

# Recommendations for the Prevention, Detection, and Control of Influenza in California Long-term Care Facilities, 2007-2008

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## Recommendations for the Prevention, Detection, and Control of Influenza in California Long-Term Care Facilities, 2007-2008

This report updates the 2006-2007 recommendations regarding the prevention, detection, and control of influenza outbreaks in California long-term care facilities (LTCFs). These recommendations were developed by the California Department of Public Health (CDPH), Division of Communicable Disease Control, Infectious Diseases and Immunization Branches, using information from the Centers for Disease Control and Prevention (CDC), in consultation with the Licensing and Certification Program, and are revised annually. This information is intended to be advisory only and was developed to assist facility infection control committees in the development of a rational approach to the control of influenza in LTCFs.

The resources used to guide these recommendations are:

Prevention and Control of Influenza, Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007

<http://www.cdc.gov/mmwrR/preview/mmwrhtml/rr56e629a1.htm>.

Infection Control Measures for Preventing and Controlling Influenza Transmission in Long-Term Care Facilities: <http://www.cdc.gov/flu/professionals/infectioncontrol/longtermcare.htm>.

Using Antiviral Medications to Control Influenza Outbreaks in Institutions:

<http://www.cdc.gov/flu/professionals/infectioncontrol/institutions.htm>.

All the CDC recommendations for infection control for influenza in healthcare facilities are available at <http://www.cdc.gov/flu/professionals/infectioncontrol/index.htm>.

Information on methods of reimbursement for influenza and pneumococcal vaccine are available from in "Prevention and Control of Vaccine-Preventable Diseases in Long-Term Care Facilities" at: [http://www.cdc.gov/vaccines/pubs/downloads/bk\\_long-term-care.pdf](http://www.cdc.gov/vaccines/pubs/downloads/bk_long-term-care.pdf)

Other infection control recommendations for long-term care facilities are available from CDHP at <http://www.dhs.ca.gov/ps/dcdc/disb/disbindex.htm> and from CDC at [http://www.cdc.gov/ncidod/dhqp/gl\\_longterm\\_care.html](http://www.cdc.gov/ncidod/dhqp/gl_longterm_care.html).

Additional information on influenza, including influenza vaccine, is available from CDC at: <http://www.cdc.gov/flu/> and from CDPH at:

[http://ww2.cdph.ca.gov/healthinfo/discond/Pages/Influenza\(Flu\).aspx](http://ww2.cdph.ca.gov/healthinfo/discond/Pages/Influenza(Flu).aspx) and

<http://www.dhs.ca.gov/dcdc/izgroup/diseasesbrowse/flu.htm>

<http://www.dhs.ca.gov/ps/dcdc/VRDL/html/FLU/Fluintro.htm>

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## I. CDPH Recommendations for LTCFs

- Vaccinate all LTCF residents and staff against influenza each autumn as soon as vaccine becomes available, and if possible by October, before influenza disease is present in the community. A federal rule requires that LTCFs serving Medicare and Medicaid (Medi-Cal) patients must provide immunizations against influenza and pneumococcal disease to all residents if they want to continue in these programs.
- LTCFs should ensure that standing orders are in place for residents  $\geq 50$  years of age to receive pneumococcal vaccination at admission and annual influenza vaccination of as permitted by California law and required by Federal mandate.
- Residents admitted during influenza season should receive influenza vaccine when they are admitted if they have not been previously vaccinated that season.
- New staff hired during influenza season who have not yet been vaccinated should receive influenza vaccine at the time of hire.
- LTCFs are encouraged to ask staff who refuse influenza vaccination to sign a declination form as a means to increase staff vaccination rates. A sample declination form is provided in [Appendix 1](#).
- Consider requesting that staff who state they have been vaccinated elsewhere submit proof of vaccination to the facility.
- **Immediately report all outbreaks of respiratory illness to the local health department and the Licensing and Certification district office.** Health department personnel can provide information about influenza activity in the area and about diagnostic specimen collection and coordination.
- During influenza outbreaks, consider the use of antiviral medications (oseltamivir or zanamivir) and implement the other outbreak prevention and control measures described in this guidance.

## II. Influenza and Influenza-Like Illness

Influenza is a respiratory illness caused by influenza type A or type B viruses. Typical symptoms of influenza include the acute onset of fever, respiratory symptoms (such as cough, sore throat, and other “cold-like” symptoms), muscle aches and headache. Persons with acute onset of fever and cough, often with nasal congestion, are most likely to have influenza. However, elderly LTCF residents, particularly those with underlying illness, may not have typical symptoms, such as a fever. Some have underlying conditions or are receiving medications with antipyretic (anti-fever) effects that modify the manifestations of influenza. Many also have chronic cough and other respiratory symptoms due to chronic lung disease. Some cannot reliably report symptoms such as sore throat or muscle aches. Therefore, the presentation of influenza in LTCF residents is not consistent or predictable. Influenza should be considered (particularly during influenza season) in residents with any combination of the following:

- Fever  $\geq 37.8^{\circ}\text{C}$  (may be absent or low in elderly LTCF residents)
- New onset cough and/or sore throat
- Nasal congestion
- Malaise (feeling ill)
- Chills
- Muscle aches, joint aches, or headache
- Change in respiratory status (increased cough, sputum production, breathing rate); change in mental status or appetite

Other respiratory viruses and some bacteria can cause similar illnesses, particularly in elderly LTCF residents. These are referred to as “influenza-like illnesses.” The difference between influenza and other acute respiratory infections cannot be determined on the basis of symptoms alone and laboratory testing is necessary (see Section VI).

Most young, healthy people who are infected with influenza recover completely within 1-2 weeks. However, influenza can cause serious illness and death in LTCF residents because of their age and chronic health problems. LTCF residents may also be at high risk of exposure to influenza, since the virus spreads easily in environments where people live close to each other and once influenza enters a LTCF, it can spread rapidly. Influenza occurs annually, typically in the winter between October and April and peak activity in a community usually lasts from 6 to 8 weeks, often spanning the New Year period.

These recommendations are being issued in anticipation of possible influenza outbreaks in California LTCFs this season. During the influenza season, information on influenza activity in California can be accessed at: <http://www.dhs.ca.gov/dcdc/VRDL/html/FLU/Fluintro.htm>

### III. Influenza Transmission

Influenza is thought to be primarily spread from person-to-person by large droplets of respiratory secretions from an infected person. This occurs when infected persons cough, sneeze, or talk, expelling droplets, which are then directly deposited onto the surfaces of the upper respiratory tracts (nose, throat) of susceptible persons who are within approximately 3 feet of the infected person.

Transmission also may occur by direct or indirect (person-object-person) contact when a susceptible person picks up the virus on their hands and then touches their nose. Influenza virus can survive for 24-48 hours on nonporous surfaces and 8-12 hours on porous surfaces such as paper or cloth. Airborne transmission, inhalation of small droplets (droplet nuclei) expelled into the air when an infected person is coughing or during aerosol-generating procedures, may also occur. The degree to which airborne transmission contributes to influenza transmission is uncertain and has not been adequately studied.

The most important sources of influenza virus are infected persons. Infected persons are most infectious during the first 3 days of illness; however, they can shed the virus beginning the day before, and up to 7 or more days after the onset of symptoms. Children and severely immunodeficient persons may shed virus for longer periods. In addition, infected but asymptomatic persons can shed the virus and be infectious.

### IV. Influenza Vaccine

People 65 years of age and older account for more than 90% of influenza deaths. Vaccination is the most effective measure for reducing the illness and deaths from influenza. Since the primary source of infection in residents is staff and the efficacy of vaccination is often reduced in elderly residents, facilities should make a concerted effort to ensure the annual vaccination of staff. Studies have shown that staff vaccination reduces deaths from respiratory infections in residents. Vaccination can also lower staff absenteeism.

California law now requires that acute care hospitals offer influenza vaccine to staff at no charge and to require those declining vaccination to sign a declination form.

There are two types of influenza vaccine: trivalent inactivated influenza vaccine (TIV) and live, attenuated influenza vaccine (LAIV).

#### **Trivalent Inactivated Influenza Vaccine (TIV)**

TIV must be injected and contains inactivated (killed) influenza virus; it cannot cause influenza. TIV is the type of vaccine typically used in LTCFs because live vaccines are not recommended for LTCF residents. When the vaccine and circulating virus strains are similar, TIV is expected to prevent influenza in 70%--90% of healthy vaccinated adults <65 years of age.

Although TIV effectiveness in preventing illness in elderly LTCF residents is estimated at 20%-40%, it can be up to 80% effective in preventing influenza-related death.

The following persons should not receive TIV:

- persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician;
- persons with moderate-to-severe acute febrile illness usually should not be vaccinated until their symptoms have abated (minor illnesses with or without fever do not contraindicate use of influenza vaccine, particularly among children with mild upper-respiratory tract infection or allergic rhinitis);
- avoid vaccination of persons who are not at high risk for severe influenza complications and who are known to have experienced Guillain-Barré syndrome within 6 weeks after a previous influenza vaccination is prudent.

### **Live Attenuated Influenza Vaccine (LAIV)**

FluMist®, the nasal-spray LAIV, is an option for healthy individuals, ages 2 to 49 years of age, and may be used as a substitute for standard inactivated injectable influenza vaccine for staff in LTCFs. LAIV is given intranasally.

LAIV is **not** recommended for LTCF residents. Staff who care for patients with severely weakened immune systems (i.e., patients who have recently had a bone marrow transplant and require a protected environment) can receive LAIV, but should refrain from contact with severely immunosuppressed patients for 7 days after vaccine receipt.

The following persons should not receive LAIV:

- persons aged <2 years or those aged  $\geq 50$  years of age;
- history of recurrent wheeze in those < 5 years of age;
- persons with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; persons with other underlying medical conditions, including metabolic diseases such as diabetes, renal dysfunction, and hemoglobinopathies; or persons with known or suspected immunodeficiency diseases or who are receiving immunosuppressive therapies;
- children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza infection);
- persons with a history of Guillain-Barré syndrome;
- pregnant women; or
- persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs.

LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after receipt of LAIV. LAIV should not be given within 4 weeks of another live vaccine.

### **Vaccine Storage**

Both types of vaccine should be stored in the refrigerator at 35°-46° F at all times and should not be exposed to freezing temperature.

**Thimerosal**

Multidose vials of TIV contain the mercury-containing preservative, thimerosal. California law specifies that thimerosal containing influenza vaccines given to pregnant women or children younger than 3 years of age in California may not exceed 1.0 microgram of mercury per 0.5 milliliters of vaccine. Therefore, women who are “knowingly pregnant” or children < 3 years of age may only receive influenza vaccines that contain < 1.0 mcg of mercury per 0.5 ml of vaccine. **All single dose influenza vaccines approved for use in the U.S. for the 2007-2008 influenza season meet this requirement.**

Non-influenza vaccines given to pregnant women or children younger than 3 years of age may not contain more than 0.5 mcg of mercury per 0.5 ml of vaccine per California law. For more information on the thimerosal law see: [http://www.dhs.ca.gov/ps/dcdc/izgroup/shared/mercury\\_law.htm](http://www.dhs.ca.gov/ps/dcdc/izgroup/shared/mercury_law.htm)

**Approved U.S. influenza vaccines, 2007-2008**

The following list of approved influenza vaccines, is from “Prevention and Control of Influenza, Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2007” at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr56e629a1.htm>

**TABLE 4. Approved influenza vaccines for different age groups — United States, 2007–08 season**

Vaccine	Trade name	Manufacturer	Presentation	Thimerosal mercury content (mcg Hg/0.5 mL dose)	Age group	No. of doses	Route
TIV*	Fluzone®	Sanofi Pasteur	0.25-mL prefilled syringe	0	6–35 mos	1 or 2†	Intramuscular§
			0.5-mL prefilled syringe	0	≥36 mos	1 or 2†	Intramuscular§
			0.5 mL vial	0	≥36 mos	1 or 2†	Intramuscular§
			5.0-mL multidose vial	25	≥6 mos	1 or 2†	Intramuscular§
TIV*	Fluvirin™	Novartis Vaccine	5.0-mL multidose vial	24.5	≥4 yrs	1 or 2†	Intramuscular§
TIV*	Fluarix™	GlaxoSmithKline	0.5-mL prefilled syringe	<1.0	≥18 yrs	1	Intramuscular§
TIV*	FluLaval™	GlaxoSmithKline	5.0-mL multidose vial	25	≥18 yrs	1	Intramuscular§
LAIV¶	FluMist™**	MedImmune	0.2-mL sprayer	0	5–49 yrs	1 or 2††	Intranasal

\* Trivalent inactivated vaccine (TIV). A 0.5-mL dose contains 15 mcg each of A/Solomon Islands/3/2006 (H1N1)-like, A/Wisconsin/67/2005 (H3N2)-like, and B/Malaysia/2506/2004-like antigens.  
 † Two doses administered at least 1 month apart are recommended for children aged 6 months–8 years who are receiving TIV for the first time and those who only received 1 dose in their first year of vaccination should receive 2 doses in the following year.  
 § For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.  
 ¶ Live attenuated influenza vaccine (LAIV).  
 \*\* FluMist dosage and storage requirements have changed for the 2007–08 influenza season. FluMist is now shipped to end users at 35°F–46°F (2°C–8°C). LAIV should be stored at 35°F–46°F (2°C–8°C) upon receipt and should remain at that temperature until the expiration date is reached. The dose is 0.2 mL, divided equally between each nostril.  
 †† Two doses administered at least 6 weeks apart are recommended for children aged 5–8 years who are receiving LAIV for the first time, and those who received only 1 dose in their first year of vaccination should receive 2 doses in the following year.

**2007-2008 Influenza Vaccine Availability**

It is expected that sufficient supplies of influenza vaccine will be available for the 2007-2008 influenza season. Manufacturers began to ship influenza vaccine in September and almost all of the vaccine is expected to be shipped and distributed in October and November. Up to date information and recommendations can be obtained at: <http://www.dhs.ca.gov/ps/dcdc/izgroup/flu.htm> and <http://www.cdc.gov/flu/>. The toll-free CDPH Influenza Vaccine Information Line is 866-470-3788.

## V. Laboratory Diagnosis of Influenza

A person with influenza may not appear or feel different than when infected with many other respiratory pathogens. However, during outbreaks where influenza has been confirmed through laboratory tests, it can be presumed that other persons with similar symptoms also have influenza. Therefore, **when a cluster of cases of acute respiratory illness with symptoms suggestive of influenza (see Section I above) occurs, it is of critical importance to try to establish the diagnosis through laboratory testing.**

Several commercial rapid diagnostic tests are available that can detect influenza viruses within 30 minutes. Some of these rapid tests detect only influenza A viruses, whereas other rapid tests detect both influenza Type A and B viruses but do not distinguish between the two types. These tests can be performed on nasopharyngeal-swab or nasal-wash specimens. This information can then be used to determine if influenza antiviral drug therapy should be implemented to prevent the outbreak from spreading. Precise identification of the strain of virus can be made by growing the virus from nasopharyngeal secretions of acutely ill persons. Viral culture and molecular tests are available at the CDPH Viral and Rickettsial Disease Laboratory and some local health departments for the investigation of outbreaks.

## VI. Infection Prevention and Control Precautions for Seasonal Influenza and Other Respiratory Infections

The implementation of infection prevention measures for influenza-like respiratory infections, including seasonal influenza, can prevent their spread in LTCFs. Although vaccinating all facility personnel and residents is the primary influenza control measure, outbreaks of influenza and other viruses that mimic influenza can be prevented if the following recommendations are implemented as soon as possible to prevent person-to-person transmission.

### A. Education and Monitoring

- Provide education about the facility's respiratory hygiene/cough etiquette program (below) and how to report signs and symptoms of influenza and influenza-like respiratory infections to residents, facility personnel, visitors and volunteers at least annually and when influenza-like respiratory infections are identified in the facility.
- Develop an influenza or influenza-like illness outbreak management plan that includes vaccination for seasonal influenza and the use of the influenza vaccine declination form (see [Appendix 1](#)).
- Monitor residents and facility personnel for symptoms of respiratory infection, especially during the influenza season (October to April).
- If influenza or influenza-like respiratory illnesses are suspected, promptly contact the local health department and request assistance with laboratory testing.

## B. Respiratory Hygiene/Cough Etiquette

Respiratory hygiene/cough etiquette procedures should be implemented at the first point of contact with a potentially infected person to prevent the transmission of respiratory tract infections in healthcare settings. Additional information is available at:

[www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm](http://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm)

Respiratory hygiene/cough etiquette programs include:

- Posting visual alerts instructing residents, staff, visitors and volunteers to report symptoms of respiratory infection to a designated person.
- Providing tissues or masks to residents who are coughing or sneezing so that they can cover their nose and mouth.
- Encouraging coughing persons to remain at least 3 feet away from others, if possible.
- Ensuring that supplies for hand washing are available where sinks are located; and/or providing dispensers of alcohol-based hand rubs.
- Excluding staff, visitors, and volunteers with symptoms of respiratory infection.

## C. Visitor Precautions

- During influenza season, post signs notifying visitors that adults with respiratory symptoms should not visit for 5 days and children with symptoms should not visit for 10 days following the onset of illness..
- During an outbreak, consider restricting all children from visiting.
- Provide written information about influenza-like infections and seasonal influenza to visitors and why the infection control precautions are necessary.
- Provide visitors with written instructions (respiratory hygiene/cough etiquette) about the precautions implemented by the facility.
- Encourage visitors to get vaccinated for influenza.
- If visitation is necessary (e.g., visitation of a dying resident) instruct symptomatic visitors to: (1) wear a surgical or procedure mask over their mouth and nose while in the resident's room; (2) cough and sneeze into a tissue and discard contaminated tissues a waste receptacle; and (3) sanitize their hands before entering the resident's room, before and after resident contact and upon leaving the resident's room.
- Ensure that hand hygiene, tissues and masks are available.

## **VII. Outbreak Control Procedures for Influenza and Influenza-like Respiratory Infections**

### **A. Definitions**

- Cluster: Three or more cases of acute respiratory illness occurring within 48-72 hours in residents who are in close proximity to each other (e.g., in the same area of the facility).
- Outbreak: A sudden increase in acute respiratory illness cases over the normal background rate or when any resident tests positive for influenza. One case of confirmed influenza by any testing method in a LTCF resident is an outbreak.

### **B. Confirm Diagnosis by Laboratory Testing**

- The first three to four residents and/or staff suspected of influenza or influenza-like illness (acute respiratory illness with or without fever) should have specimens obtained for laboratory testing to confirm the diagnosis of influenza.
- Contact the local health department for appropriate diagnostic laboratory test recommendations. If rapid antigen tests and/or viral cultures are recommended, determine the appropriate laboratory to process the specimens.

### **C. Infection Control Precautions for Residents with Influenza-Like Illness**

- As soon as a resident develops an influenza-like acute respiratory illness (see Section II), confine the symptomatic resident and exposed roommate(s) to their room, restrict them from group activities, and serve meals in their room for 5 days after the onset of symptoms.
- If other residents become symptomatic, cancel group activities and serve all meals in residents' rooms.
- If residents are ill on specific nursing units, do not move residents or staff to other units, or admit new residents to the units with symptomatic residents.
- Avoid rotating staff between nursing units until no new cases have been identified for at one week.
- Limit admission of new and returning residents, if possible.
- If admissions are necessary, ensure that new or returning residents do not have acute respiratory illness and are not being transferred from a facility experiencing an influenza outbreak. Admit asymptomatic new or returning residents to unaffected nursing units.
- Wear a surgical or procedure mask when within 3 feet of ill residents or when entering the resident's room.
- Place a surgical or procedure mask over the ill resident's nose and mouth, if tolerated, when transport or movement of the resident is necessary outside of their room.
- Instruct ill residents to use tissues to cover their nose and mouth when coughing and sneezing. Provide a bag or other waste receptacle conveniently located for disposal of contaminated tissues.
- Wash or sanitize the hands of ill residents with an alcohol-based hand hygiene product frequently throughout the day, before they leave their room and after hand contact with respiratory secretions or contaminated tissues.

#### D. Healthcare Worker Infection Control Precautions

- Wear gloves when contact with the ill resident or contaminated environmental surfaces or objects in close vicinity to the resident is anticipated. Keep a supply of gloves in the resident's room.
- Wear gowns when providing direct care to an ill resident.
- Change gloves and gowns after each encounter with an ill resident and perform hand hygiene.
- Wear a surgical or procedure mask upon entering the ill resident's room or when working within 3 feet of a coughing or sneezing resident. Remove the mask upon leaving the resident's room and dispose in a waste receptacle.
- Wash or sanitize hands before and after touching the ill resident, after touching environmental surfaces and items potentially contaminated with respiratory secretions, whether or not gloves are worn. If hands are not visibly soiled, use an alcohol-based hand rub for routine decontamination of hands. Alternatively, wash hands with soap (either plain or antimicrobial) and water.
- Exclude staff with influenza-like illness from patient care for 5 days after the onset of symptoms and advise them not work in other facilities (i.e., a second job) during the same time period. During a facility outbreak, even well facility personnel should not work at another facility until the local health department has determined that the outbreak is controlled.
- Implement enhanced environmental cleaning of commonly touched surfaces such as door handles, hallway banisters, toilet or bath rails, bedrails, overbed tables, and nursing station counters.

#### E. Collect, Analyze, and Report Data

- Initiate the use of the daily active surveillance log (see [Appendix 2, page 14](#)) and collect data on all newly symptomatic residents and staff until at least one week after the last influenza case occurs.
- Monitor facility personnel absenteeism due to influenza-like respiratory illness.
- Report all resident(s) and facility personnel with symptoms of influenza-like illness to the infection prevention and control practitioner (ICP). New cases should be reported and recorded daily using the case log (see [Appendix 2, page 14](#)).
- Analyze reports of resident and facility personnel illness submitted by the nursing unit and other departments (environmental services) daily.
- Determine the infection attack rates for residents and facility personnel (# of infected residents/total number of vaccinated **and** total of non-vaccinated residents) and (# total number of infected facility personnel/total number of vaccinated **and** the total number of non-vaccinated facility personnel).
- Report data to the quality assurance/infection control committee and the Licensing and Certification district office with jurisdiction over the facility (see notification).
- Review the infection surveillance and outbreak management plan to determine necessary revisions.
- Make revisions for implementing the outbreak management plan and influenza vaccination during the next influenza year.

#### F. Outbreak Notification

- Notify the facility medical director immediately.
- Notify the local health department **and** the Licensing and Certification district office with jurisdiction over your facility ([www.dhs.ca.gov/lnc/org/default.htm](http://www.dhs.ca.gov/lnc/org/default.htm)).

#### G. Vaccination

- Vaccinate unvaccinated facility personnel and residents as soon as possible.

#### H. Antiviral Drugs (see next section)

### VIII. Antiviral Drugs for the Control of Influenza Outbreaks

Four currently licensed antiviral agents are available in the U.S.: amantadine, rimantadine, oseltamivir, and zanamivir. In the past, amantadine and rimantadine (together known as adamantanes) were commonly used for treatment and prophylaxis of influenza type A. However, recent evidence indicates that a high proportion of currently circulating influenza A viruses in California and in the U.S. have developed resistance to adamantanes. Therefore, **neither amantadine nor rimantadine should be used for the treatment or prophylaxis of influenza A in the U.S.**

The two remaining antiviral agents, oseltamivir (Tamiflu®) and zanamivir (Relenza®), are an important additional measure for the control of influenza outbreaks. While they are not a substitute for vaccination, CDC recommends their use during outbreaks and they should be considered for use when an influenza outbreak occurs. During an outbreak, these antiviral drugs should be given to residents and offered to staff in accordance with current recommendations at: <http://www.cdc.gov/flu/professionals/treatment>

When oseltamivir or zanamivir are used for treatment or chemoprophylaxis, adverse reactions to these drugs should be monitored using the format of [Appendix 5, page 17](#). Side effects can include bronchospasm (zanamivir) as well as gastrointestinal disturbances (oseltamivir).

#### **Antiviral Treatment**

Oseltamivir and zanamivir (together called neuraminidase inhibitors) are effective against both type A and type B influenza. Both medications can reduce the duration of uncomplicated influenza A and B illnesses by about one day compared with a placebo. If used, it is recommended that antiviral treatment be started **within 2 days of illness onset**. Oseltamivir is currently approved for treatment of persons aged  $\geq 1$  year, and zanamivir is approved for treatment of persons aged  $\geq 7$  years.

#### **Antiviral Treatment Recommendations**

For treatment, oseltamivir is administered twice a day orally for 5 days and zanamivir is administered as 2 oral inhalations twice a day for 5 days. Separate symptomatic residents on antiviral treatment from others, including those taking antiviral chemoprophylaxis, to the

extent possible in the facility to decrease the possibility of transmitting antiviral-resistant influenza.

### **Antiviral Chemoprophylaxis**

Oseltamivir and zanamivir can also be used for chemoprophylaxis of influenza. Oseltamivir is licensed for chemoprophylaxis in persons aged  $\geq 1$  year, and zanamivir is licensed for use in persons  $\geq 5$  years. When considering the use of antiviral medications for chemoprophylaxis, cost, compliance, and potential side effects should be evaluated. For maximal results, chemoprophylaxis medication should be taken daily for at least two weeks and as long as one week after the last resident case occurs. For additional information on antiviral drugs see [Appendix 6](#).

When outbreaks of influenza occur in a LTCF, and antiviral chemoprophylaxis is undertaken, drug administration should begin as early in the outbreak as possible to reduce influenza transmission. Contingency planning is needed to ensure immediate availability and rapid administration of the drugs. This might include obtaining prior approval from personal physicians for administration of antiviral drugs to residents in the event of an outbreak. Since it is difficult to know in advance how long antiviral drugs will need to be administered, some nursing homes have a policy that also allows facility staff or a consultant to decide when they should be discontinued.

### **Antiviral Chemoprophylaxis Recommendations**

Immediately upon confirmation of influenza A or B, consider the use of the antiviral medications oseltamivir or zanamivir to prevent further spread of influenza in the facility. The CDC recommends that when confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis should be started as early as possible to reduce the spread of the virus. For additional information see: <http://www.cdc.gov/flu/professionals/infectioncontrol/institutions.htm>.

In these situations, having pre-approved orders from physicians or plans to obtain orders for antiviral medications on short notice can substantially expedite administration of antiviral medications. When used in an outbreak, antiviral chemoprophylaxis should be administered to all residents, regardless of whether they have received influenza vaccine, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 1 week after the end of the outbreak. The dosage for each resident should be determined individually.

- Oseltamivir and zanamivir have both been approved for chemoprophylaxis, community studies of healthy adults indicate that both drugs are about 80-85% effective in preventing influenza illness.
- For chemoprophylaxis, oseltamivir is administered once a day orally and zanamivir is administered as 2 oral inhalations once a day. The dosage of oseltamivir may need to be decreased for those with impaired renal function (see [Table 1, Appendix 6](#) for additional dosing information).

- Chemoprophylaxis can also be offered to unvaccinated staff members (or staff vaccinated less than 2 weeks prior to the outbreak. Antivirals may be considered for chemoprophylaxis of all LTCF staff, regardless of their vaccination status, if the outbreak is suspected to be caused by a strain of influenza virus that is not well-matched to the vaccine.
- When considering the use of oseltamivir or zanamivir, clinicians must consider the patient's age, weight, and renal function (see [Table 1, Appendix 6](#)).
- Exercise caution when administering oseltamivir or zanamivir to persons with:
  - decreased renal function (adjust the dose based on creatinine clearance for oseltamivir);
  - concomitant use for drugs excreted in urine via glomerular filtration and tubular secretion via the anionic pathway; or
  - pregnancy.
- Zanamivir is not recommended for treatment for patients with underlying airway disease (e.g., asthma, chronic obstructive pulmonary disease). If physicians choose to prescribe zanamivir to patients with underlying chronic respiratory disease after considering potential risks and benefits, the medication should be used with caution under conditions of appropriate monitoring and supportive care, including short-acting bronchodilators (see [Appendix 6](#) for more details).

Note: There are no current studies of oseltamivir or zanamivir use among persons with hepatic dysfunction, or underlying respiratory or cardiac disease. Seizure events have been reported during postmarketing use of oseltamivir and zanamivir although no epidemiologic studies have reported any increased risk for seizures with either oseltamivir or zanamivir use. For a more detailed description on dosing, drug-drug interactions, side effects and contraindications of the use of anti-influenza drugs, see [Appendix 6, page 18](#). Also consult the package inserts for these drugs.

## IX. References and Other Sources of Information

See page 1 for references and resources used in the development of these recommendations.

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7. Infection Control Measures for Preventing and Controlling Influenza Transmission in Long-Term Care Facilities. <http://www.cdc.gov/flu/professionals/infectioncontrol/longtermcare.htm>
8. Immunization Branch of the California Department of Health Services Influenza Information: [http://www.cdph.ca.gov/healthinfo/discond/Pages/Influenza\(Flu\).aspx](http://www.cdph.ca.gov/healthinfo/discond/Pages/Influenza(Flu).aspx) and the Influenza Pandemic Response Plan. <http://www.dhs.ca.gov/ps/dcdc/izgroup/pdf/pandemic.pdf>
9. California Influenza Surveillance Project, Viral and Rickettsial Disease Laboratory Branch, California Department of Health Services. <http://www.dhs.ca.gov/ps/dcdc/VRDL/html/FLU/Fluintro.htm>

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*Appendix 1. Sample Influenza Declination Form***Declination of Influenza Vaccination**

My employer \_\_\_\_\_, has offered that I receive influenza vaccination in order to protect myself and the patients I serve.

I acknowledge that I am aware of the following facts:

- Influenza vaccination is strongly recommended for me and all other healthcare workers to prevent influenza disease and its complications, including death.
- Due to my occupation, I may transmit influenza to my patients and other healthcare workers, as well as to my family and friends, even though I have no symptoms.
- If I become infected with influenza, even when my symptoms are mild, I can spread severe illness to others, particularly to those in this healthcare facility that are at high risk for influenza complications.
- I understand that the strains of virus that cause influenza infection change almost every year, which is why a different influenza vaccine is recommended each year.
- I have received education about the effectiveness of influenza vaccination as well as possible adverse events.
- I cannot get the influenza disease from the influenza vaccine.
- I understand that if I have not been vaccinated, by declining this vaccine, I continue to be at risk of acquiring influenza, which could endanger my health and the health of those with whom I have contact, including:
  - patients in this healthcare facility
  - my coworkers
  - my family
  - my community

I have been given the opportunity to be immunized with influenza vaccine at no charge to myself. However, I decline influenza vaccination at this time.

I understand that I may change my mind at any time and accept influenza vaccination, if vaccine is available.

I have read and fully understand the information on this declination form.

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Name (print): \_\_\_\_\_





*Appendix 4. Sample Summary Log of Acute Respiratory Illness and Pneumonia*

From: Month, day, year

To: Month, day, year

Enter the number of persons with the indicated symptoms, test results, and illness outcomes, as indicated

Location	Vaccination status of ill persons		Summary of symptoms										Influenza test results		Pneumo coccal test results		Antibiotics	Antivirals	Illness outcomes					
	No. vaccinated: influenza	No. vaccinated: pneumococcal	Temp ≥99°F	Cough	Malaise/fatigue	Chills/rigors	Sore throat	Arthralgias/myalgias	Sore throat	Change in respiratory status	Pneumonia	CXR confirmed	Rapid antigen (+/-/ND)	Viral culture (+/-/ND)	Gram stain (+/-/ND)	Sputum culture (+/-/ND)			On antibiotics	On antivirals	Influenza positive (Y/N)	S. Pneumo positive (Y/N)	Hospitalized	Died in hospital

From Reference 2

*Appendix 5. Sample Line List of Residents with Adverse Reactions to Antiviral Medication*

Facility name: \_\_\_\_\_  
 Infection Control Coordinator: \_\_\_\_\_  
 Phone Number: \_\_\_\_\_  
 Dates: \_\_\_\_\_

Resident identification			Resident location			Respiratory illness		Antiviral drug/dosing					Adverse reaction						Actions taken				
Name	Age	Sex (M/F)	Building	Unit	Room #	AFRI (Y/N)	Date of illness onset	Osetamivir (O)	Zanamivir (Z)	Date antiviral started	Dose (mg)	Frequency	Creatinine	Nervous/anxious	Confusion	Nausea	Anorexia	Agitation	Seizure	Other symptom	Antiviral discontinued (Y/N)	Date discontinued	Dose reduced (Y/N)

From Reference 2

## Appendix 6. Antiviral Drugs

(from Reference 1; reference numbers in text refer to Reference 1 references)

Although annual vaccination is the primary strategy for preventing complications of influenza virus infections, antiviral medications with activity against influenza viruses can be effective for the chemoprophylaxis and treatment of influenza. Four licensed influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Influenza A virus resistance to amantadine and rimantadine can emerge rapidly during treatment. On the basis of antiviral testing results conducted at CDC and in Canada indicating high levels of resistance (23,24,284), ACIP recommends that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza A in the United States until susceptibility to these antiviral medications has been re-established among circulating influenza A viruses. Oseltamivir or zanamivir can be prescribed if antiviral treatment of influenza is indicated. Oseltamivir is approved for treatment of persons aged  $\geq 1$  year, and zanamivir is approved for treatment of persons aged  $\geq 7$  years. Oseltamivir and zanamivir can be used for chemoprophylaxis of influenza; oseltamivir is licensed for use in persons aged  $\geq 1$  year, and zanamivir is licensed for use in persons aged  $\geq 5$  years.

### Antiviral Agents for Influenza

Zanamivir and oseltamivir are chemically related antiviral drugs known as neuraminidase inhibitors that have activity against both influenza A and B viruses. Both zanamivir and oseltamivir were approved in 1999 for treatment of uncomplicated influenza virus infections. In 2000, oseltamivir was approved for chemoprophylaxis of influenza among persons aged  $\geq 13$  years and was approved for chemoprophylaxis of children aged  $\geq 1$  year in 2005. In 2006, zanamivir was approved for chemoprophylaxis of children aged  $\geq 5$  years.

The two drugs differ in pharmacokinetics, side effects, routes of administration, approved age groups, dosages, and costs. An overview of the indications, use, administration, and known primary side effects of these medications is presented in the following sections. Package inserts should be consulted for additional information. Detailed information regarding amantadine and rimantadine is available in the previous publication of the ACIP influenza recommendations (285).

### Role of Laboratory Diagnosis

Appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. Influenza surveillance information and diagnostic testing can aid clinical judgment and help guide treatment decisions. For example, early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, because certain bacterial infections can produce symptoms similar to influenza, bacterial infections should be considered and appropriately treated, if suspected. In addition, bacterial infections can occur as a complication of influenza.

The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza (33,42,43). Because testing all patients who might have influenza is not feasible, influenza surveillance by state and local health departments and CDC can provide information regarding the presence of influenza viruses in the community. Surveillance also can identify the predominant circulating types, influenza A subtypes, and strains of influenza viruses.

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR), and immunofluorescence assays (28). The sensitivity and specificity of any test for influenza can vary by the laboratory that performs the test, the type of test used, the type of specimen tested, and the timing of specimen collection. Among respiratory specimens for viral isolation or rapid detection, nasopharyngeal specimens are typically more effective than throat swab specimens (286). As with any diagnostic test, results should be evaluated in the context of other clinical and epidemiologic information available to health-care providers.

Commercial rapid diagnostic tests are available that can detect influenza viruses in 30 minutes (28,287). Some tests are approved for use in any outpatient setting, whereas others must be used in a moderately complex clinical laboratory. These rapid tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Different tests can detect 1) only influenza A viruses; 2) both influenza A and B viruses, but not distinguish between the two types; or 3) both influenza A and B and distinguish between the two.

None of the rapid tests provide any information regarding influenza A subtypes. The types of specimens acceptable for use (i.e., throat, nasopharyngeal, or nasal; and aspirates, swabs, or washes) also vary by test. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test (288,289).

Because of the lower sensitivity of the rapid tests, physicians should consider confirming negative tests with viral culture or other means because of the possibility of false-negative rapid test results, especially during periods of peak community influenza activity. In contrast, false-positive rapid test results are less likely but can occur during periods of low influenza activity. Therefore, when interpreting results of a rapid influenza test, physicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid diagnostic tests. Additional information concerning diagnostic testing is available at <http://www.cdc.gov/flu/professionals/labdiagnosis.htm>

Despite the availability of rapid diagnostic tests, collecting clinical specimens for viral culture is critical because only culture isolates can provide specific information regarding circulating strains and subtypes of influenza viruses. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor the emergence of antiviral resistance and the emergence of novel influenza A subtypes that might pose a pandemic threat.

#### **Antiviral Drug-Resistant Strains of Influenza Virus**

CDC recently reported that 193 (92%) of 209 influenza A (H3N2) viruses isolated from patients in 26 states demonstrated a change at amino acid 31 in the M2 gene that confers resistance to adamantanes (23,24). In addition, two of eight influenza A (H1N1) viruses tested were resistant (24). Canadian health authorities also have reported the same mutation in a comparable proportion of isolates recently tested (284). Until these findings, previous screenings of epidemic strains of influenza A viruses found few amantadine- and rimantadine-resistant viruses (290--292).

Viral resistance to adamantanes can emerge rapidly during treatment because a single point mutation at amino acid positions 26, 27, 30, 31, or 34 of the M2 protein can confer cross resistance to both amantadine and rimantadine (293,294). Drug-resistant viruses can emerge in approximately one third of patients when either amantadine or rimantadine is used for therapy (293,295,296). During the course of amantadine or rimantadine therapy, resistant influenza strains can replace susceptible strains within 2--3 days of starting therapy (290,297). Resistant viruses have been isolated from persons who live at home or in an institution in which other residents are taking or have taken amantadine or rimantadine as therapy (298,299); however, the frequency with which resistant viruses are transmitted and their effect on efforts to control influenza are unknown.

Persons who have influenza A virus infection and who are treated with either amantadine or rimantadine can shed susceptible viruses early in the course of treatment and later shed drug-resistant viruses, including after 5--7 days of therapy (295).

Resistance to zanamivir and oseltamivir can be induced in influenza A and B viruses in vitro (300--307), but induction of resistance usually requires multiple passages in cell culture. By contrast, resistance to amantadine and rimantadine in vitro can be induced with fewer passages in cell culture (308,309).

Development of viral resistance to zanamivir and oseltamivir during treatment has been identified but does not appear to be frequent (310--314). In one pediatric study, 5.5% of patients treated with oseltamivir had posttreatment isolates that were resistant to neuraminidase inhibitors. One small study of Japanese children treated with oseltamivir reported a high frequency of resistant viruses (315). However, no transmission of neuraminidase inhibitor-resistant viruses in humans has been documented to date. No isolates with reduced susceptibility to zanamivir have been reported from clinical trials, although the number of posttreatment isolates tested is limited (316), and the risk for emergence of zanamivir-resistant isolates cannot be quantified (317). Only one clinical isolate with reduced susceptibility to zanamivir, obtained from an immunocompromised child on prolonged therapy, has been reported (312). Available diagnostic tests are not optimal for detecting clinical resistance to the neuraminidase inhibitor antiviral drugs, and additional tests are being developed (316,318). Postmarketing surveillance for neuraminidase inhibitor-resistant influenza viruses is being conducted (319).

#### **Indications for Use of Antivirals When Susceptibility Exists**

##### **Treatment**

When administered within 2 days of illness onset to otherwise healthy adults, zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day compared with placebo (91,320--334). More clinical data are available concerning the efficacy of zanamivir and oseltamivir for treatment of influenza A virus infection than for treatment of influenza B virus infection (324,335--344). However, in vitro data and studies of treatment among mice and ferrets (345--352), in addition to clinical studies, have documented that zanamivir and oseltamivir have activity against influenza B viruses (310,317,325,329,353,354).

Data are limited regarding the effectiveness of the antiviral agents in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Evidence for the effectiveness of these antiviral drugs is principally based on studies of patients with uncomplicated influenza (355). Data are limited concerning the effectiveness of zanamivir and oseltamivir for treatment of influenza among persons at high risk for serious complications of influenza (31,321,322,324,325,330--338). Among influenza virus infected participants in 10 clinical trials, the risk for pneumonia among those participants receiving oseltamivir was approximately 50% lower than among those persons receiving a placebo (339). A similar significant reduction was also found for hospital admissions; a 50% reduction was observed in the small subset of high-risk participants, although this reduction was not statistically significant. Fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations (295,322,328,329). One study of oseltamivir treatment documented a decreased incidence of otitis media among children (323). Inadequate data exist regarding the safety and efficacy of any of the influenza antiviral drugs for use among children aged <1 year (289).

Initiation of antiviral treatment within 2 days of illness onset is recommended. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

### **Chemoprophylaxis**

Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in preventing and controlling influenza. In community studies of healthy adults, both oseltamivir and zanamivir are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%) (324,340,356). Both antiviral agents also have been reported to prevent influenza illness among persons administered chemoprophylaxis after a household member had influenza diagnosed (341,353,356). Experience with chemoprophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited in comparison with the adamantanes (310,337,338,342--344). One 6-week study of oseltamivir chemoprophylaxis among nursing home residents reported a 92% reduction in influenza illness (310,357). Use of zanamivir has not been reported to impair the immunologic response to influenza vaccine (317,358). Data are not available regarding the efficacy of any of the four antiviral agents in preventing influenza among severely immunocompromised persons.

When determining the timing and duration for administering influenza antiviral medications for chemoprophylaxis, factors related to cost, compliance, and potential side effects should be considered. To be maximally effective as chemoprophylaxis, the drug must be taken each day for the duration of influenza activity in the community.

**Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun.** Persons at high risk for complications of influenza still can be vaccinated after an outbreak of influenza has begun in a community. However, development of antibodies in adults after vaccination takes approximately 2 weeks (265,266). When influenza vaccine is administered while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccine for the first time can require 6 weeks of chemoprophylaxis (i.e., chemoprophylaxis for 4 weeks after the first dose of vaccine and an additional 2 weeks of chemoprophylaxis after the second dose).

**Persons Who Provide Care to Those at High Risk.** To reduce the spread of virus to persons at high risk during community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact include employees of hospitals, clinics, and chronic-care facilities; household members; visiting nurses; and volunteer workers. If an outbreak is caused by a strain of influenza that might not be covered by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status.

**Persons Who Have Immune Deficiencies.** Chemoprophylaxis can be considered for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV, chiefly those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if chemoprophylaxis is administered.

**Other Persons.** Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated. Chemoprophylaxis also can be offered to persons who wish to avoid influenza illness. Health-care providers and patients should make this decision on an individual basis.

### Control of Influenza Outbreaks in Institutions

Using antiviral drugs for treatment and chemoprophylaxis of influenza is a key component of influenza outbreak control in institutions. In addition to antiviral medications, other outbreak-control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, reoffering influenza vaccinations to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients (359--361) (see Additional Information Regarding Influenza Virus Infection Control Among Specific Populations).

The majority of published reports concerning use of antiviral agents to control influenza outbreaks in institutions are based on studies of influenza A outbreaks among nursing home populations that received amantadine or rimantadine (335,362--366). Less information is available concerning use of neuraminidase inhibitors in influenza A or B institutional outbreaks (337,338,344,357,367). When confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis should be started as early as possible to reduce the spread of the virus. In these situations, having preapproved orders from physicians or plans to obtain orders for antiviral medications on short notice can substantially expedite administration of antiviral medications.

When outbreaks occur in institutions, chemoprophylaxis should be administered to all residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 1 week after the end of the outbreak. The dosage for each resident should be determined individually. Chemoprophylaxis also can be offered to unvaccinated staff members who provide care to persons at high risk. Chemoprophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is suspected to be caused by a strain of influenza virus that is not well-matched to the vaccine.

In addition to nursing homes, chemoprophylaxis also can be considered for controlling influenza outbreaks in other closed or semiclosed settings (e.g., dormitories or other settings in which persons live in close proximity).

To limit the potential transmission of drug-resistant virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact as much as possible between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis (see Antiviral Drug-Resistant Strains of Influenza Virus).

#### Dosage

Dosage recommendations vary by age group and medical conditions (Table 1).

#### Children

**Zanamivir.** Zanamivir is approved for treatment of influenza among children aged  $\geq 7$  years. The recommended dosage of zanamivir for treatment of influenza is two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart); the chemoprophylaxis dosage of zanamivir for children aged  $\geq 5$  years is 10 mg (two inhalations) once a day (317).

**Oseltamivir.** Oseltamivir is approved for treatment and chemoprophylaxis among persons aged  $\geq 1$  year. Recommended treatment and chemoprophylaxis dosages of oseltamivir for children vary by the weight of the child. The treatment dosage recommendation of oseltamivir for children who weigh  $\leq 15$  kg is 30 mg twice a day; for children weighing  $>15$ --23 kg, 45 mg twice a day; for those weighing  $>23$ --40 kg, 60 mg twice a day; and for children weighing  $>40$  kg, 75 mg twice a day (310). The chemoprophylaxis recommended dosage of oseltamivir for children weighing  $\leq 15$  kg is 30 mg once a day; for those weighing  $>15$ --23 kg, 45 mg once a day; for those weighing  $>23$ --40 kg, 60 mg once a day; and for those weighing  $>40$  kg, 75 mg once a day.

#### Persons Aged $\geq 65$ Years

**Zanamivir and Oseltamivir.** No reduction in dosage is recommended on the basis of age alone.

#### Persons with Impaired Renal Function

**Zanamivir.** Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir, decreases in renal clearance, increases in half-life, and increased systemic exposure to zanamivir were observed (317,368).

However, a limited number of healthy volunteers who received high doses of zanamivir intravenously tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose (369,370). On the basis of these considerations, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild-to-moderate or severe impairment in renal function (317).

**Oseltamivir.** Serum concentrations of oseltamivir carboxylate, the active metabolite of oseltamivir, increase with declining renal function (310,371). For patients with creatinine clearance of 10--30 mL/min (310), a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the chemoprophylaxis dosage to 75 mg every other day is recommended. No treatment or chemoprophylaxis dosing recommendations are available for patients undergoing routine renal dialysis treatment.

#### **Persons with Liver Disease**

**Zanamivir and Oseltamivir.** Neither of these medications has been studied among persons with hepatic dysfunction.

#### **Persons with Seizure Disorders**

**Zanamivir and Oseltamivir.** Seizure events have been reported during postmarketing use of zanamivir and oseltamivir, although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

#### **Route**

Oseltamivir is administered orally in capsule or oral suspension form. Zanamivir is available as a dry powder that is self-administered via oral inhalation by using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of correct use of this device.

#### **Pharmacokinetics**

##### **Zanamivir**

In studies of healthy volunteers, approximately 7%--21% of the orally inhaled zanamivir dose reached the lungs, and 70%--87% was deposited in the oropharynx (317,372). Approximately 4%--17% of the total amount of orally inhaled zanamivir is systemically absorbed. Systemically absorbed zanamivir has a half-life of 2.5--5.1 hours and is excreted unchanged in the urine. Unabsorbed drug is excreted in the feces (317,370).

##### **Oseltamivir**

Approximately 80% of orally administered oseltamivir is absorbed systemically (371). Absorbed oseltamivir is metabolized to oseltamivir carboxylate, the active neuraminidase inhibitor, primarily by hepatic esterases. Oseltamivir carboxylate has a half-life of 6--10 hours and is excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway (310,373). Unmetabolized oseltamivir also is excreted in the urine by glomerular filtration and tubular secretion (325).

#### **Side Effects and Adverse Reactions**

When considering use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (Table 1); presence of other medical conditions; indications for use (i.e., chemoprophylaxis or treatment); and the potential for interaction with other medications.

##### **Zanamivir**

In a study of zanamivir treatment of ILI among persons with asthma or chronic obstructive pulmonary disease where study medication was administered after use of a B<sub>2</sub>-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a >20% decline in forced expiratory volume in 1 second (FEV<sub>1</sub>) after treatment (317,330). However, in a phase I study of persons with mild or moderate asthma who did not have ILI, one of 13 patients experienced bronchospasm after administration of zanamivir (317). In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Certain patients had underlying airway disease (e.g., asthma or chronic obstructive pulmonary disease). Because of the risk for serious adverse events and because the efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying airway disease (317). If physicians decide to prescribe zanamivir to patients with underlying chronic respiratory disease after carefully considering potential risks and benefits, the drug should be used with caution under conditions of appropriate monitoring and supportive care, including the availability of short-acting bronchodilators (355). Patients with asthma or chronic obstructive pulmonary disease who use zanamivir are advised to 1) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and 2) stop using zanamivir and contact their physician if they experience difficulty breathing (317).

No definitive evidence is available regarding the safety or efficacy of zanamivir for persons with underlying respiratory or cardiac disease or for persons with complications of acute influenza (355). Allergic reactions, including oropharyngeal or facial edema, also have been reported during postmarketing surveillance (317,337). In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and for those receiving placebo (i.e., inhaled lactose vehicle alone) (320--325,337).

The most common adverse events reported by both groups were diarrhea; nausea; sinusitis; nasal signs and symptoms; bronchitis; cough; headache; dizziness; and ear, nose, and throat infections. Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined (317).

**Oseltamivir**

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%) (310,326,327,374). Among children treated with oseltamivir, 14% had vomiting, compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect (329), whereas a limited number of adults who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (310). Similar types and rates of adverse events were reported in studies of oseltamivir chemoprophylaxis (310). Nausea and vomiting might be less severe if oseltamivir is taken with food (317,310).

**Use During Pregnancy**

No clinical studies have been conducted regarding the safety or efficacy of zanamivir or oseltamivir for pregnant women. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these two drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus. Oseltamivir and zanamivir are both "Pregnancy Category C" medications (see manufacturers' package inserts) (317,375).

**Drug Interactions**

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro data and data from studies using rats (310,373).

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential exists for interaction with other agents excreted by this pathway. For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of oseltamivir carboxylate by approximately 50% and a corresponding approximate twofold increase in the plasma levels of oseltamivir carboxylate (304,367).

No published data are available concerning the safety or efficacy of using combinations of any of these influenza antiviral drugs. For more detailed information concerning potential drug interactions for any of these influenza antiviral drugs, package inserts should be consulted.

Table 1: (use Table 6 in MMWR) Recommended daily dosage of influenza medications for treatment and chemoprophylaxis

**Table 1. Recommended adult<sup>1</sup> daily dosage of antiviral medication for treatment and prophylaxis**

Antiviral agent	Age Group <sup>1</sup>	
	13-64 years	≥65 years
<b>Zanamivir<sup>2</sup></b>		
Treatment	10 mg (two inhalations) twice daily x 5 days	10 mg (two inhalations) twice daily x 5 day
Prophylaxis	10 mg (two inhalations) twice daily	10 mg (two inhalations) twice daily
<b>Oseltamivir<sup>3</sup></b>		
Treatment	75 mg twice daily x 5 days	75 mg twice daily x 5 days
Prophylaxis	75 mg once daily	75 mg once daily

<sup>1</sup> Dosage for children available from Reference 1.

<sup>2</sup> Zanamivir is administered via inhalation using a plastic device included in the package with the medication. 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.

<sup>3</sup> A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.