

Annex 7. Part 1. Use of Antivirals

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Rationale:

Drugs with activity against influenza viruses (“antivirals”) include the adamantanes *amantadine* and *rimantadine* and the neuraminidase inhibitors *oseltamivir* and *zanamivir* (see Appendix B and Appendix D Table 1). 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 Maine 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.

Planning Assumptions:

1. 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.
2. Influenza infections may be due to:
 - a. Interpandemic (i.e., ‘normal’) seasonal strains of influenza
 - b. 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)
 - c. Novel strains of influenza that demonstrate person-to-person transmission and therefore have pandemic potential (e.g., a new human pandemic strain)
3. 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.
4. Interim recommendations will also be updated as an effective influenza vaccine becomes available.
5. The Maine CDC will assess the antiviral guidance released by federal partners on an ongoing basis during a pandemic and will align state guidelines accordingly.
6. Treatment with a neuraminidase inhibitor will decrease hospitalization by about half and will also decrease mortality
7. Antiviral resistance to the adamantanes may limit their use during a pandemic.
8. Treating early after the onset of disease is most effective in decreasing the risk of complications and shortening illness duration. Treatment should begin within the first 48 hours. Initiation of antiviral treatment for priority groups may be restricted to persons who are within 48 hours of disease onset.
9. For antiviral drugs, the number of priority groups that can be covered should be known at the start of the pandemic based on the amount of drug that is stockpiled.

Overview:

Part 1. of Annex 7 provides recommendations on 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 use of antiviral drugs (e.g., defining priority groups, data collection for monitoring 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. 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. (See Appendix A: Strategies for Antiviral Use in Pandemic Influenza Treatment and Prophylaxis)

A. Use of Antivirals for Management of Novel Influenza

1. Treatment

A patient with a suspected case of avian influenza A (H5N1) or another novel strain of influenza should be isolated as described in **Annex 4** and treated in accordance with the clinical algorithm for the Pandemic Alert Period provided in **Annex 5**. 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 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 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. 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 Appendix D, Table 2. Recommendations for the selection of antiviral treatment using laboratory test results and viral surveillance data are provided in Appendix D, Table 4.

2. Prophylaxis of Contacts

Maine CDC, in consultation with federal 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 and the treating clinician, 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. Current U.S. recommended doses for antiviral prophylaxis are provided in Appendix D, Table 2. Recommendations for the selection of antiviral treatment using laboratory test results and viral surveillance data are provided in Appendix D, Table 4.

3. Containment of Clusters and Outbreaks

Maine CDC will consider “targeted antiviral prophylaxis” as a community-based measure for containing small clusters of infection with novel strains of influenza (see Annex 8). This measure could be implemented in small, well-defined settings such as the initial introduction of a virus with pandemic potential into a healthcare facility, residential facility, or a military base. However, once a pandemic is underway, such a strategy would not represent an efficient use of limited antiviral supplies.

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 setting. Targeted antiviral prophylaxis would also require intensive case-finding in the affected area as well as effective communication.

4. Use of Antivirals in those with contraindications to vaccine or or inadequate vaccine response

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.

B. Preparedness planning for use of antivirals during a pandemic

1. 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 Appendix B. Table 1)
- 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.

2. Establishing priority groups

Based on interim recommendations on priority groups for antiviral treatment and prophylaxis (Appendix B), Maine CDC will determine how certain priority groups (e.g., public safety workers, essential service providers, key decision makers) will be defined in their jurisdictions (Appendix C).

During an actual pandemic, these recommendations will be modified by Maine CDC 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.

Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged <1 year when indicated. (Table 5 Appendix D)

3. 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
- 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 Annex 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. ME CDC will designate a representative (e.g., the state epidemiologist or the PHEP 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 (e.g., state health department; existing SNS receipt, storage, staging site). The state SNS coordinator will provide logistical guidance on the receipt and distribution of federal assets to priority groups. (**See Annex 7, Part II Antiviral Distribution**)

4. Monitoring and data collection

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

- Distribution of state or federal supplies of antiviral drug
- Occurrence of adverse events following administration of antiviral drugs
- Effectiveness of treatment and prophylaxis
- Development of antiviral drug resistance

5. Legal preparedness

ME CDC will ensure that appropriate legal authorities are in place to facilitate implementation of plans for distributing antivirals.

6. Training

ME CDC will facilitate training opportunities with state and local stakeholders to ensure that distributions systems are in place and roles and responsibilities are well understood.

7. Public Health Communications

Maine CDC will develop information 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

8. Contingency planning for Investigational New Drug (IND) use

ME CDC will distribute unlicensed antiviral drugs (if needed) under FDA's Investigational New Drug (IND) provisions. It is understood that IND provisions require strict inventory control and recordkeeping, completion of assigned 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>

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Maine Inter-Pandemic Period

Mitigation and Preparedness

ME Level 0, I, II

1. Maintain a current state plan to include: define anticipated antiviral need, method of procurement, transport, receipt, storage, security, tracking and distribution, and define (current) targeted use
2. Develop information to education the public, the medical community and other stakeholders re: the role of antivirals in responding to pandemic influenza, the need to prioritize use of limited antiviral supplies, the rationale for the priority groups identified, and the importance of appropriate use to minimize the development of drug resistance.
3. Develop and maintain a list of priority groups for receiving antiviral treatment or prophylaxis and the rationale for prioritization
4. Develop standing orders for treatment of certain priority groups
5. Estimate the quantities of antiviral drugs needed for treatment and prophylaxis of priority groups
6. Identify sources of antiviral drugs
7. Designate a state official that is authorized to make emergency requests for federal assets in the SNS
8. Create a state stockpile; encourage healthcare facilities to create institutional stockpiles
9. Manage state antiviral stockpile/inventory re: expiration dates
10. Create agreements with suppliers for emergency purchase of antivirals
11. Identify storage, staging and ship-to sites
12. Develop plan for data collection and reporting
13. Seek clarification on any remaining legal issues
14. Coordinate planning and exercising of plans with community partners to clarify role and responsibilities

Maine Pandemic Alert Period

Heightened Preparedness: On Standby

ME Levels III, IV

1. Review and update antiviral distribution and use plans
2. Update internal and external contact information

3. Alert partners of “standby” status
4. Update priority group list as indicated
5. Obtain latest treatment and prophylaxis guidelines and inform medical partners of any changes\
 - a. Consider providing antiviral prophylaxis to persons at highest risk for pandemic influenza
 - b. Disseminate guidelines that encourage drug-use practices that help to minimize the development of drug resistance
6. Assess antiviral stocks, and place emergency order for additional antivirals as needed
7. Prepare to collect and report data on antiviral distribution, effectiveness, adverse events, and drug resistance as requested
8. Communicate and coordinate with federal, state and local partners
9. Provide information to the public, the medical community and other stakeholders as appropriate

Maine Pandemic Period

Activate Response Plan ME Levels V, IV

1. Activate state plans for distributing and administering antivirals to persons in currently identified priority groups
2. Obtain updated national guidelines for appropriate use of antivirals and updates as they become available
3. Make modifications, if any, to interim recommendations on antiviral prophylaxis in selected groups or circumstances
4. Provide just-in-time training on appropriate use of antiviral drugs among public health staff and health care partners as needed
5. Work with other governmental agencies and non-government organizations to ensure effective public health communications
6. Request antiviral drugs, as needed from previously identified sources including the SNS as it becomes available
7. Activate plans to distribute and deliver supplies of antivirals, as appropriate, to healthcare facilities that will administer them to appropriate groups
8. Activate plan for dispensing for treatment in hospitals, for use in post-exposure prophylaxis and for prophylaxis
9. Work with healthcare providers to ensure appropriate use of antivirals
10. Work with HHS to monitor antiviral drug use and effectiveness and the emergence of antiviral resistance;
11. Work with HHS to monitor and investigate adverse events
12. Provide reports to HHS as requested
13. Provide updated information to the public via the news media
14. Treat with oseltamivir or zanamivir, administered as early as possible and ideally within 48 hours after onset of symptoms
15. Determine whether it is necessary and feasible to trace a patient’s close contacts and provide them with post-exposure antivirals prophylaxis
16. Consider “targeted antiviral prophylaxis” as a community-based measure for containing small clusters of infection with novel

strains of influenza. This involves 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 people in the affected area. (Not an efficient strategy once a pandemic is underway.)

17. Once the pandemic is widespread, antivirals will be used to treat those at highest risk of severe illness and death and to preserve the delivery of healthcare and other critical services.
18. Once a vaccine is available, antivirals will be used to protect persons who have an inadequate vaccine response, or persons with contraindications to vaccination.
19. Continue to provide information to the public, the medical community and other stakeholders.

Maine Post Pandemic Recovery

Recovery Activities ME Levels VII

1. Return to Maine Interpandemic Period activities
2. Provide feedback to and receive feedback from partners and stakeholders
3. Confer with providers regarding effectiveness and timeliness of antiviral treatment and prophylaxis guidelines
4. Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary
5. Restock antiviral stockpile
6. Reaffirm MOUs and MAAs
7. Provide reports to HHS as requested
8. Identify Lessons Learned
9. Participate in the After Action Report and Improvement Plan with corrective actions
10. Revise Antiviral Use and Distribution Plans as indicated

Annex 7. Part 1. Use of Antivirals Summary Matrix

Service / Function: Use of Antivirals	Maine Inter-Pandemic Period: Awareness Mitigation/ Preparedness ME Level 0, I, II	Maine Pandemic Alert Period: Standby Heightened Preparedness ME Levels III, IV	Maine Pandemic Period: Activate Response Plan Response ME Levels V, VI	Maine Post Pandemic Recovery Period Recovery ME Level VII
Treatment	The recommended treatment includes the use of oseltamivir or zanamivir, administered as early as possible and ideally within 48 hours after onset of symptoms. Current U.S. recommended doses for antiviral treatment are provided in Table 2 →	Make changes to the recommendations as indicated; Prepare for implementation →	When the pandemic is widespread, the goal of antiviral use will be to treat those at highest risk of severe illness and death	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners
Prophylaxis	If deemed necessary by public health authorities and the treating clinician, the patient's close contacts may receive post-exposure prophylaxis with oseltamivir, as zanamivir is not currently indicated for prophylaxis. →	Make changes to the recommendations as indicated; Prepare for implementation →	After a vaccine becomes available, antivirals may be used to protect persons who have an inadequate vaccine response as well as persons with contraindications to vaccination	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners
Containment of Clusters and Outbreaks	Targeted antiviral prophylaxis would	Make changes to the recommendations as	Implement early in the pandemic.	Return to Maine Interpandemic Period

	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 setting. (This strategy is only useful early in the pandemic)→	indicated; Prepare for implementation →		activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners
Establishing Priority Groups	Maine CDC will determine how certain priority groups (e.g., public safety workers, essential service providers, key decision makers) will be defined in their jurisdictions for antiviral treatment and prophylaxis. →	Alter priority groups as indicated by the data on the circulating novel virus and the effectiveness of implemented strategies.	Implement plan according to most recommended priority groups	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners
Procurement	Estimate the quantities of antiviral drugs needed; Identify sources of antiviral drugs; Create a state stockpile; Encourage other HC facilities to stockpile; Establish mechanism to	Assess antiviral stockpile; Obtain antivirals from SNS as it becomes available; Place emergency order of antivirals with supplier as indicated →	Ongoing procurement as needed and as available →	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary;

	request antivirals from SNS; Develop MOU for emergency purchase of antivirals; Manage antiviral inventory			Restock antiviral stockpile; Provide feedback to partners
Distributing and Dispensing (See Annex 7 Part II for additional details)	Identify state official who will request SNS assets; Coordinate with partners and stakeholders to develop plan for distribution and dispensing of antivirals including transport, receipt, storage, security, tracking and delivery of antivirals; Consider/prepare standing orders for treatment of certain priority groups; Communicate, plan and exercise with partners	Review plan, modify as needed; Complete final preparations in anticipation of plan activation; Alert partners and stakeholders of pending activation;	Designated state official will request SNS assets once they become available through HHS; Activate plan for distribution and dispensing of antivirals; Coordinate with partners; Dispense: for treatment in hospitals, for use in post-exposure prophylaxis, and for prophylaxis	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners; Reaffirm MOUs and MAAs
Antiviral Effectiveness: data	Maine CDC will prepare to participate with federal, state, and local partners in collecting information to evaluate	Prepare for data collection →	Begin data collection and reporting →	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and

	antiviral effectiveness; Report data →			feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners; Report data
Adverse Events: data	Maine CDC will prepare to participate with federal, state, and local partners in collecting information to monitor for adverse events →	Prepare for data collection →	Begin data collection and reporting →	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners; Report data
Antiviral Drug Resistance: data (see Antiviral Stewardship)	Maine CDC will prepare to participate with federal, state, and local partners in collecting information to monitor for antiviral drug resistance →	Prepare for data collection →	Begin data collection and reporting →	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners; Report data
Public Health Communications	Maine CDC will develop and disseminate	Updated information →	Updated information →	Updated information; Return to Maine

	information to educate the public, the medical community, and other stakeholders re: the role of antivirals in responding to pandemic influenza, the need to prioritize use of limited antiviral supplies, the rationale for the priority groups identified, and the importance of appropriate use to minimize the development of drug resistance			Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners
Investigational New Drug Use	Maine CDC will prepare to distribute unlicensed antiviral drugs (if needed) under FDA's Investigational New Drug (IND) provisions.	Final preparation as indicated →	Maine CDC will distribute unlicensed antiviral drugs (if needed) under FDA's Investigational New Drug (IND) provisions.	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners; Report data
Directing Antivirals to Priority Groups	Develop plan in collaboration with healthcare partners for providing antivirals to priority groups	Work with healthcare partners to consider providing antiviral prophylaxis to priority groups including persons	Direct treatment and prophylaxis to those at highest risk of severe illness and death, and to preserve the delivery of	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and

		at highest risk for pandemic influenza. (e.g. public health workers who investigate suspected cases of pandemic influenza)	healthcare and other essential critical services through early treatment and limited prophylaxis.	feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners
Antiviral Stewardship	Prepare public health guidelines that educate on proper drug-use practices to minimize the development of drug resistance.	Disseminate public health guidelines that encourage drug-use practices that help minimize the development of drug resistance.	Ensure that available antivirals are used in accordance with federal and local recommendations.	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners
Use of Antivirals in those with contraindications to vaccine or inadequate vaccine response			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.	Return to Maine Interpandemic Period activities; Re-evaluate effectiveness and feasibility of antiviral guidelines and update/modify as necessary; Provide feedback to partners

Appendix A

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 (January 2011 recommendations of the ACIP

(<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>). Oseltamivir and zanamivir should therefore be reserved for treatment whenever possible. 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

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).

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 Part C [below] and **Annex 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.
- 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 ACIP (<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 ACIP (<http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf>)).
- Prophylaxis with amantadine or rimantadine decreased the risk of influenza illness during the 1968 pandemic and the 1977 reappearance of H1N1 viruses (see July 2005 recommendations of the ACIP (<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 January 2011 recommendations of the ACIP). (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>). 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 Appendix B 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 below).
 - 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.

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 prophylaxis to contain disease clusters is considered in **Annex 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.

Appendix B

NVAC RECOMMENDATIONS ON PANDEMIC ANTIVIRAL DRUG USE

A. Critical assumptions

Assumptions regarding groups at highest risk during a pandemic and impacts on the healthcare system and other critical infrastructures are the same as those underlying the vaccine priority recommendations. Additional assumptions specific for antiviral drugs included:

- Treatment with a neuraminidase inhibitor (oseltamivir [Tamiflu®] or zanamivir [Relenza®]) will be effective in decreasing risk of pneumonia, will decrease hospitalization by about half (as shown for inter-pandemic influenza), and will also decrease mortality.
- Antiviral resistance to the adamantanes (amantadine and rimantadine) may limit their use during a pandemic.
- The primary source of antiviral drugs for a pandemic response will be the supply of antiviral drugs that have been stockpiled. Before annual influenza seasons about 2 million treatment courses of oseltamivir are available in the U.S. U.S.-based production of oseltamivir is being established; expected capacity is projected at about 1.25 million courses per month.
- Treating earlier after the onset of disease is most effective in decreasing the risk of complications and shortening illness duration. Generally, treatment should be given within the first 48 hours.
- Assumptions for the amount of antiviral drug needed for defined priority groups is based on the population in those groups and assumptions that 35% of persons in the priority groups will have influenza-like illness and 75% will present within the first 48 hours and be eligible for treatment. For persons admitted to the hospital, it is assumed that 80% would be treated, as the 48-hour limit may sometimes be relaxed in more ill patients.
- Unlike vaccines, where each tier would be protected in turn as more vaccine is produced, for antiviral drugs, the number of priority groups that can be covered would be known at the start of the pandemic based on the amount of drug that is stockpiled. Additional supply that would become available during the pandemic could provide some flexibility.

Table B-1: Maine Antiviral Drug Priority Groups Recommendations

Group	*Tx Strategy	Courses	Rationale
Patients admitted to hospital**	T	33,225	Consistent with medical practice and ethics to treat those with serious illness and who are most likely to die
Health care workers (HCW) with direct patient contact and emergency medical service (EMS) providers	T	10,632	Healthcare workers are required for Quality medical care. There is little surge capacity among healthcare sector personnel to meet increased demand.
Highest risk outpatients—immunocompromised persons and pregnant women	T	3,101	Groups at greatest risk of hospitalization and death; immunocompromised cannot be protected by vaccination.
Pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire, corrections), and government decision-makers	T	3,987	Groups are critical for an effective public health response to a pandemic.
Increased risk outpatients—young children 12-23 months old, persons > 65 yrs old, and persons with underlying medical conditions	T	99,232	Groups are at high risk for hospitalization and death.
Outbreak response in nursing homes and other residential settings	PEP	8,860	Treatment of patients and prophylaxis of contacts is effective in stopping outbreaks; vaccination priorities do not include nursing home residents
HCWs in emergency departments, intensive care units, dialysis centers, and EMS providers	P	21,264	These groups are most critical to an effective healthcare response and have limited surge capacity. Prophylaxis will best prevent absenteeism.
Pandemic societal responders (e.g., critical infrastructure groups as defined in the vaccine priorities) and HCW without direct patient contact	T	11,961	Infrastructure groups that have impact on maintaining health, implementing a pandemic response, and maintaining societal functions
Other outpatients	T	209,539	Includes others who develop influenza and do not fall within the above groups
Highest risk outpatients	P	44,300	Prevents illness in the highest risk groups for hospitalization and death.
Other HCWs with direct patient contact	P	-	Prevention would best reduce absenteeism and preserve optimal function.

*Strategy: Treatment (T) requires a total of 10 capsules and is defined as 1 course. Post-exposure prophylaxis (PEP) also requires a single course. Prophylaxis (P) is assumed to require 40 capsules (4 courses) though more may be needed if community outbreaks last for a longer period.

**There are no data on the effectiveness of treatment at hospitalization. If stockpiled antiviral drug supplies are very limited, the priority of this group could be reconsidered based on the epidemiology of the pandemic and any additional data on effectiveness in this population.

B. Definitions and rationale for draft priority groups

1. Persons admitted to hospital with influenza infection

a) Definition

Persons admitted to acute care facilities (traditional or non-traditional with a clinical diagnosis of influenza; laboratory confirmation not required). Excludes persons admitted for a condition consistent with a bacterial superinfection (e.g., lobar pneumonia developing late after illness onset) or after viral replication and shedding has ceased (e.g., as documented by a negative sensitive antigen detection test)

b) Strategy

Treatment within 48 hours of system onset.

c) Rationale

This group is at greatest risk for severe morbidity and mortality. Although there are no data to document the impacts of antiviral drug treatment among persons who already suffer more severe influenza illness, benefit is biologically plausible in persons with evidence of ongoing virally-mediated pathology (e.g., diffuse pneumonia, ARDS). Providing treatment to those who are most ill is also consistent with standard medical practices, would be feasible to implement, and would be acceptable to the public.

d) Population size

The number of persons admitted to hospital in an influenza pandemic would vary substantially depending on the severity of the pandemic and on the ability to expand inpatient capacity, if needed.

e) Unresolved issues

More specific guidance should be provided to healthcare workers on implementing antiviral treatment, including when and when not to treat. In some persons with severe illness, the ability to take oral medication or its absorption may be important issues. For infants <1 year old admitted to hospital, decisions about whether to treat with antiviral drugs may depend on the child's age and potential risk versus benefit as the neuraminidase inhibitors are not licensed for use in infants. If possible, data on time from symptom onset to hospital admission, current use of antiviral drug treatment among inpatients, and its impacts should be collected during interpandemic influenza seasons.

2. Healthcare workers and emergency medical service providers who have direct patient contact

a) Definition

Persons providing direct medical services in inpatient and outpatient care settings. Includes doctors, nurses, technicians, therapists, EMS providers, laboratory workers, other care providers who come within 3 feet of patients with influenza, and persons performing technical support functions essential to quality medical care.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Maintaining high quality patient care is critical to reduce health impacts of pandemic disease and to prevent adverse outcomes from other health conditions that will present for care during the pandemic period. Treatment of healthcare providers will decrease absenteeism due to influenza illness and may decrease absenteeism from fear of becoming ill, given the knowledge that treatment can prevent serious complications of influenza. Good data exist documenting the impacts of early treatment on duration of illness and time off work, and on the occurrence of complications such as lower respiratory infections. Treating healthcare providers is feasible to implement, especially for inpatient care providers who can be provided drugs through the occupational health clinic. It also would be acceptable to the public, who would recognize the importance of maintaining quality healthcare and would understand that persons with direct patient contact are putting themselves at increased risk.

d) Population size

In Maine there are approximately 10,632 HCWs with direct patient contact and emergency medical services providers.

e) Unresolved issues

Further work is needed to hone definitions and estimate population sizes. Implementation issues include the approach to identifying healthcare providers who would be eligible for treatment and where the treatment would be provided, particularly for outpatient care providers.

3. Outpatients at highest risk for severe morbidity or mortality from influenza infection

a) Definition

The Advisory Committee on Immunization Practices defines groups at high risk (or increased risk) of complications from influenza infection during annual outbreaks based on age (6-23 months and >65 years) and underlying illnesses. Among this population, some can be identified who are at highest risk of severe disease and death. These include persons with hematopoietic stem cell transplants (HSCT) and solid organ transplants; those with severe immunosuppression due to cancer therapy or hematological malignancy; persons receiving immunosuppressive therapy for other illnesses (e.g., rheumatoid arthritis); persons with HIV infection and a CD4 count <200; persons on dialysis; and women who are in the second or third trimester of pregnancy.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Of the large group of persons who are at increased risk of severe disease or death from influenza, these groups represent the population at highest risk and who are least likely to be protected by vaccination. Studies show that neuraminidase inhibitor therapy decreases complications and hospitalizations from influenza in high-risk persons and one unpublished study shows a significant decrease in mortality among patients who have undergone a hematopoietic stem cell transplant.

d) Population size

In Maine, the number of persons who are in this group (the immune-compromised and pregnant women) is approximated at 3,101.

e) Unresolved issues

Specific definition of included groups and population sizes.

4. Pandemic health responders, public safety workers, and key government decision-makers

a) Definition

Public health responders include those who manufacture vaccine and antiviral drugs; persons working at health departments who are not included as healthcare workers; and those who would be involved in implementing pandemic vaccination or other response components.

Public safety workers include police, fire, and corrections personnel. Key government decision-makers include chief executives at federal, state, and local levels.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Preventing adverse health outcomes and social and economic impacts in a pandemic depend on the ability to implement an effective pandemic response. Early treatment of pandemic responders will minimize absenteeism and ensure that vaccination and other critical response activities can be maintained. Implementing early treatment for public health workers and vaccine manufacturers is feasible at workplace settings. Public safety workers prevent intentional and unintentional injuries and death, are critical to maintaining social functioning, and will contribute to a pandemic response, for example by ensuring order at vaccination clinics. A small number of decision-makers at federal, state, and local levels are needed to for an effective pandemic response.

d) Population size

The approximate number of persons in this category of pandemic health responders, public safety and government decisions makers in Maine is 3,987.

e) Unresolved issues

Need to define the exact composition and size of this group.

5. Outpatients at increased risk of severe morbidity or mortality from influenza

a) Definition

For planning purposes, this group would include those currently designated as high-risk groups, except for those who have been categorized as being at highest-risk and included in a separate category. This increased-risk group includes persons 6-23 months and >65 years old, or who have underlying illnesses defined by the ACIP as associated with increased risk. Definition of this group may change based on the epidemiology of the pandemic.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Early treatment has been shown to significantly decrease lower respiratory infections and to reduce the rate of hospitalization in elderly and high-risk populations. By extrapolation and based on the results of one small uncontrolled study, significant reductions of mortality can be expected as well. As these risk groups are familiar to the public given recommendations for annual vaccination, communication would be easy and acceptability high.

d) Population size

In Maine, about 99,232 persons are considered high risk outpatients including young children 12-23 months old, persons > 64 years old, and persons with underlying medical conditions. Although all are at increased risk of annual influenza compared with the healthy under-65 year old population, there are different levels of increased risk for severe complications and death within this category. Further stratification may be possible based on several parameters including number of underlying conditions; recent hospitalization for a high-risk condition, pneumonia, or influenza; and age.

e) Unresolved issues

Stratifying this group into those at greater and lesser risk may be important if antiviral supplies are limited. Implementing treatment will be challenging given that it should be provided at the initial point of care to accrue the greatest benefit from early therapy.

6. Outbreak control

a) Definition

Use of antiviral drugs to support public health interventions in closed settings where an outbreak of pandemic influenza is occurring.

b) Strategy

Treatment of cases and post-exposure prophylaxis of contacts (once daily antiviral medication for 10 days).

c) Rationale

Influenza outbreaks in nursing homes are associated with substantial mortality and morbidity. Nursing home residents also are less likely to respond to vaccination. Post-exposure prophylaxis has been shown to be effective in stopping influenza outbreaks in closed settings.

d) Population size

The number of outbreaks that may occur during a pandemic is unclear. Measures should be implemented to prevent outbreaks including limiting visitors, vaccination of staff, furloughing non-critical staff, and screening and exclusion for illnesses consistent with influenza. Approximately 8,860 Maine persons are in this closed settings grouping.

e) Unresolved issues

Should this policy also be implemented in prisons or other settings where explosive spread of illness may occur but the risk for severe complications is not high?

7. Healthcare workers in ER, ICU, EMS, and dialysis settings

a) Definition

Includes all staff in these settings who are required for effective functioning of these health care units.

b) Strategy

Prophylaxis

c) Rationale

Optimally effective functioning of these units is particularly critical to reducing the health impacts of a pandemic. Prophylaxis will minimize absenteeism in these critical settings.

d) Population size

The approximate number of individuals in this healthcare worker group (ER, ICU, EMS and dialysis) in Maine is 21,264.

e) Unresolved issues

Population sizes

8. Pandemic societal responders and healthcare workers who have no direct patient contact

a) Definition

This group includes persons who provide services that must be sustained at a sufficient level during a pandemic to maintain public well-being, health, and safety. Included are workers at healthcare facilities who have no direct patient contact but are important for the operation of those facilities; utility (electricity, gas, and water), waste management, mortuary, and some transport workers.

b) Strategy

Treatment within 48 hours of symptom onset.

c) Rationale

Maintaining certain key functions is important to preserve life and decrease societal disruption. Heat, clean water, waste disposal, and corpse management all contribute to public health. Ensuring functional transportation systems also protects health by making it possible for people to access medical care and by transporting food and other essential goods to where they are needed.

d) Population size

Including workers in healthcare facilities who do not have direct patient contact, utility workers, waste management workers, mortuary workers and transportation workers, the approximate number of persons in this group in Maine is 11,961. Estimates are that 35% of this population will develop illness and present within 48 hours of onset regardless of pandemic severity.

e) Unresolved issues

Need to stratify within these groups to identify who fills specific pandemic societal response functions and to assess whether those functions could still operate if a substantial proportion of the workforce became ill during a 6-8 week pandemic outbreak within a community. Implementation issues need to be addressed, especially with respect to how persons would be identified as falling within this priority group when presenting for treatment and where that treatment would be provided.

9. Other outpatients

a) Definition

Includes persons not in one of the earlier priority groups.

b) Strategy

Treatment within 48 hours of illness onset.

c) Rationale

Treatment reduces the risk of complications and mortality, reduces duration of illness and shortens time off work, and decreases viral shedding and transmission. If sufficient antiviral supplies are available, providing treatment to all who are ill achieves equity and will be most acceptable to the public.

d) Population size

This group of outpatients that are not included in previously targeted groups is approximated at 209,539 in Maine.

e) Unresolved issues

Consider whether there are any strata that can be defined within this population.

C. Additional NVAC recommendations on antiviral drugs for pandemic influenza

In addition to recommendations for priority groups, NVAC unanimously adopted the following recommendations:

- Sufficient drugs should be stockpiled to address top priorities. NVAC recommends that the minimum stockpile size be enough to allow coverage of the top 7 priority groups.
- Oseltamivir should be the primary drug stockpiled, but some zanamivir also should be obtained as it is effective against some oseltamivir-resistant strains, may be preferred for treatment of pregnant women, and supporting two manufacturers enhances security against supply disruptions. Approximately 10% of the stockpile should be zanamivir if feasible and cost effective. No additional adamantanes should be stockpiled.
- Antiviral drugs can also be used as part of an international effort to contain an initial outbreak and prevent a pandemic. Use to slow disease spread early in a pandemic may be useful but requires large amounts of drug.
- Critical research should be conducted to support development and implementation of recommendations for pandemic influenza antiviral drug use, including:
 - Impact of treatment at hospital admission on outcome
 - Optimal treatment dose for H5N1 and other potential pandemic strains
 - Sensitivity and use of rapid diagnostic tests for H5N1 and other influenza strains with pandemic potential
 - Safety and pharmacokinetics of oseltamivir among infants <1 year old
 - Investigation of the impact of other drugs (new antiviral agents and other classes such as statins) on influenza
- Additional work with public and private sector groups should be done to further hone definitions of target groups and their estimated population sizes, and to provide further guidance on antiviral drug distribution and dispensing.

Source: Adapted from HHS Pandemic Influenza Plan, 2005

Appendix C

Maine Priority Groups Established During H1N1 2009 Pandemic Response

Priority Groups

Maine has adopted the priority groups for antivirals outlined in the national recommendations. County and hospital plans should be based on these recommendations. The antiviral priority groups are as follows but may be revised as needed (type of use and estimated number of courses for Maine based on national data are given in parentheses):

1. Patients admitted to hospital (treatment; 33,225 courses)
2. Health care workers with direct patient contact and emergency medical service providers (treatment; 10,632 courses)
3. Highest risk outpatients – immuno-compromised persons and pregnant women (treatment; 3,101 courses)
4. Pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire, corrections), and government decision makers (treatment; 3,987 courses)
5. Increased risk outpatients – young children 12-23 months old, persons ≥ 65 years old, and persons with underlying medical conditions (treatment; 99,232 courses)
6. Outbreak response in nursing homes and other residential settings (post-exposure prophylaxis; 8,860 courses)
7. Health care workers in emergency departments, intensive care units, dialysis centers, and EMS responders (prophylaxis; 21,264 courses)
8. Pandemic societal responders (e.g., critical infrastructure groups as defined in the vaccine priorities) and health care workers without direct patient contact (treatment: 11,961 courses)
9. Other outpatients (treatment: 209,539 courses)
10. Highest risk outpatients (prophylaxis: 44,300 courses)

Appendix D

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, pharmacokinetics, FDA-approved indications, dosages, cost, and potential for emergence of drug resistance (see July 2005 ACIP recommendations at <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.

*Because of resistance in circulating influenza A virus strains, amantadine is not currently recommended for antiviral treatment or chemoprophylaxis of influenza A. The daily dosage of amantadine for persons aged ≥ 65 years should not exceed 100 mg for chemoprophylaxis or treatment of amantadine-susceptible influenza A viruses, because renal function declines with increasing age. For certain older persons, the dose should be reduced further (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>)

†Because of resistance in circulating influenza A virus strains, rimantadine is not recommended for antiviral treatment or chemoprophylaxis of influenza A. Among older persons, the incidence and severity of central nervous system (CNS) side effects are substantially lower among those taking rimantadine at a dosage of 100 mg/day than among those taking amantadine at dosages adjusted for estimated renal clearance. However, chronically ill older persons have had a higher incidence of CNS and gastrointestinal symptoms and serum concentrations two to four times higher than among healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day. (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>)

†For chemoprophylaxis of rimantadine-susceptible influenza A viruses among persons aged ≥ 65 years, the recommended dosage is 100 mg/day. For treatment of amantadine-susceptible influenza A virus infection in older persons in the community, a reduction in dosage to 100 mg/day should be considered if they experience side effects when taking a dosage of 200 mg/day. For treatment of older nursing home residents, the dosage of rimantadine should be reduced to 100 mg/day. (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>)

Appendix D

TABLE 2. Recommended dosage and schedule of influenza antiviral medications* for treatment† and chemoprophylaxis§

Antiviral agent		Age group (yrs)				
		1--6	7--9	10--12	13--64	≥65
Zanamivir	Treatment, influenza A and B	NA	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
	Chemoprophylaxis, influenza A and B	NA for ages 1--4	Ages 5--9 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily
Oseltamivir¶	Treatment,** influenza A and B	Dose varies by child's weight* *	Dose varies by child's weight**	Dose varies by child's weight** >40 kg = adult dose	75 mg twice daily	75 mg twice daily
	Chemoprophylaxis, influenza A and B	Dose varies by child's weight† †	Dose varies by child's weight††	Dose varies by child's weight†† >40 kg = adult dose	75 mg once daily	75 mg once daily

Abbreviation: NA = not approved

* Zanamivir is manufactured by GlaxoSmithKline (Relenza --- inhaled powder). Zanamivir is approved for treatment of persons aged ≥7 years and approved for chemoprophylaxis of persons aged ≥5 years. Zanamivir is administered through oral inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device. Zanamivir is not recommended for those persons with underlying airway disease. Oseltamivir is manufactured by Roche Pharmaceuticals (Tamiflu --- tablet). Oseltamivir is approved for treatment or chemoprophylaxis of persons aged ≥1 year.

Oseltamivir is available for oral administration in 30 mg, 45 mg, and 75 mg capsules and liquid suspension. No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children aged <1 year. This information is based on data published by the Food and Drug Administration (FDA), available at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm100228.htm>.

† Recommended duration for antiviral treatment is 5 days. Longer treatment courses can be considered for patients who remain severely ill after 5 days of treatment.

§ Recommended duration is 10 days when administered after a household exposure and 7 days after the most recent known exposure in other situations. For control of outbreaks in long-term care facilities and hospitals, CDC recommends antiviral chemoprophylaxis for a minimum of 2 weeks and up to 1 week after the most recent known case was identified

¶ See Table 4 for information about use of oseltamivir for infants aged <1 year. A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.

** The treatment dosing recommendation for oseltamivir for children aged ≥1 year who weigh ≤15 kg is 30 mg twice a day. For children who weigh >15 kg and up to 23 kg, the dose is 45 mg twice a day. For children who weigh >23 kg and up to 40 kg, the dose is 60 mg twice a day. For children who weigh >40 kg, the dose is 75 mg twice a day.

†† The chemoprophylaxis dosing recommendation for oseltamivir for children aged ≥1 year who weigh ≤15 kg is 30 mg once a day. For children who weigh >15 kg and up to 23 kg, the dose is 45 mg once a day. For children who weigh >23 kg and up to 40 kg, the dose is 60 mg once a day. For children who weigh >40 kg, the dose is 75 mg once a day.

Source: Table 1 from <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001al.htm>

Appendix D

TABLE 3. Summary of antiviral resistance among influenza viruses worldwide, December 2010*

Antiviral	Influenza A viruses		Influenza B viruses†
	2009 H1N1	H3N2	B
Adamantanes (not recommended currently)	Resistant	Resistant	No activity
Oseltamivir	Susceptible	Susceptible	Susceptible
Zanamivir	Susceptible	Susceptible	Susceptible

* Information regarding antiviral resistance is updated weekly and is available at <http://www.cdc.gov/flu/weekly>. Rare instances of infection with oseltamivir-resistant 2009 H1N1 virus strains have been reported; >99% of influenza viruses circulating since September 2009 have been sensitive to oseltamivir.

† Yamagata and Victoria lineages

Source: Table 2 from <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>

Appendix D

Table 4. Recommendations for the selection of antiviral treatment using laboratory test results and viral surveillance data*		
Rapid antigen, RT-PCR or other laboratory test	Preferred medication(s)†	Alternative (combination antiviral treatment)
Not performed or negative but clinical suspicion for influenza†	Oseltamivir or zanamivir	None
Positive A or positive A+B§	Oseltamivir or zanamivir	None
Positive 2009 influenza A(H1N1)	Oseltamivir or zanamivir	None
Positive A(H3N2), or B	Oseltamivir or zanamivir	None

Abbreviation: RT-PCR = reverse transcription-polymerase chain reaction.

* Antiviral recommendations might change over time. Influenza antiviral medications used for treatment are most beneficial when initiated within the first 2 days of illness. Clinicians should consult the package insert of each antiviral medication for specific dosing information, approved indications and ages, contraindications/warnings/precautions, and adverse effects.

† Influenza viral surveillance data might help guide antiviral choices if oseltamivir resistance becomes more prevalent among circulating influenza viruses. Consult guidance from local or state public health laboratories or CDC for further information regarding currently circulating viruses. CDC viral surveillance data are updated weekly during the influenza season and is available at <http://www.cdc.gov/flu/weekly>.

§ Positive A+B indicates a rapid antigen test that cannot distinguish between influenza A and influenza Bviruses.

Source: Table 3 from <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>

Appendix D

TABLE 5. Dosing recommendations for treatment or chemoprophylaxis of children aged <1 year using oseltamivir*		
Age	Recommended treatment dose for 5 days†	Recommended chemoprophylaxis dose for 10 days†
<3 mos	3 mg/kg/dose twice daily	Not recommended unless situation judged critical because of limited data on use in this age group
3–11 mos	3 mg/kg/dose twice daily	3 mg/kg/dose once daily

* Oseltamivir is not approved by the Food and Drug Administration (FDA) for use in children aged <1 year. An Emergency Use Authorization (EUA) was issued by the FDA on April 28, 2009, and expired on June 23, 2010 (available at <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafety/InformationforPatientsandProviders/UCM216494.pdf>). This EUA allowed use of oseltamivir for treatment or chemoprophylaxis of 2009 pandemic influenza A (H1N1) virus infection during the pandemic in infants aged <1 year. Currently circulating 2009 H1N1, seasonal influenza A (H3N2), and B viruses have similar sensitivity to oseltamivir.

† Current weight-based dosing recommendations are not appropriate for premature infants. Premature infants might have slower clearance of oseltamivir because of immature renal function, and doses recommended for full-term infants might lead to very high drug concentrations in this age group. Very limited data from a small cohort of premature infants suggested that oseltamivir concentrations among premature infants administered oseltamivir 1 mg/kg twice daily would be similar to those observed with the recommended treatment dose in term infants (3 mg/kg twice daily). Observed drug concentrations were highly variable among premature infants. These data are insufficient to recommend a specific dose of oseltamivir for premature infants (202).

Source: Table 4 from <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>