provide these specimens on a periodic basis, preferably after testing them by RT-PCR, viral culture, or rapid diagnostic testing to confirm the presence of strains of influenza A (see **Supplement 2**).

Surveillance for antiviral resistance may be particularly important during the later stages of the pandemic, especially if M2 agents have been widely used. Under these circumstances, the detection of widespread M2 inhibitor resistance might require a re-evaluation of priorities for prophylaxis and treatment.

e) Coordination with bordering jurisdictions

State and local health departments should review and coordinate antiviral drug distribution plans with health authorities in bordering jurisdictions, including:

- Counties
- States
- Tribal governments and other unique populations

During an influenza pandemic, states should share details regarding their distribution of antivirals with bordering jurisdictions to optimize targeting of antiviral use and clarify, in advance, any apparent inconsistencies in proposed policies.

f) Legal preparedness

State and local health departments should ensure that appropriate legal authorities are in place to facilitate implementation of plans for distributing antivirals. For example, if a state plan includes a provision for the state health commissioner to issue a blanket prescription for dispensing of antivirals, then the state health officer will need the authority and the plan will need to be consistent with state prescription laws. In addition, legal issues may include reviewing worker's compensation laws to determine how they apply to healthcare workers and other essential workers who take antivirals for prophylaxis.

g) Training

State and local health departments should enhance training and education efforts related to use of antiviral drugs during a pandemic. Exercises that involve healthcare providers who will administer antivirals to individual patients are essential to ensure that distribution systems are in place and that roles and responsibilities are well understood. It may be useful, for example, to provide healthcare providers with educational materials and to practice emergency distribution of antiviral drugs to target groups.

h) Public health information

State and local health departments should develop and implement plans to educate the public, the medical community, and other stakeholders about:

- Role of antivirals in responding to pandemic influenza
- Need to prioritize use of limited antiviral supplies for treatment and prophylaxis
- Rationale for the priority groups identified in the interim recommendations
- Importance of appropriate use (i.e., using the drugs as prescribed and for the full number of days recommended) to minimize the development of drug resistance

i) Contingency planning for Investigational New Drug (IND) use

State and local health departments should be prepared to distribute unlicensed antiviral drugs (if needed) under FDA's Investigational New Drug (IND) provisions. IND provisions require strict inventory control and recordkeeping, completion of a signed consent form from each person who receives the medication, and mandatory reporting of specified types of adverse events. IND provisions also require approval of the protocol and consent form by an Institutional Review Board (IRB). The FDA regulations permit the use of a national or "central" IRB. A treatment IND is one IND mechanism that FDA has available for use and is especially suited for large scale use of investigational products. http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr_99.html

As an alternative to IND use of an unapproved antiviral drug, HHS may utilize the drug product under Emergency Use Authorization procedures as described in the FDA draft Guidance "Emergency Use Authorization of Medical Products" http://www.fda.gov/cber/gdlns/emeruse.pdf

S7-IV. Recommendations for the Pandemic Period

Interim recommendations for use of antivirals may be updated throughout the course of an influenza pandemic to reflect current epidemiologic and laboratory data. Interim recommendations may also be updated as an effective influenza vaccine becomes available.

A. When pandemic influenza is reported abroad, or sporadic pandemic influenza cases are reported in the United States, without evidence of spread

If an influenza pandemic has begun in other countries, state and local health departments should:

- Use antiviral drugs in the management of persons infected with novel strains of influenza and their contacts, as described in S7-III.A or its updates.
- Work with healthcare partners to consider providing antiviral prophylaxis to persons at highest risk for pandemic influenza. Examples of such persons include:
  - Public health workers who investigate suspected cases of pandemic influenza
- Meet with local partners and stakeholders to review the state-based antiviral drug distribution plan (see S7-III.B). As part of this effort, state and local partners could:
  - Modify the distribution plan to take into account possible updated recommendations on target groups and updated information on projected supplies of antiviral drugs.
  - Notify the medical community about the status of the plan and the availability of antiviral drugs.
  - Disseminate public health guidelines that encourage drug-use practices that help minimize the development of drug resistance.
  - Provide the public with information on interim recommendations and their rationale for the use of antiviral drugs during an influenza pandemic.
- Work with federal partners to monitor the safety and effectiveness of drugs and ensure that available antivirals are used in accordance with federal and local recommendations.

B. When there is limited transmission of pandemic influenza in the United States

When there is limited transmission of pandemic influenza in the United States, state and local health departments should:

- Activate state-based plans for targeting antiviral drugs to priority groups for prophylaxis and treatment (see S7-III.B).

- Request antiviral drugs, as needed, from previously identified sources (see S7-III.B), including the SNS.
- Continue to work with healthcare partners to ensure appropriate use of antivirals in the medical management of early cases and contacts (see S7-IV.A).
- Assist hospitals in implementing procedures for early detection and treatment of influenza in healthcare workers (see **Supplement 3**).
- Work with federal partners to begin monitoring the safety and effectiveness of drugs and ensure that available antivirals are used in accordance with federal and local recommendations.

C. When there is widespread transmission of pandemic influenza in the United States

When transmission of pandemic influenza has become widespread, the paramount goals of antiviral use will be to treat those at highest risk of severe illness and death and to preserve the delivery of healthcare and other essential critical services through early treatment and limited prophylaxis.

After a vaccine becomes available, antiviral drugs may be used to protect persons who have an inadequate vaccine response (e.g., the elderly and those with underlying immunosuppressive disease) as well as persons with contraindications to vaccination, such as anaphylactic hypersensitivity to eggs or other vaccine components.

Until the pandemic has waned, state and local health departments should continue to work with healthcare and federal partners to monitor the safety and effectiveness of antivirals and to encourage appropriate drug use practices that help minimize the development of drug resistance.

BOX 1. STRATEGIES FOR ANTIVIRAL USE IN PANDEMIC INFLUENZA TREATMENT AND PROPHYLAXIS

The goals of vaccine and antiviral use during an influenza pandemic are to limit mortality and morbidity, minimize social disruption, and reduce economic impact. Because a pandemic vaccine is unlikely to be available during the first 4 to 6 months of the pandemic, appropriate use of antivirals may play an important role in achieving these goals.

A. Treatment

1. Planning considerations

- The effectiveness of antivirals against a new pandemic influenza virus cannot be predicted.
- Pooled analyses of clinical trials of neuraminidase inhibitors administered to outpatients with seasonal influenza suggest that early treatment may reduce the risk of hospitalization by ~50%. There are no data on the effectiveness of neuraminidase inhibitors in preventing either serious morbidity (e.g., requirement for intensive care) or mortality (see July 2005 recommendations of the AHIC (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf).
- Antiviral agents used against seasonal influenza have demonstrated efficacy in clinical trials when treatment is initiated within 48 hours of the onset of symptoms. Assuming that they have a similar level of effectiveness against pandemic influenza, rapid diagnosis, distribution and administration of antivirals during a pandemic will be essential.
- Early treatment is a more efficient use of antivirals than widespread prophylaxis. Because prophylaxis for approximately 6 weeks would require at least four times the number of doses as a 5-day treatment course per individual, huge antiviral stockpiles would be required to permit prophylaxis of more than a small proportion of the U.S. population.
- Most influenza A(H5N1) viruses currently in circulation in southeast Asia are resistant to the M2 ion channel inhibitors (amantadine and rimantadine), and strains that may evolve from these viruses may become resistant to this class of antivirals.

The emergence of drug resistant strains is less likely during treatment with neuraminidase inhibitors (oseltamivir and zanamivir) than with M2 inhibitors (amantadine and rimantadine). Neuraminidase inhibitors may also have a lower incidence of severe side effects (see July 2005 recommendations of the AHIC (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf). Oseltamivir and zanamivir should therefore be reserved for treatment whenever possible. Because supplies of oseltamivir and zanamivir are currently depleted, early depletion of oseltamivir and widespread use of M2 inhibitors could lead to increased rates of side effects and drug resistance.

2. Strategies for treatment

Treatment strategies for optimizing the use of limited stocks of antiviral drugs will vary depending on the phase of the pandemic. The following interim guidance will be updated as more information becomes available. Strategies for consideration include:

At all stages of a pandemic:

- Targeting therapy to influenza patients admitted to a hospital who present within 48 hours of symptom onset.
- Implementing mechanisms to detect the emergence of drug-resistant variants of a pandemic influenza strain (e.g., obtaining specimens from persons who develop influenza while on prophylaxis or who progress to severe disease despite treatment).

BOX 1. STRATEGIES FOR ANTIVIRAL USE IN PANDEMIC INFLUENZA TREATMENT AND PROPHYLAXIS (CONT.)

During the earliest stages of a pandemic in the United States:

- Basing treatment decisions on laboratory-confirmed subtype identification of the pandemic strain by viral isolation, RT-PCR, or other means recommended by CDC. A positive rapid antigen test for influenza A would be sufficient grounds for initiating treatment, with a confirmatory, definitive laboratory test required for continuation of treatment.
- Interpreting negative results of influenza testing as permitting termination of treatment, given the overall low rate of infection in a particular community.
- Considering targeted use of antivirals to contain small, well-defined disease clusters, to possibly delay or reduce spread to other communities (see also Part C [below] and Supplement 8).

When there is increasing disease activity in the United States:

- Basing treatment decisions on:
  - Laboratory-confirmed identification of the pandemic subtype by viral isolation and subtyping, RT-PCR, or other means recommended by CDC, *or*
  - Detection of influenza A by rapid antigen test, *or*
  - Epidemiologic and clinical characteristics.
- Permitting initiation of antiviral treatment before results from viral isolation, IFA, RT-PCR assays, or rapid antigen tests become available, since early treatment is more likely to be effective.

Once infection becomes more common, negative rapid antigen test results are more likely to represent false negatives; therefore, treatment should continue while awaiting results from confirmatory testing.

When the pandemic is widespread in the United States:

- Basing treatment decisions on clinical features and epidemiologic risk factors, taking into account updated knowledge of the epidemiology of the pandemic virus.

As the pandemic progresses, strategies for antiviral treatment may be revised as new information is obtained about the pandemic strain.

B. Prophylaxis

1. Planning considerations for prophylaxis

- Primary constraints on the use of antivirals for prophylaxis will be:
  - Limited supplies
  - Increasing risk of side effects with prolonged use
  - Potential emergence of drug-resistant variants of the pandemic strain, particularly with long-term use of M2 inhibitors
- The need for antiviral prophylaxis may decrease once an effective pandemic influenza vaccine becomes available for use among healthcare workers and other groups receiving prophylactic antivirals.

BOX 1. STRATEGIES FOR ANTIVIRAL USE IN PANDEMIC INFLUENZA TREATMENT AND PROPHYLAXIS (CONT.)

- Post-exposure prophylaxis might be useful in attempts to control small, well-defined disease clusters (e.g., outbreaks in long-term care facilities [see section C below]). A study of post-exposure prophylaxis using amantadine—conducted during the 1968 pandemic—demonstrated little effectiveness, possibly due to rapid development of resistance (see July 2005 recommendations of the AHIC (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf).
- Oseltamivir has demonstrated >70% efficacy as prophylaxis against laboratory-confirmed febrile influenza illness during interpandemic periods in unimmunized adults (see July 2005 recommendations of the AHIC (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf).
- Prophylaxis with amantadine or rimandatine decreased the risk of influenza illness during the 1968 pandemic and the 1977 reappearance of H1N1 viruses (see July 2005 recommendations of the AHIC (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf).
- The number of persons who receive prophylaxis with oseltamivir should be minimized, primarily to extend supplies available to treat persons at highest risk of serious morbidity and mortality. If sufficient antiviral supplies are available, prophylaxis should be used only during peak periods of viral circulation to protect small groups of front-line healthcare workers and other providers of essential community services prior to availability of vaccine.
- If a pandemic virus is susceptible to M2 ion channel inhibitors, amantadine and rimantadine should be reserved for prophylaxis, although drug resistance may emerge quickly.
- Rimantadine is preferred over amantadine, because it is associated with a lower incidence of serious side effects (see July 2005 recommendations of the AHIC (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf). Strains that are resistant to one M2-class antiviral are likely resistant to the other.

2. Strategies for prophylaxis

Strategies for effective use of antiviral prophylaxis during a pandemic include:

- Targeting prophylaxis to priority groups (see Part 1, Appendix D for interim recommendations) throughout the first wave of the pandemic. Data from 20th century influenza pandemics suggest that the first wave of these pandemics lasted approximately 4 to 8 weeks in a community.
- Using post-exposure prophylaxis (generally for 10 days) to:
  - Control small, well-defined disease clusters, such as outbreaks in nursing homes or other institutions, to delay or reduce transmission to other communities (see part C above).
  - Protect individuals with a known recent exposure to a pandemic virus (e.g., household contacts of pandemic influenza patients).

When a vaccine becomes available, post-exposure prophylaxis may also be used to protect key personnel during the period between vaccination and the development of immunity.

Strategies for antiviral prophylaxis may be revised as the pandemic progresses, depending on supplies, on what is learned about the pandemic strain and on when a vaccine becomes available.

BOX 1. STRATEGIES FOR ANTIVIRAL USE IN PANDEMIC INFLUENZA TREATMENT AND PROPHYLAXIS (CONT.)

C. Strategies for Combined Treatment and Prophylaxis

During the Pandemic Alert Period, combined antiviral treatment for ill persons and targeted post-exposure prophylaxis of contacts might be considered in attempts to contain small disease clusters (e.g., institutional outbreaks or household introductions). The potential use of targeted prophylaxis to contain disease clusters is considered in **Supplement 8**.

The administration of oseltamivir does not interfere with the development of antibodies to influenza viruses after administration of trivalent inactivated influenza vaccine. Therefore, persons receiving prophylaxis can continue to receive oseltamivir during the period between vaccination and the development of immunity. Whether oseltamivir can interfere with the immune response elicited by a live-attenuated pandemic vaccine is unknown.

D. Pediatric Use

None of the available influenza antivirals are currently FDA approved for use among children aged <1 year. In particular, the safety and efficacy of oseltamivir have not been studied in children aged <1 year for either treatment or prophylaxis of influenza (see oseltamivir package insert). The decision by an individual physician to treat children aged <1 year in an emergency setting on an off-label basis with an antiviral must be made on a case-by-case basis with full consideration of the potential risks and benefits. Additional human data on the safety of these agents in the treatment of influenza in young children are needed.

Oseltamivir is available as an oral suspension for use in children. This formulation of oseltamivir may not be available in sufficient supply during a pandemic to treat all pediatric patients. If physicians consider opening 75 mg oseltamivir capsules and using the contents in an attempt to deliver a partial, pediatric dose to children, it must be recognized that there are insufficient data on palatability, stability, and dosing consistency to predict the safety or effectiveness of such unapproved use. Additional study of these issues is needed.

BOX 2. FEDERAL SUPPLIES OF ANTIVIRAL DRUGS IN THE STRATEGIC NATIONAL STOCKPILE

During an influenza pandemic, a decision to deploy federal assets from the Strategic National Stockpile (SNS) will be made by HHS. As of October 2005, the SNS (http://www.bt.cdc.gov/stockpile/) contained 2.26 million treatment regimens of oseltamivir (capsules and suspension), 5 million treatment regimens of rimantadine (tablets and syrup), and 84,000 treatment regimens of zanamivir. Two million additional oseltamivir courses will be delivered to the SNS by November 2005 and additional purchases of antivirals are pending.

The details of the HHS approach for allocation and distribution of SNS assets during an influenza pandemic are currently under consideration. State and local health departments and federal agencies with direct patient care responsibilities should begin to:

- Develop plans to allot antivirals to healthcare facilities, assuming that distribution of limited supplies of antivirals will initially be targeted to patients hospitalized with pandemic influenza and for treatment or prophylaxis of essential healthcare workers.
- Consider the use of standing orders for the prescription of antivirals, particularly for use in healthcare workers.
- Consider the use of occupational health clinics in hospitals and other healthcare organizations for delivery of antivirals to healthcare workers.

It is not recommended that individuals, fearing a pandemic, stockpile oseltamivir in homes or that healthcare providers prescribe oseltamivir to individuals for prophylaxis against pandemic influenza. At the present time, quantities are insufficient to address all of the interim pre-determined groups, and thus stockpiling oseltamivir will take away limited resources from those with highest priority.

TABLE 1. CHARACTERISTICS OF ANTI-INFLUENZA ANTIVIRAL DRUGS

	Inhibits	Acts on	Administration	Common Side Effects
Amantadine	M2 ion channel	Influenza A	Oral	CNS, GI
Rimantadine	M2 ion channel	Influenza A	Oral	CNS, GI (less often than amantadine)
Oseltamivir	Neuraminidase	Influenza A and B	Oral	GI
Zanamivir	Neuraminidase	Influenza A and B	Inhaler	Bronchospasm

These agents differ in mechanisms of action, pharmokinetics, FDA-approved indications, dosages, cost, and potential for emergence of drug resistance (see July 2005 recommendations of the AHIC (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf).

The neuraminidase inhibitors and rimantadine are superior to amantadine with regard to the frequency of serious side effects.

The use of M2 inhibitors, particularly for treatment, is likely to lead to the emergence and spread of drug-resistant influenza viruses.

TABLE 2. RECOMMENDED DAILY DOSAGE OF ANTIVIRALS FOR TREATMENT AND PROPHYLAXIS

(From *Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices [ACIP], July 2005*)

Antiviral Agent	Age Groups (years) 1–6	7–9	10–12	13–64	≥65
Amantadine[a]					
Treatment, influenza A	5mg/kg body weight/day up to 150 mg in two divided doses[b]	5mg/kg body weight /day up to 150 mg in two divided doses[b]	100 mg twice daily[c]	100 mg twice daily[c]	≤100 mg/day
Prophylaxis, influenza A	5mg/kg body weight /day up to 150 mg in two divided doses[b]	5mg/kg body weight /day up to 150 mg in two divided doses[b]	100 mg twice daily[c]	100 mg twice daily[c]	≤100 mg/day
Rimantadine[d]					
Treatment,[e] influenza A	NA[f]	NA	NA	100 mg twice daily[c,g]	100 mg/day
Prophylaxis, influenza A	5m/kg body weight /day up to 150 mg in two divided doses[b]	5mg/kg body weight /day up to 150 mg in two divided doses[b]	100 mg twice daily[c]	100 mg twice daily[c]	100 mg/day[h]
Zanamivir[i,j]					
Treatment, influenza A and B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment,[k] influenza A and B	dose varies by child's weight[l]	dose varies by child's weight[l]	dose varies by child's weight[l]	75 mg twice daily	75 mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75 mg/day	75 mg/day

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel (R)–tablet and syrup) and Geneva Pharms Tech (Amantadine HCL–capsule); USL Pharma (Amantadine HCL–capsule and tablet); and Alpharma, Carolina Medical, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL–syrup), and Sandoz. Rimantadine is manufactured by Forest Laboratories (Flumadine (R)–tablet and syrup); Corepharma , Impax Labs (Rimantadine HCL–tablet), and Amide Pharmaceuticals (Rimantadine HCL–tablet). Zanamivir is manufactured by GlaxoSmithKline (Relenza (R)–inhaled powder). Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu (R)–tablet). Information based on data published by the U.S. Food and Drug Administration at www.fda.gov, accessed 3/30/2005.

[a] The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 ml/min/1.73m2 .

[b] 5 mg/kg body weight of amantadine or rimantadine syrup = 1 tsp/2.2 lbs.

[c] Children aged ≥10 years who weigh <40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg body weight /day.

[d] A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

[e] Approved by FDA only for treatment among adults.

[f] Not applicable.

[g] Rimantadine is approved by FDA for treatment among adults. However, certain experts in the management of influenza consider it appropriate for treatment among children. (See American Academy of Pediatrics, 2003 Red Book.)

[h] Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years if they experience possible side effects when taking 200 mg/day.

[i] Zanamivir administered via inhalation using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device.

[j] Zanamivir is not approved for prophylaxis.

[k] A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 ml/min.

[l] The dose recommendation for children who weigh ≤15 kg is 30 mg twice a day. For children who weigh >15 to 23 kg, the dose is 45 mg twice a day. For children who weigh >23 to 40 kg, the dose is 60 mg twice a day. And for children who weigh >40 kg, the dose is 75 mg twice a day.