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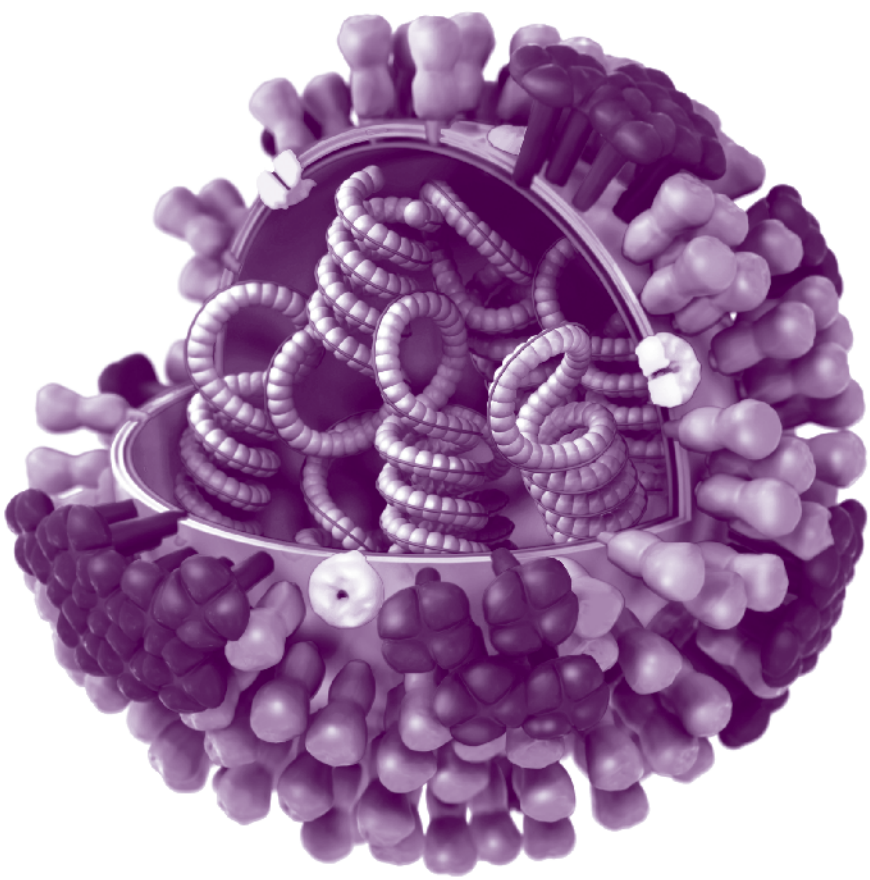
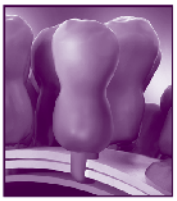
Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)





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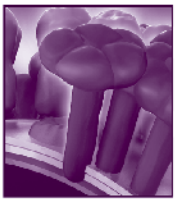

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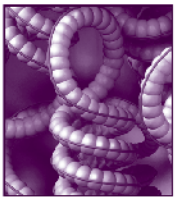

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On the cover: This illustration depicts the influenza A virus. Graphic created by Dan J. Higgins, Division of Communication Services, CDC.

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Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

This report updates previous recommendations by CDC's Advisory Committee on Immunization Practices (ACIP) regarding the use of antiviral agents for the prevention and treatment of influenza (CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR *2008;57[No. RR-7]). This report contains information on treatment and chemoprophylaxis of influenza virus infection and provides a summary of the effectiveness and safety of antiviral treatment medications. Highlights include recommendations for use of 1) early antiviral treatment of suspected or confirmed influenza among persons with severe influenza (e.g., those who have severe, complicated, or progressive illness or who require hospitalization); 2) early antiviral treatment of suspected or confirmed influenza among persons at higher risk for influenza complications; and 3) either oseltamivir or zanamivir for persons with influenza caused by 2009 H1N1 virus, influenza A (H3N2) virus, or influenza B virus or when the influenza virus type or influenza A virus subtype is unknown; 4) antiviral medications among children aged <1 year; 5) local influenza testing and influenza surveillance data, when available, to help guide treatment decisions; and 6) consideration of antiviral treatment for outpatients with confirmed or suspected influenza who do not have known risk factors for severe illness, if treatment can be initiated within 48 hours of illness onset. Additional information is available from CDC's influenza website at http://www.cdc.gov/flu, including any updates or supplements to these recommendations that might be required during the 2010–11 influenza season. Health-care providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information. Recommendations related to the use of vaccines for the prevention of influenza during the 2010–11 influenza season have been published previously (CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices [ACIP], 2010.* MMWR *2010;59[No. RR-8]).*

Introduction

In the United States, annual epidemics of influenza occur typically during the late fall through early spring. Influenza viruses can cause disease among persons in any age group, but rates of illness are highest among children (*1,2*). During most influenza seasons, rates of serious illness and death are highest among persons aged ≥65 years, children aged <2 years, and persons of any age who have medical conditions that place them at increased risk for complications from influenza (*3,4*). In addition, data from epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicated that the risk for influenza complications was also increased among persons who are morbidly obese (body-mass index [BMI] ≥40) and American Indians/Alaska Natives (*5–8*). Influenza illness caused by 2009 pandemic influenza A (H1N1) (2009 H1N1) virus is expected to occur during winter influenza seasons in the Northern and Southern hemispheres. The extent of influenza activity caused by strains of the two seasonal influenza A virus subtypes (seasonal H1N1 and H3N2) that have cocirculated since 1977 and influenza B virus strains is unpredictable, although seasonal H1N1 virus strains have been detected very rarely

The material in this report originated in the National Center for Immunization and Respiratory Diseases, Anne Schuchat, MD, Director, and the Influenza Division, Nancy Cox, PhD, Director.
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worldwide since 2009. In the postpandemic period, 2009 H1N1 virus strains now are considered to be the predominant seasonal influenza A (H1N1) virus strains.

On the basis of epidemiologic studies of seasonal influenza or 2009 H1N1, persons at higher risk for influenza complications include:

- children aged <5 years (especially those aged <2 years);
- adults aged ≥65 years;
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury) (*9*);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged ≤18 years who are receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- persons who are morbidly obese (i.e., BMI ≥40); and
- residents of nursing homes and other chronic-care facilities.

For children, the risk for severe complications from seasonal influenza is highest among those aged <2 years, who have much higher rates of hospitalization for influenza-related complications compared with older children (*3*). Medical care and emergency department visits attributable to influenza are increased among children aged <5 years compared with older children (*10*). Persons aged ≤18 years who receive long-term aspirin therapy and have influenza are at risk for Reye's syndrome.

Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. All persons aged ≥6 months are recommended for annual influenza vaccination (*11*). Antiviral medications are effective for the prevention of influenza, and, when used for treatment, can reduce the duration and severity of illness (*6,12–23*). Early antiviral treatment can reduce the risk for severe illness or death related to influenza (*6,12,23–27*). However, the emergence of resistance to one or more of the four licensed antiviral agents (oseltamivir, zanamivir, amantadine, and rimantadine) among some circulating influenza virus strains during the past 5 years has complicated antiviral treatment and chemoprophylaxis recommendations. The selection of antiviral medications should be considered in the context of any available information about surveillance data on influenza antiviral resistance patterns among circulating influenza viruses, local, state, and national influenza surveillance information on influenza virus type or influenza A virus subtype, the characteristics of the person who is ill, and results of influenza testing if testing is done. Empiric antiviral treatment often is required to avoid treatment delays (*28*).

Methods

CDC's Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Work Group* meets monthly throughout the year to discuss newly published studies, review current guidelines, and consider potential revisions to the recommendations. As they review the annual recommendations for consideration of the full ACIP, members of the Work Group consider a variety of issues, including burden of influenza illness, vaccine efficacy and effectiveness, safety and coverage in groups recommended for vaccination, feasibility, cost-effectiveness, and anticipated vaccine supply. Work group members also request periodic updates on antiviral production, supply, safety, efficacy, and effectiveness from clinician researchers, regulatory agencies, public health epidemiologists, and manufacturers and review influenza surveillance and antiviral resistance data obtained from CDC's Influenza Division.

Published, peer-reviewed studies are the primary source of data used by ACIP in making recommendations for the prevention and control of influenza, but unpublished data that are relevant to issues under discussion also are considered. The best evidence for antiviral efficacy comes from randomized, controlled trials that assess laboratory-confirmed influenza virus infection as an outcome measure. However, randomized, placebo-controlled trials might be difficult to perform in populations for which antiviral treatment already is recommended. Observational studies that assess outcomes associated with laboratory-confirmed influenza virus infection can provide important antiviral effectiveness data but are more subject to biases and confounding that can affect validity and the size of effects measured. Randomized, placebo-controlled clinical trials are the best source of antiviral safety data for common adverse events; however, such studies do not have the power to identify rare but potentially serious adverse events. In cited studies that included statistical comparisons, a difference was considered to be statistically significant if the p-value was <0.05 or the 95% confidence interval (CI) around an estimate of effect allowed rejection of the null hypothesis (i.e., no effect).

These recommendations were presented to the full ACIP and approved in June 2009. Modifications were made to the ACIP statement during the subsequent review process at CDC to update and clarify wording in the document. Data presented in this report were current as of December 2010. Further updates, if needed, will be posted at CDC's influenza website (http://www.cdc.gov/flu).

Primary Changes and Updates in the Recommendations

These recommendations include six principal changes or updates from previous recommendations for use of antivirals for the prevention and control of influenza:

* A list of the members appears on page 25 of this report.

- Antiviral treatment is recommended as soon as possible for patients with confirmed[†] or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization.
- Antiviral treatment is recommended as soon as possible for outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions; clinical judgment should be an important component of outpatient treatment decisions.
- Recommended antiviral medications include oseltamivir and zanamivir, on the basis of recent viral surveillance and resistance data indicating that >99% of currently circulating influenza virus strains are sensitive to these medications. Amantadine and rimantadine should not be used because of the high levels of resistance to these drugs among circulating influenza A viruses, but information about these drugs is provided for use if current recommendations change because of the reemergence of adamantane-susceptible strains.
- Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants aged <1 year when indicated.
- Antiviral treatment also may be considered on the basis of clinical judgment for any outpatient with confirmed or suspected influenza who does not have known risk factors for severe illness if treatment can be initiated within 48 hours of illness onset.
- Because antiviral resistance patterns can change over time, clinicians should monitor local antiviral resistance surveillance data.

Influenza Virus Transmission

Influenza viruses are thought to spread from person to person primarily through large-particle respiratory droplet transmission (e.g., when an infected person coughs or sneezes near a susceptible person) (*29*). Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets generally travel only short distances (approximately ≤6 feet) through the air. Indirect contact transmission via hand transfer of influenza virus from virus-contaminated surfaces or objects to mucosal surfaces of the face (e.g., nose and mouth) or airborne transmission via small-particle aerosols in the vicinity of the infectious person also might occur; however, the relative contribution of the different modes of influenza transmission is unclear (*29–34*). Airborne transmission over longer distances (e.g., from one patient's room to another) has not been documented and is not thought to occur. However, generation of aerosols is thought to have been a possible source of nosocomial transmission from a patient receiving noninvasive ventilation to other patients on a medical ward (*35*). The typical incubation period for influenza is 1–4 days (average: 2 days) (*36*). The serial interval (time between onsets among epidemiologically related cases) for influenza among household contacts is estimated to be 3–4 days (*37,38*). Adults can shed influenza virus from the day before symptoms begin through 5–10 days after illness onset (*39,40*). However, the amount of virus shed, and presumably infectivity, decreases rapidly by 3–5 days after illness onset in an experimental adult human infection model, with shedding completed in most persons by 5–7 days after illness onset (*39,40*). Young children also might shed virus several days before illness onset, and children can be infectious for ≥10 days after onset of symptoms (*41*). Prolonged viral replication has been reported in adults with severe disease, including those with comorbidities or those receiving corticosteroid therapy (*42,43*). Severely immunocompromised persons can shed virus for weeks or months (*44–48*). Epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicate that viral shedding, clinical illness, and transmissibility in a household setting are similar compared with seasonal influenza (*38*).

Clinical Signs and Symptoms of Influenza

Uncomplicated influenza illness, including illness caused by seasonal influenza viruses or 2009 H1N1 virus, is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis) (*49,50*). Mild illness without fever also can occur and has been reported in 6%–33% of persons infected with 2009 H1N1 virus (*38,51,52*). Asymptomatic infection also can occur, but the contribution of asymptomatic infection to influenza virus transmission is uncertain. In one study, household contacts of persons with laboratory-confirmed 2009 H1N1 virus infection had baseline and convalescent serum samples collected. Among those who had serologic evidence of 2009 H1N1 virus infection, 36% did not shed detectable virus or report illness (*38*). Among children, otitis media, nausea, and vomiting also are reported commonly with influenza illness (*53,54*). Uncomplicated influenza illness typically resolves after 3–7 days for the majority of persons, although cough and malaise can persist for >2 weeks (*49*).

Complications from influenza virus infection can include primary influenza viral pneumonia (*55*); exacerbation of underlying medical conditions (e.g., pulmonary or cardiac disease); secondary bacterial pneumonia, sinusitis, or otitis media; or coinfections with other viral or bacterial pathogens (*49,51,54*). Young children with influenza virus infection might have initial symptoms mimicking bacterial sepsis with high fevers (*10,54,56,57*), and febrile seizures have been reported in 6%–20% of children hospitalized with influenza virus infection (*54,58,59*). One study of children hospitalized with laboratory-confirmed influenza-associated pneumonia reported a higher risk for intensive care admission, respiratory failure, and death compared with children hospitalized with influenza without pneumonia (*60*). Age <5 years and asthma were associated significantly with influenza-associated pneumonia (*60*). Severe illness with seasonal influenza virus infection can occur even among young and previously healthy persons; in one case series, 19 (50%) of 38 adults (median

[†] Influenza virus infection can be confirmed by different testing methods that might be available in a clinical setting or laboratory (e.g., rapid influenza diagnostic test, immunoflorescence, reverse transcription-polymerase chain reaction, or viral culture).

age: 52 years) with severe viral pneumonia caused by influenza were previously healthy; 11 (29%) had a concomitant or secondary bacterial pneumonia, 24 (63%) required intensive care unit admission for a median of 11 days, and 17 (45%) died (*55*).

During the 2009 H1N1 pandemic, the clinical syndrome most likely to be the cause of hospitalization was diffuse viral pneumonitis, which in some instances led to shock and respiratory failure (*6,7,61–64*). Infection with any influenza virus strain can lead to bacterial pneumonia and other bacterial coinfections. Secondary or concomitant bacterial pneumonia caused by *Staphylococcus aureus, Streptococcus pneumoniae, S. pyogenes*, or other virulent bacteria has been suspected or identified in 20%–38% of 2009 H1N1 patients who died or required intensive care unit admission (*51,63–67*). Exacerbation of underlying comorbidities such as asthma, chronic obstructive pulmonary disease (COPD) or cardiac disease was also a major contributor to morbidity and mortality. One or more underlying comorbidities were present in 50%–80% of adults and children requiring hospitalization (*6,7,63*). Pregnant and postpartum (within 2 weeks of delivery) women were at increased risk for severe illness requiring hospitalization in multiple studies, accounting for 6%–10% of patients who required hospitalization or died in some case series (*6,7,12,25,68*).

Population-based studies among hospitalized children with laboratory-confirmed seasonal influenza have demonstrated that although the majority of hospitalizations are brief (≤2 days), 4%–11% of children hospitalized with laboratory-confirmed influenza required treatment in the intensive care unit, and 3% required mechanical ventilation (*10,54*). Among 1,308 hospitalized children in one study, 1,046 (80%) were aged <5 years, and 353 (27%) were aged <6 months (*54*). In another study of 4,015 laboratory-confirmed seasonal influenza hospitalizations in children, the median length of hospitalization was 3–4 days; 1,894 (40%) children had at least one chronic high-risk medical condition, and the highest hospitalization rate was in children aged <6 months (*69*). Influenza virus infection also has been associated rarely with encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye's syndrome (*53,59,70–76*). Secondary bacterial pneumonia or bacterial co-infection can lead to severe illness (*77,78*). Influenza complications among children during the 2009 influenza A (H1N1) pandemic were generally similar to those observed among children with seasonal influenza. However, much higher rates of illness among children observed during the 2009 H1N1 pandemic compared with most influenza seasons resulted in much higher rates of children hospitalized with complications. One study reported more neurologic complications associated with 2009 H1N1 virus infection among children compared with seasonal influenza virus infections (*79*). In one study, rates of hospitalization were estimated to be tenfold higher during the pandemic compared with a typical influenza season (*62*).

Respiratory illnesses caused by influenza virus infection are difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of signs and symptoms alone. Sensitivity and positive predictive value of clinical definitions vary, depending on the prevalence of other respiratory pathogens and the level of influenza activity in the community. Among generally healthy older adolescents and adults living in areas with confirmed influenza virus circulation, estimates of the positive predictive value of a simple clinical case definition of influenza (acute onset of cough and fever) for laboratory-confirmed influenza virus infection have varied (range: 79%–88%) (*80–82*).

Young children are less likely to experience typical influenza signs and symptoms (e.g., fever and cough). In studies conducted during a winter influenza season among children aged 5–12 years, the positive predictive value of fever and cough together was 71%–83%, compared with 64% among children aged <5 years (*81*). In one large, population-based surveillance study in which all children with fever or symptoms of acute respiratory tract infection during influenza season were tested for influenza (with test results not available until after discharge), 55 (70%) of 79 hospitalized children aged <6 months with laboratory-confirmed influenza were reported to have fever and cough, compared with 74 (91%) of 81 hospitalized children aged 6 months–5 years (*10*). Among children aged <5 years who subsequently were shown to have laboratory-confirmed influenza, only 22 (28%) of 79 hospitalized children and 47 (17%) of 274 children treated as outpatients had a discharge diagnosis of influenza (*10*). The predominance of atypical presentations involving primarily dehydration, irritability or poor oral intake have been reported among some young children with 2009 H1N1 virus infection (*77,78*).

Clinical case definitions have performed poorly in some studies of older patients. A study of nonhospitalized patients aged ≥60 years indicated that the presence of fever, cough, and acute onset had a positive predictive value of 30% for influenza (*83*). Among 56 hospitalized patients aged ≥65 years with chronic cardiopulmonary disease, a combination of fever, cough, and illness of <7 days had a positive predictive value of 53% for confirmed influenza virus infection (*84*). In addition, the absence of symptoms of influenza-like illness (ILI) does not effectively rule out influenza; among hospitalized adults with laboratory-confirmed influenza in two studies, only 44%–51% had typical ILI symptoms (*85,86*). A study of 94 vaccinated older persons with chronic lung disease reported that cough was not predictive of laboratory-confirmed influenza virus infection, although having both fever or feverishness and myalgia had a positive predictive value of 41% (*87*). These results highlight the challenges of identifying influenza illness in the absence of laboratory confirmation and indicate that the diagnosis of influenza should be considered in patients with respiratory symptoms or fever during influenza season.

Role of Laboratory Diagnosis

Influenza surveillance information and diagnostic testing can aid clinical judgment and help guide treatment decisions. In some surveys, 60%–69% of practitioners reported testing patients for influenza during the influenza season (*88,89*). 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 (*80–87*) (see Clinical Signs and Symptoms of Influenza).

Diagnostic tests available for influenza include viral culture, serology, rapid diagnostic (antigen) testing, reverse transcription-

polymerase chain reaction (RT-PCR), and immunofluorescence assays (*90*). Serologic testing requires paired acute and convalescent sera, is not widely available, and is not recommended except for epidemiologic investigations and research. As with any diagnostic test, influenza test results should be evaluated in the context of other clinical and epidemiologic information available to health-care providers. Sensitivity and specificity of any test for influenza, including those that detect 2009 H1N1 virus, can vary by the laboratory that performs the test, the type of test used, the type of specimen tested, the quality of the specimen, and the timing of specimen collection in relation to illness onset. Among respiratory specimens for viral isolation or rapid detection of influenza viruses, nasopharyngeal and nasal specimens generally have higher yields than throat swab specimens (*91*). In addition, positive influenza tests that yield vaccine virus strains have been reported up to 7 days after receipt of live attenuated influenza virus vaccine (*92*).

Commercial rapid influenza diagnostic tests (RIDTs) are available that can detect influenza virus antigens within 15 minutes of testing (*93,94*). Certain tests are cleared by the Food and Drug Administration (FDA) for use in any outpatient setting whereas others must be used in a moderately complex clinical laboratory. These RIDTs differ by whether they can distinguish between influenza virus types. Available tests can either 1) detect influenza A and B viruses but not distinguish between the two types or 2) detect both influenza A and B viruses and also distinguish between the two types. None of the rapid influenza diagnostic tests specifically identifies any influenza A virus subtypes.

The types of specimens acceptable for use (i.e., nasopharyngeal or nasal aspirates, swabs, and washes or throat swabs) also vary by test, but all perform best when collected as close to illness onset as possible (e.g., ≤72 hours after onset). RT-PCR can be used to detect viral RNA in upper and lower respiratory tract specimens. Endotracheal aspirate or bronchoalveolar lavage specimens have higher yields in patients with lower respiratory tract illness, especially later in the course of illness. In addition, repeated collection of specimens from the upper and lower respiratory tract might be necessary if results are initially negative for a patient in whom clinical suspicion of influenza is high (*51*).

Rapid diagnostic tests for influenza have high specificity (>90%) but have low to moderate sensitivity (20%–70%) compared with other influenza tests. The sensitivities of RIDTs are lower than for viral culture or RT-PCR and vary by test (*94–98*). Recent studies have found sensitivity to be as low as 42% in clinical practice and 19% among adults participating in a clinical study (*96,99*). RIDTs appear to have higher sensitivity when used in young children, compared with adults, possibly because young children with influenza typically shed higher concentrations of influenza viruses than adults (*100*). Similar to results for other influenza virus strains, the specificity of available RIDTs for detection of 2009 H1N1 virus is high (>95%), but sensitivity is 11%–70%. These data indicate that negative RIDT results should not be used to make treatment or infection-control decisions especially when influenza viruses are known to be circulating in the community (*51,101–104*).

The limitations of RIDTs must be understood for results to be interpreted properly. Positive rapid influenza diagnostic test results are generally reliable when community influenza activity is high and might be useful in deciding whether to initiate antiviral treatment. Negative rapid test results are not helpful in making treatment decisions for individual patients when influenza activity in a community is high because of the limited sensitivity of the rapid tests. If a definitive diagnosis is needed, providers should consider confirming negative test results with more sensitive and specific influenza testing. More sensitive and specific tests include viral culture or RT-PCR. The positive predictive value of RIDTs will be lower during periods of low influenza activity, and clinicians should consider the positive and negative predictive values of any test in the context of the level of influenza activity in their community when interpreting results (*105*). When local influenza activity is high, persons with severe respiratory symptoms or persons with acute respiratory illness who are at higher risk for influenza complications are recommended for empirical influenza antiviral treatment despite a negative rapid influenza test result unless illness can be attributed to another cause. However, because certain bacterial infections can produce symptoms similar to influenza, providers should consider the possibility of bacterial infections or coinfections and treat accordingly. In addition, secondary invasive bacterial infections can be a severe complication of influenza. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid influenza diagnostic tests. Additional updated information concerning diagnostic testing is available at http://www.cdc.gov/flu/professionals/labdiagnosis.htm.

Clinical specimens collected in virus surveillance systems for viral culture are critical for monitoring influenza virus activity. Only culture isolates of influenza viruses can provide specific information regarding the antigenic characteristics of influenza viruses, and data on antiviral resistance and influenza A virus subtype cannot be obtained from RIDTs. This information is needed to compare current circulating influenza virus strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis, and to select vaccine virus strains for the coming year. Virus isolates are needed to monitor antiviral resistance in circulating human influenza virus strains and the emergence of novel influenza A virus infections in humans that might pose a pandemic threat (e.g., human infection with swine or avian influenza A viruses). Influenza surveillance by state and local health departments and CDC can provide information regarding the circulation of influenza viruses in the community, which can help inform decisions about the likelihood that a compatible clinical syndrome is indeed influenza. Influenza testing guidance for clinicians is available from the Infectious Diseases Society of America (IDSA) (*105,106*).

RT-PCR is the most accurate and sensitive test for detecting influenza viruses, including the 2009 H1N1 virus (*51,105*). RT-PCR platforms capable of subtyping influenza A viruses are available in state public health and some reference laboratories. A standardized influenza real-time RT-PCR protocol and platform developed by CDC has been distributed (*107*). The capacity to subtype influenza

A viruses can be important when antiviral resistance patterns differ between circulating influenza A virus subtypes. The time required for testing and the limited availability of RT-PCR capable of subtyping limits the usefulness of this test for medical management of individual patients. However, surveillance data provided by public health departments or other laboratories with RT-PCR subtyping capacity can be useful in identifying the presence of each influenza A virus subtype in the community, and should be consulted routinely by clinicians when feasible (*108*). RT-PCR tests for seasonal influenza are unable to provide subtyping information when used to test specimens from patients with 2009 H1N1 virus infections. RT-PCR tests for the detection of 2009 H1N1 virus were developed by CDC and distributed to state public health and other reference laboratories. One RT-PCR test that can distinguish 2009 pandemic H1N1 virus from other influenza A viruses has been cleared by FDA, and this test appears to have similar sensitivity and specificity compared with the test developed by CDC (*109*).

Antiviral Agents for Influenza

Four licensed prescription influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Zanamivir and oseltamivir are related antiviral medications in a class of medications known as neuraminidase inhibitors. These two medications are active against both influenza A and B viruses. They differ in pharmacokinetics, safety profiles, routes of administration, approved age groups, and recommended dosages (Table 1).

Amantadine and rimantadine are related antiviral drugs in a class of medications known as adamantanes. These medications are active against influenza A viruses but not influenza B viruses. In recent years, widespread adamantane resistance among influenza A (H3N2) virus strains has made this class of medications less useful clinically. In addition, circulating 2009 H1N1 virus strains are resistant to adamantanes (*110*). Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.

Antiviral Drug Resistance Among Influenza Viruses

Oseltamivir and Zanamivir (Neuraminidase Inhibitors)

Oseltamivir or zanamivir are the primary antiviral agents recommended for the prevention and treatment of influenza (*28,51,105*). Antiviral resistance profiles for currently circulating influenza A and B viruses are listed (Table 2).

Because currently circulating influenza A (H3N2) and 2009 H1N1 viruses are resistant to adamantanes, these medications are not recommended for use against influenza A virus infections. However, influenza A and B virus strains are, with rare exception, susceptible to oseltamivir and zanamivir (*110*). Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified, including with rare episodes of limited transmission (*111–115*), but the public health impact has been limited to date. However, additional sporadic cases of oseltamivir-resistant 2009 H1N1 virus infection can be expected, and ongoing surveillance for oseltamivir resistance among influenza

TABLE 1. 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.

TABLE 2. Summary of antiviral resistance among influenza viruses worldwide, December 2010*

	Influenza A viruses		Influenza B viruses†
Antiviral	**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

viruses is essential for public health because oseltamivir is the most widely used antiviral medication.

Development of resistance to zanamivir or oseltamivir also has been identified during treatment of seasonal influenza (*116–120*). One study reported that oseltamivir-resistant seasonal influenza A viruses were isolated from nine (18%) of 50 Japanese children during treatment with oseltamivir (*121*). Transmission of neuraminidase-inhibitor–resistant influenza B viruses has been reported among household contacts (*122*). Development of resistance to oseltamivir during treatment was more common among seasonal influenza A (H1N1) virus infections (27%) compared with seasonal influenza A (H3N2) (3%) or B (0) viruses in another study (*123*). Sporadic cases of resistance to oseltamivir have been observed among persons with 2009 H1N1 virus infection (e.g., immunosuppressed patients with prolonged viral replication during oseltamivir treatment and persons who developed illness while receiving oseltamivir chemoprophylaxis) (*114,124*). Emergence of oseltamivir-resistant 2009 H1N1 virus strains within 48 hours after initiation of treatment has been reported (*125*). Transmission of oseltamivir-resistant influenza B virus strains or 2009 H1N1 virus strains acquired from persons treated with oseltamivir is rare but has been documented (*112,122*). Isolation of influenza A viruses with reduced susceptibility to zanamivir have been reported rarely, although the number of posttreatment isolates tested is limited (*117–119,126*). Clinical isolates with reduced susceptibility to zanamivir have been obtained occasionally from immunocompromised children on prolonged therapy (*118,127*). Prolonged shedding of oseltamivir- or zanamivir-resistant virus by severely immunocompromised patients, even after cessation of oseltamivir treatment, has been reported (*118,127–129*). Rare cases of infection with 2009 H1N1 virus resistant or with reduced susceptibility to multiple neuraminidase inhibitors in severely immunosuppressed pediatric patients with prolonged viral replication have been reported (*130,131*).

During 2007–2008, increased resistance to oseltamivir associated with a specific mutation causing a histidine to tyrosine substitution (H275Y) in neuraminidase was reported among seasonal influenza A (H1N1) virus strains in many countries and became prevalent worldwide (*132–134*). Most persons infected with oseltamivir-resistant seasonal influenza A (H1N1) virus strains had not received oseltamivir treatment previously and were not known to have been exposed to a person receiving oseltamivir treatment or chemoprophylaxis (*133,135*). Influenza caused by oseltamivir-resistant seasonal influenza A (H1N1) virus strains appears to be similar to illness caused by oseltamivir-sensitive virus strains (*133,134,136*). Since the recent emergence of 2009 H1N1 virus, oseltamivir-resistant seasonal influenza A (H1N1) virus has been of less clinical concern because very few seasonal influenza A (H1N1) virus strains have been circulating (*113*). Nearly all sporadic cases of oseltamivir-resistant 2009 H1N1 virus infections identified to date also have been associated with the H275Y mutation in neuraminidase; these oseltamivir-resistant H275Y virus infections are susceptible to zanamivir. As of December 2010, no evidence existed of ongoing transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide.

Amantadine and Rimantadine (Adamantanes)

Adamantane resistance among circulating influenza A viruses increased rapidly worldwide beginning during 2003–2004. The percentage of influenza A virus isolates submitted from throughout the world to the World Health Organization Collaborating Center for Surveillance, Epidemiology, and Control of Influenza at CDC that were adamantane-resistant increased from 0.4% during 1994–1995 to 12.3% during 2003–2004 (*137*). During the 2005–06 influenza season, CDC determined 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 (*138*). Resistance to adamantanes remains high among influenza A isolates, with resistance detected among all tested influenza A (H3N2) and 2009 H1N1 viruses tested (*113*). Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A virus strains.

Use of Antivirals

Treatment Efficacy and Effectiveness Studies

Randomized, controlled trials conducted primarily among persons with mild illness in outpatient settings have demonstrated that zanamivir or oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day when administered within 48 hours of illness onset compared with placebo (*15,16,19–21,139–142*). One randomized, controlled trial of oseltamivir treatment among 408 children aged 1–3 years reported that when oseltamivir was started within 24 hours of illness onset, the median time to illness resolution was shortened by 3.5 days compared with placebo (*143*). Minimal or no benefit was reported in healthy children and adults when antiviral treatment was initiated >2 days

after onset of uncomplicated influenza. The amount of influenza viral shedding was reduced among those treated, but studies on whether the duration of viral shedding is reduced have been inconsistent (*38,40,144,145*) and the temporal and causal relationships between changes in influenza viral shedding and clinical outcomes have not been well-established. One evidence review concluded that neuraminidase inhibitors were not effective in reducing the severity or duration of ILI (defined as acute respiratory infection with fever and cough). However, a variety of pathogens can cause ILI besides influenza viruses, and this review did not conclude that neuraminidase inhibitors were ineffective in reducing laboratory-confirmed influenza among adults (*146,147*).

Data are limited about the effectiveness of zanamivir and oseltamivir treatment in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). In a study that combined data from 10 clinical trials, the risk for pneumonia among those participants with laboratory-confirmed influenza receiving oseltamivir treatment was approximately 50% lower than among those persons receiving a placebo and 34% lower among patients at risk for complications ($p<0.05$ for both comparisons) (*22*). Although a similar significant reduction also was determined for hospital admissions among the overall group, the 50% reduction in hospitalizations reported in the small subset of high-risk participants was not statistically significant (*22*). One randomized, controlled trial found a decreased incidence of otitis media among children treated with oseltamivir (*21*). A randomized, controlled trial among children aged 1–3 years found an 85% reduction in acute otitis media when oseltamivir treatment was started within 12 hours of illness onset, but no reduction when treatment was started >24 hours from symptom onset (*143*). Another randomized, controlled study conducted among influenza virus-infected children with asthma reported greater improvement in lung function and fewer asthma exacerbations among oseltamivir-treated children compared with those who received placebo but did not determine a difference in symptom duration (*148*). Insufficient data exist regarding the effectiveness of any of the influenza antiviral drugs for use among children aged <1 year.

Observational studies have determined that oseltamivir reduces severe clinical outcomes in patients hospitalized with influenza. A large prospective observational study assessed clinical outcomes among 327 hospitalized adults with laboratory-confirmed influenza whose health-care provider chose to use oseltamivir treatment compared with untreated influenza patients. The average age of adults in this study was 77 years, and 71% began treatment >48 hours after illness onset. In a multivariate analysis, oseltamivir treatment was associated with a significantly decreased risk for death within 15 days of hospitalization (odds ratio [OR] = 0.2; 95% CI = 0.1–0.8). Benefit was observed even among those starting treatment >48 hours after symptom onset. However, oseltamivir treatment did not reduce either the duration of hospitalization or 30-day mortality after hospitalization significantly. An additional 185 hospitalized children with laboratory-confirmed influenza were identified during this study, but none received antiviral treatment, and no assessment of outcomes based on receipt of antiviral treatment of hospitalized children could be made (*23*). A study in Thailand of patients with laboratory-confirmed influenza also found a significant (OR = 0.13 (95% CI = 0.04–0.40) reduction in mortality among patients who received oseltamivir treatment (*149*). A retrospective cohort study of 99 hospitalized persons (median age: 70 years) with laboratory-confirmed influenza who received oseltamivir indicated that persons who received oseltamivir treatment >48 hours from illness onset had a median length of stay of 6 days, compared with 4 days for persons who received oseltamivir within 48 hours of symptom onset ($p<0.0001$) (*26*), and a subsequent analysis of these data showed benefit for patients who received oseltamivir up to 96 hours after illness onset (*27*). A prospective study of 754 hospitalized adults (mean age: 70 years) with laboratory-confirmed seasonal influenza reported that oseltamivir treatment initiated within 2 days was associated with earlier hospital discharge, and improved survival was observed when oseltamivir was administered within 4 days from illness onset (*150*). One small observational study found that treatment of persons with leukemia who acquired influenza was associated with a decreased risk for death (*151*).

In one observational study, oseltamivir treatment of young adults with mild illness from 2009 H1N1 virus infection was reported to reduce the development of radiographically confirmed pneumonia, and initiation of treatment within 2 days of onset reduced the duration of fever and viral RNA shedding (*152*). Earlier neuraminidase inhibitor treatment was associated with less severe disease, and any neuraminidase inhibitor treatment had a survival benefit in observational studies of patients hospitalized with 2009 H1N1 virus infection (*6,12,65,153,154*). However, additional data on the impact of antiviral treatment on severe outcomes are needed.

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. Data from human clinical studies have indicated that zanamivir and oseltamivir have activity against influenza B viruses (*21,116,145,155,156*). However, an observational study among Japanese children with culture-confirmed influenza and treated with oseltamivir demonstrated that children with influenza A virus infection resolved fever and stopped shedding virus more quickly than children with influenza B, suggesting that oseltamivir might be less effective for the treatment of influenza B (*157*).

Treatment Indications

Clinical judgment based on underlying conditions, disease severity, and time since symptom onset are also important factors in treatment decisions. Antiviral treatment is recommended as soon as possible for all persons with suspected or confirmed influenza requiring hospitalization or who have progressive, severe or complicated illness regardless of previous health or vaccination status (*28,51,105*). In observational studies conducted among severely ill patients, both early initiation of antiviral treatment (<2 days from illness onset) and treatment up to <5 days after onset were associated with reduced morbidity and mortality, with greater benefit associated with earlier initiation of treatment (*6,7,51*). Additional research is needed to better assess the impact of treatment, but on the basis of these limited data, treatment of severely ill patients as soon as possible is strongly

BOX. Summary of influenza antiviral treatment recommendations

- Early antiviral treatment can reduce the risk of complications from influenza (e.g., pneumonia, respiratory failure, and death). Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who
  - — is hospitalized;
  - — has severe, complicated, or progressive illness; or
  - — is at higher risk for influenza complications.
- Persons at higher risk for influenza complications recommended for antiviral treatment include:
  - — children aged <2 years;*
  - — adults aged ≥65 years;
  - — persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
  - — persons with immunosuppression, including that caused by medications or by HIV infection;
  - — women who are pregnant or postpartum (within 2 weeks after delivery);
  - — persons aged <19 years who are receiving long-term aspirin therapy;
  - — American Indians/Alaska Natives;
  - — persons who are morbidly obese (i.e., body-mass index ≥40); and
  - — residents of nursing homes and other chronic-care facilities.
- Clinical judgment, on the basis of the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important to consider when making antiviral treatment decisions for high-risk outpatients. When indicated, antiviral treatment should be started as soon as possible after illness onset.
- The greatest benefit is when antiviral treatment is started within 48 hours of influenza illness onset. However, antiviral treatment might still be beneficial in patients with severe, complicated, or progressive illness and in hospitalized patients when administered >48 hours from illness onset.
- Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset.†

* Although all children aged <5 years are considered at higher risk for complications from influenza, the highest risk is for those aged <2 years, with the highest hospitalization and death rates among infants aged <6 months. Because many children with mild febrile respiratory illness might have other viral infections (e.g., respiratory syncytial virus, rhinovirus, or parainfluenza virus, or human metapneumovirus), knowledge about other respiratory viruses as well as influenza virus strains circulating in the community is important for treatment decisions. The likelihood of influenza virus infection in a patient depends on the prevalence of influenza activity in the local community and on the patient's signs and symptoms. Information about influenza activity in the United States during the influenza season is available at http://www.cdc.gov/flu/weekly. For information on local community influenza activity, clinicians should contact their local and state health departments.

† Recommended antiviral medications (neuraminidase inhibitors) are not licensed for treatment of children aged <1 year (oseltamivir) or those aged <7 years (zanamivir). Oseltamivir was used for treatment of 2009 pandemic influenza A (H1N1) virus infection in children aged <1 year under an Emergency Use Authorization, which expired on June 23, 2010. Limited information regarding use of oseltamivir for children from birth through age 1 year is available (see Table 4). Confirmation of influenza virus infection may be performed by different influenza testing methods. Information on influenza testing is available at http://www.cdc.gov/flu/professionals/diagnosis/index.htm. In areas with limited antiviral medication availability, local public health authorities might provide additional guidance about prioritizing treatment within groups at higher risk for complications. Current CDC guidance on treatment of influenza should be consulted; updated recommendations from CDC are available at http://www.cdc.gov/flu.

recommended. Treatment should not be delayed while the results of diagnostic testing are awaited (Box). Empiric antiviral treatment is often necessary, and providers should not delay initiation of treatment while awaiting confirmatory diagnostic tests results or if specimens are not obtained. Patients with suspected influenza should complete antiviral treatment for a full treatment course regardless of negative initial test results unless an alternative diagnosis can be established and clinical judgment suggests that influenza is unlikely (*28,51*).

Among outpatients, antiviral treatment with a neuraminidase inhibitor is recommended for all persons with suspected or confirmed influenza who are at higher risk for influenza complications because of age or underlying medical conditions (Box). Although all children aged <5 years are considered at higher risk for complications from influenza, the highest risk is for those aged <2 years, with the highest hospitalization and death rates among infants aged <6 months. On the basis of epidemiologic studies of patients with seasonal influenza or 2009 H1N1, persons at higher risk for influenza complications who are recommended for antiviral treatment for suspected or confirmed influenza (*11*) include:

- children aged <2 years;
- adults aged ≥65 years;
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including

diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
- persons with immunosuppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged <19 years who are receiving long-term aspirin therapy;
- American Indians/Alaska Natives;
- persons who are morbidly obese (i.e., BMI ≥40); and
- residents of nursing homes and other chronic-care facilities.

Some treatment recommendations from other expert advisory groups are more definite about the need to treat all persons at higher risk for influenza complications who are suspected of having influenza, especially if the suspected cause is 2009 H1N1 virus infection. The World Health Organization (WHO) has recommended empiric neuraminidase inhibitor treatment for all persons with suspected or confirmed 2009 H1N1 virus infection who are at increased risk for influenza complications (*51*), and similar recommendations were made by CDC during the 2009 H1N1 pandemic and the subsequent 2009–10 influenza season (*28*). IDSA recommends that all persons with laboratory-confirmed or highly suspected influenza virus infection who are at high risk for developing complications receive treatment, when treatment can begin within 48 hours after symptom onset (*105*). Clinicians who prefer not to treat empirically should discuss signs and symptoms of worsening illness with such patients and arrange for follow up by telephone or in the clinic. Options for close follow-up should be considered carefully.

Clinicians should monitor local, state, and national recommendations during the influenza season to determine the most appropriate treatment practices and receive updates on antiviral resistance profiles of the circulating viruses (Table 3). Treatment options could become complicated if oseltamivir-resistant seasonal influenza A (H1N1) virus strains that circulated during 2007–2009 reappear or if neuraminidase inhibitor resistance becomes more common among circulating H3N2 or 2009 H1N1 virus strains. The lack of influenza A virus subtyping and antiviral resistance testing availability in most settings might present additional challenges in determining optimal antiviral therapy if oseltamivir resistance among circulating influenza virus strains becomes more prevalent.

The benefits of antiviral treatment are likely to be greatest if treatment is started as soon as possible after illness onset, and evidence for benefit is strongest in studies in which treatment was started within 48 hours of illness onset. However, treatment of any person with confirmed or suspected influenza who requires hospitalization is recommended, even if the patient presents >48 hours after illness onset (*12,28,51,105*). Patients with influenza are at high risk for such secondary bacterial complications as bacterial pneumonia. Antibacterial therapy plus antiviral treatment are recommended for patients with community-acquired pneumonia when influenza also is suspected. Antibiotic treatment should be directed at likely bacterial pathogens associated with influenza such as *S. pneumoniae, S. pyogenes,* and *S. aureus*, including methicillin-resistant (MRSA), especially for hospitalized patients (*158,159*). Clinicians should consider influenza virus infection as the possible cause of any febrile respiratory illness requiring hospitalization during influenza season and consider testing for influenza and starting empiric antiviral therapy (*159*).

Treatment also can be considered, on the basis of clinical judgment, for outpatients with uncomplicated, suspected, or confirmed influenza who are not known to be at increased risk for developing severe or complicated illness if antiviral treatment can be initiated within 48 hours of illness onset. Persons with influenza who present with an uncomplicated febrile illness typically do not require treatment unless they are at higher risk for influenza complications, but early empiric antiviral treatment of these patients also might provide benefit (e.g., a shortened duration of illness). Persons with influenza who are already beginning to recover do not need to start treatment. Treatment decisions, especially those involving empiric treatment, should be informed by knowledge of influenza activity in the community. Empiric treatment for febrile respiratory illness when influenza activity in the community is low is likely to result in a large proportion of persons without influenza receiving unnecessary influenza antivirals. In addition, patients not at increased risk

TABLE 3. 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 B viruses.

for developing severe or complicated illness and who have mild, uncomplicated illness are less likely to benefit from treatment if initiated more than 48 hours after illness onset.

Treatment Issues for Patients Hospitalized with Suspected or Confirmed Influenza

Treatment of patients with severe influenza (e.g., those requiring hospitalization) presents multiple challenges. The effect of specific antiviral strategies in serious or life-threatening influenza is not established from clinical trials conducted to support licensure of oseltamivir and zanamivir, as those studies were conducted primarily among previously healthy outpatients with uncomplicated illness. However, a number of more recent observational studies have reported that oseltamivir treatment up to 96 hours after illness onset of patients hospitalized with suspected or confirmed influenza is associated with lower risk for severe outcomes (*12,23,27,65,150*). For this reason, recommendations in this report do not necessarily represent FDA-approved uses of antiviral products but are based on published expert opinion and observational studies and are subject to change as the developmental status of investigational products and the epidemiologic and virologic features of influenza change over time.

Initiation of antiviral treatment as early as possible is recommended for hospitalized patients. However, antiviral treatment might be effective in reducing morbidity and mortality in hospitalized patients even if treatment is not started until >48 hours after onset of illness. Data from observational studies indicates the benefit of antiviral treatment for hospitalized persons even when treatment is delayed (*12,23,26–28,150*). Careful attention to ventilator and fluid management and to the prevention and treatment of secondary bacterial pneumonia (e.g., *S. pneumoniae, S. pyogenes,* and *S. aureus,* including MRSA) also is critical for severely ill patients (*66,158–161*).

Treatment regimens might need to be altered to fit the clinical circumstances. For example, clinical judgment should be the guide regarding the need to extend treatment regimens longer than 5 days for patients whose illness is prolonged. No data are available to evaluate the effectiveness of larger doses of antivirals to treat severe influenza illness (e.g., viral pneumonia requiring admission to an intensive care unit), and one study indicated that enteric absorption among critically ill patients was adequate (*162*). However, doubling the dose of oseltamivir (e.g.,150 mg twice daily in adults) has been advocated as an appropriate strategy in the treatment of severely ill patients with influenza A (H5N1), and limited data suggest this dosage is well tolerated (*163*) and might be beneficial (*164*).

Limited data indicate that administering oseltamivir via a gastric tube can provide systemic absorption in some critically ill patients with 2009 H1N1 or H5N1 (*162,165,166*), and these findings might be applicable to severe illness with other influenza virus infections. However, gastric stasis or bleeding can make this administration route problematic because of the potential for reduced absorption of medication (*165,167*). For these patients, parenteral medications might be preferable, but no clinical trials have demonstrated increased benefit, and none are FDA-approved. Clinical trials are needed to better understand optimal treatment approaches, and clinicians interested in enrolling patients in clinical trials of experimental intravenous antivirals and combination antiviral treatment should consult the National Institutes of Health (available at http://www.clinicaltrials.gov). For patients who are not eligible for clinical trial enrollment, physicians might wish in some instances to pursue single-patient emergency Investigational New Drug (IND) protocols for antivirals that are not licensed. Clinicians may contact the study sponsor or manufacturer to explore this possibility and obtain information about implementing an IND protocol; contact information is available at http://www.clinicaltrials.gov.

Patients receiving antiviral medications who do not respond to treatment might have an infection with an antiviral-resistant influenza virus. Oseltamivir resistance, sometimes within 1 week of treatment initiation, has been reported particularly among immunocompromised patients with 2009 H1N1 virus infection who were receiving treatment with oseltamivir (*114,168–170*). Infection-control measures are especially important for patients who are immunocompromised to reduce the risk for transmission of oseltamivir-resistant viruses (*104,105*).

Investigational parenterally administered products that can be obtained via IND or other protocols in clinical trials include peramivir and zanamivir. Peramivir is an investigational neuraminidase inhibitor medication that has variable activity against influenza A and B viruses as reported in human and animal studies with small sample sizes (*171,172*). Investigational preparations of zanamivir that can be administered parenterally have been reported to reduce the likelihood of infection in a challenge model of experimental infection with influenza A virus (*171,173*). Intravenous zanamivir has been used with success in clinical settings (*169,170*). Intravenous zanamivir is the recommended antiviral treatment for severely ill patients with highly suspected or confirmed oseltamivir-resistant 2009 H1N1 virus infection (*51,169,174*).

For patients who are intubated, use of the zanamivir disc inhaler is not possible. Suboptimal delivery to sites of infection in patients with pneumonic or extrapulmonary disease is also of concern for patients with severe respiratory illness (*171*). Limited experimental use of an unlicensed nebulized formulation of zanamivir has been well tolerated (*175*), but use of the nebulized preparation of the licensed powder formulation contained in the disc inhaler is not recommended because it has been demonstrated to clog ventilator tubing (*176*).

Concerns about influenza viruses with pandemic potential, the appearance and widespread transmission of 2009 pandemic influenza A (H1N1), and the limited treatment options available for severely ill patients has prompted renewed interest in development of additional antiviral drugs with activity against influenza viruses (*171,177*). Clinicians should be alert to the future availability of new therapeutic options and recommendations. In addition, careful attention to infection-control measures is recommended (*104,105*), particularly in hospital areas that house immunocompromised patients.

Postexposure Chemoprophylaxis Effectiveness

In randomized, placebo-controlled trials, both oseltamivir and zanamivir were efficacious in the prevention of influenza illness among persons administered chemoprophylaxis after a household member or other close contact had laboratory-confirmed influenza (zanamivir: 72%–82%; oseltamivir: 68%–89%) (*13,14,17,18,141,178,179*). Postexposure chemoprophylaxis with neuraminidase inhibitors generally should be reserved for those who have had recent close contact with a person with influenza. Persons who can be considered for antiviral chemoprophylaxis include family or other close contacts of a person with a suspected or confirmed case who are at higher risk for influenza complications but have not been vaccinated against the influenza virus strains circulating at the time of exposure (*28,105*). Unvaccinated health-care workers who have occupational exposures and who did not use adequate personal protective equipment at the time of exposure are also potential candidates for chemoprophylaxis (*28*). Because of widespread resistance among currently circulating influenza A virus strains and inherent nonsusceptibility among influenza B viruses, adamantanes have limited use in the prevention of influenza. Persons who receive an antiviral medication for chemoprophylaxis might still acquire influenza virus infection and be potentially able to transmit influenza virus, even if clinical illness is prevented (*180,181*). Development of illness caused by oseltamivir resistant 2009 H1N1 virus infection has been reported among persons receiving oseltamivir chemoprophylaxis (*115*), and one report of a small community cluster indicates that person-to-person transmission is possible among healthy persons who are not receiving oseltamivir (*112*).

Postexposure Chemoprophylaxis Indications

Clinical judgment and advice from local authorities are important factors in making postexposure chemoprophylaxis decisions. Decisions on whether to administer antivirals for chemoprophylaxis should take into account the exposed person's risk for influenza complications, the type and duration of contact, recommendations from local or public health authorities, and clinical judgment. Generally, postexposure chemoprophylaxis for persons should be only used when antivirals can be started within 48 hours of the most recent exposure (*28*). In areas with limited antiviral medication availability, local public health authorities might provide additional guidance about prioritizing chemoprophylaxis within groups at higher risk for complications. In certain situations, CDC or local public health authorities might recommend that antiviral medication resources be primarily directed at treatment and that antiviral chemoprophylaxis be used only in certain limited situations (*28*).

Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available. Adverse events associated with antiviral medications are generally mild and self-limited (see Adverse Events) but might result in morbidity resulting from medication side effects that outweigh the potential benefit of antiviral chemoprophylaxis (*182,183*). In addition, indiscriminate use of chemoprophylaxis might promote resistance to antiviral medications (*115,184*) or reduce antiviral medication availability for treatment of persons at higher risk for influenza complications or who are severely ill (*28*).

Patients receiving postexposure antiviral chemoprophylaxis should be informed that chemoprophylaxis lowers but does not eliminate the risk for influenza, that susceptibility to influenza returns once the antiviral medication is stopped, and that influenza vaccination is recommended if available. Patients receiving chemoprophylaxis should be encouraged to seek medical evaluation as soon as they develop a febrile respiratory illness suggestive of influenza because influenza virus infection still can occur while a patient is on chemoprophylaxis and might indicate infection with a virus resistant to the antiviral medication used. Either oseltamivir or zanamivir is recommended for antiviral chemoprophylaxis of 2009 H1N1, influenza A (H3N2), or influenza B influenza virus infection (Table 1).

An emphasis on early treatment is an alternative to chemoprophylaxis in managing certain persons who have had a suspected exposure to influenza virus (*28*). Persons with risk factors for influenza complications who are household or close contacts of persons with confirmed or suspected cases and health-care personnel who have occupational exposures can be counseled about the early signs and symptoms of influenza and advised to contact their health-care provider immediately for evaluation and possible early treatment if clinical signs or symptoms develop. Health-care providers should use clinical judgment regarding situations in which early recognition of illness and treatment might be an appropriate alternative. In some exposure circumstances (e.g., when the person exposed is at higher risk for complications of influenza virus infection), health-care providers might choose to give the exposed patient a prescription for an influenza antiviral. Providers may request that the patient contact the provider if signs or symptoms of influenza develop, obtain an antiviral medication as quickly as possible, and initiate treatment. These patients also should be counseled about influenza antiviral medication adverse events and informed that they remain susceptible to influenza virus infection after the antiviral medications are stopped.

Preexposure Chemoprophylaxis

In community studies of healthy adults administered antiviral medications during influenza virus activity, both oseltamivir and zanamivir had similar efficacy in preventing febrile, laboratory-confirmed influenza illness (zanamivir: 84%; oseltamivir: 82%) (*13,17*). Studies also have demonstrated efficacy for prevention of influenza among patients in institutional settings (*179,185–187*). For example, a 6-week study of oseltamivir chemoprophylaxis among nursing home residents demonstrated a 92% reduction in influenza illness (*185*). A 4-week study among community-dwelling persons at higher risk for influenza complications (median age: 60 years) demonstrated that zanamivir had an 83% effectiveness in preventing symptomatic laboratory-confirmed influenza (*188*). The efficacy of antiviral agents in preventing influenza among severely immunocompromised persons is unknown. A small nonrandomized study conducted in a stem cell transplant unit suggested that oseltamivir can prevent progression to pneumonia among influenza virus-infected patients

and that therefore prevention of severe illness might be achievable with chemoprophylaxis (*189*).

When used, preexposure chemoprophylaxis must be administered for the duration of time when exposure might occur. The adverse events associated with long-term use are uncertain (*181*), and prolonged use of antivirals might select for resistance to antiviral medications. Therefore, preexposure antiviral chemoprophylaxis should be used only for persons who are at very high risk (e.g., severely immunosuppressed patients) for influenza-related complications who cannot otherwise be protected during times when a high risk for exposure exists. In the event of concern about potential shortage of antiviral medications, CDC or other health authorities might recommend prioritizing treatment of persons at higher risk for complications or who have severe influenza illness.

Duration of Chemoprophylaxis

Postexposure chemoprophylaxis is typically administered for a total of no more than 10 days after the most recent known exposure to a close contact known to have influenza (*105*). The likelihood of compliance and adverse events should be considered when determining the timing and duration for administering influenza antiviral medications for chemoprophylaxis. Failure to complete a course of oseltamivir for chemoprophylaxis because of gastrointestinal adverse events is common and might lead to antiviral resistance. In one study, only 15 (48%) of 31 primary school children and 41 (76%) of 54 secondary school children who started oseltamivir chemoprophylaxis completed a full course. Gastrointestinal adverse events (e.g., nausea and stomach discomfort) were cited as the most common reason for stopping medications before the recommended course was completed (*190*).

The duration of pre-exposure chemoprophylaxis based on potential exposure in the community depends on the duration of community influenza activity. Regimens as long as 28 days for zanamivir, and 42 days for oseltamivir, have been well tolerated, but no published data are available regarding use of regimens lasting >6 weeks (*181*). To be maximally effective as pre-exposure chemoprophylaxis, the drug must be taken each day for the duration of influenza activity in the community. During periods of widespread community activity and limited or no influenza vaccine availability, such as during the 2009 H1N1 pandemic, pre-exposure chemoprophylaxis has a very limited role because of concerns about antiviral medication supply, need for long-term use, and the potential for adverse events and selection for antiviral resistance.

Considerations for Antiviral Use if Oseltamivir-Resistant Virus Strains Are Circulating

During the 2008–09 influenza season, oseltamivir resistance among circulating seasonal influenza A (H1N1) virus strains affected clinical practice by 1) presenting challenges for the selection of antiviral medications for treatment and chemoprophylaxis of influenza and 2) providing additional reasons for clinicians to test patients for influenza virus infection and to consult available influenza viral surveillance data when evaluating persons with acute respiratory illness. However, since September 2009, almost all (99%) circulating influenza A and B viruses have been susceptible to oseltamivir (seasonal influenza A [H1N1] viruses have not been detected in the United States since 2009) (*191*). Information about antiviral treatment options has been outlined according to the results of influenza diagnostic testing (Table 3). Testing for antiviral resistance of influenza viruses is not routinely available in clinical settings, and many settings will not have access to influenza A virus subtyping information. CDC provides weekly updates on influenza virus surveillance at the national level (available at http://www.cdc.gov/flu/weekly/fluactivity.htm). If oseltamivir-resistant viruses are not circulating, antiviral treatment for influenza should consist of either oseltamivir or zanamivir. However, continued changes in antiviral resistance are likely among influenza viruses, and clinicians should remain attentive to updates in antiviral treatment guidance.

Considerations for Antiviral Use When Antiviral Supplies Are Limited

During widespread illness or a pandemic, demand for antivirals might exceed available supplies. When antiviral supplies are limited, recommendations for antiviral treatment and chemoprophylaxis might differ according to disease incidence, severity of illness, and likelihood for influenza-related complications. Conservation of antiviral supplies to prioritize use for those with higher risk for complications or severe illness might be necessary. Updated information on the most recent guidance for antiviral use from CDC and local public health officials should be sought during widespread illness or a pandemic, and medications should be reserved as much as possible for use in patients who are severely ill or at higher risk for complications.

Control of Influenza Outbreaks in Institutions

Use of antiviral drugs for treatment and chemoprophylaxis of influenza is a key component of influenza outbreak control in institutions that house patients at higher risk for influenza complications. In addition to antiviral medications, other outbreak-control measures include instituting droplet and contact precautions and establishing cohorts of patients with confirmed or suspected influenza, re-offering influenza vaccination (if available) to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients (*105,192–194*). Both adamantanes and neuraminidase inhibitors have been used successfully to control outbreaks caused by susceptible strains when antiviral medications are combined with other infection-control measures (*104,105,192–197*).

Persons who are candidates for chemoprophylaxis should be provided with medications most likely to be effective against the influenza virus that is the cause of the outbreak, if known. Respiratory specimens should be obtained from ill persons during institutional outbreaks and sent for testing to determine the virus type or subtype of influenza A virus associated with the outbreak and to guide antiviral therapy decisions. Persons whose need for

chemoprophylaxis is attributed to potential exposure to a person with laboratory-confirmed 2009 H1N1, influenza A (H3N2), or influenza B should receive oseltamivir or zanamivir. Zanamivir should be used when persons require chemoprophylaxis as a result of exposure to influenza virus strains that are suspected of being oseltamivir-resistant (*108*).

When chemoprophylaxis is indicated, a neuraminidase inhibitor medication should be started as early as possible to reduce the spread of the virus (*105*). 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. Specimens should be collected from ill persons for influenza typing, influenza A virus subtyping, or viral culture to assess antiviral resistance and provide data on the outbreak etiology. Chemoprophylaxis should be administered to all eligible residents, regardless of whether they received influenza vaccination 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 10 days after illness onset in the last patient (*105*). During institutional outbreaks, chemoprophylaxis also can be offered to unvaccinated staff members who provide care to persons at high risk of complications. Chemoprophylaxis should be considered for all employees, regardless of their influenza vaccination status, if indications exist that the outbreak is caused by a strain of influenza virus that is not well matched by the vaccine. Such indications might include multiple documented breakthrough influenza-virus infections among vaccinated persons who otherwise would be expected to respond to vaccination, studies indicating low vaccine effectiveness, or circulation in the surrounding community of suspected index case(s) of strains not contained in the vaccine.

To limit the potential transmission of antiviral drug-resistant influenza virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis. Guidelines recently published by IDSA provide a summary of the prevention and management of influenza outbreaks in institutional settings (*105*).

Dosage

Dosage recommendations vary by age group, intended use (chemoprophylaxis or treatment), and medical conditions (Table 1).

Duration of Antiviral Treatment

The recommended duration of treatment is 5 days (*105,116,156*). Longer treatment regimens might be necessary in severely ill hospitalized patients or persons with immunosuppression. Additional clinical guidelines on the use of antiviral medications to treat influenza are available and contain additional detail on treatment issues (*51,105,198*).

Adults

Zanamivir. Zanamivir is FDA-approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus, and for chemoprophylaxis of influenza among adults. Zanamivir is not recommended for persons with underlying airways disease (e.g., asthma or chronic obstructive pulmonary diseases) (*156*). Zanamivir is administered via an inhaler device in 5-mg blister doses per inhalation. The recommended dosage of zanamivir for treatment of influenza is 2 inhalations (1 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart). The chemoprophylaxis dosage of zanamivir is 10 mg (2 inhalations) once a day.

Oseltamivir. Oseltamivir is FDA-approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus and for chemoprophylaxis of influenza among adults (*116*). Oseltamivir is available for oral administration in 30 mg, 45 mg, and 75 mg capsules and liquid suspension. Dosage and schedule recommendations are listed (Table 1).

Children

Zanamivir. Zanamivir is FDA-approved for treatment of influenza among children aged ≥7 years. Zanamivir is approved for chemoprophylaxis of influenza among children aged ≥5 years. Treatment and chemoprophylaxis dosing and frequency are the same for children as for adults.

Oseltamivir. Oseltamivir is FDA-approved for treatment and chemoprophylaxis of influenza among children aged ≥1 year (*116*). Recommended treatment dosages vary by the weight of the child: 30 mg twice a day for children who weigh ≤15 kg, 45 mg twice a day for children who weigh >15kg and up to 23 kg, 60 mg twice a day for those who weigh >23 kg and up to 40 kg, and 75 mg twice a day for those who weigh >40 kg (Table 1) (*116*). Dosages for chemoprophylaxis are the same for each weight group, but doses are administered only once per day rather than twice (Table 1) (*116*).

Children aged <1 year are at higher risk for complications from influenza virus infection, but antiviral medications are not currently FDA-approved for use in children aged <1 year. During the 2009 H1N1 pandemic, recommendations for oseltamivir dosing of children aged <1 year were developed, on the basis of very limited pharmacokinetic data. The Emergency Use Authorization (EUA) issued during the 2009 H1N1 pandemic for this indication expired on June 23, 2010 (*199*), but recommendations on dosing for children aged <1 year are available (*28,51,200,201*). CDC recommends that clinicians who treat children aged 3—11 months administer 3 mg/kg/dose twice per day for treatment, and 3 mg/kg/dose once per day for chemoprophylaxis (Table 4). Infants aged <3 months are recommended to receive 3 mg/kg/dose twice per day for treatment. However, chemoprophylaxis for infants aged <3 months is not recommended unless the exposure situation was judged to be critical, because of a lack of data on use of oseltamivir on this age group. WHO subsequently recommended that children aged <14 days who are being treated for suspected or confirmed influenza receive 3 mg/kg/dose once daily (*51,201*). Lower doses should be considered

TABLE 4. 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/PostmarketDrugSafetyInformationforPatientsandProviders/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*).

for infants who are not receiving regular oral feedings or those who have substantially reduced renal function (*201*). Clinicians who are considering administering oseltamivir to infants should consult the CDC website for treatment recommendations because these might be revised if additional data become available.

Weight-based dosing recommendations for full-term infants are thought to be inappropriate for premature infants, (i.e., might lead to excessively high plasma concentrations) who might have slower clearance of oseltamivir as a result of immature renal function (*200–202*). 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*). Observed drug concentrations were highly variable among premature infants. These data are insufficient to recommend a specific dose of oseltamivir for premature infants (*200–202*).

Amantadine. Because of resistance in circulating influenza A virus strains, amantadine is not recommended for antiviral treatment or chemoprophylaxis of influenza A. Amantadine is FDA-approved for treatment and chemoprophylaxis of influenza A virus infections among adults and children aged ≥1 year. Use of amantadine among children aged <1 year has not been evaluated adequately. The FDA-approved dosage for children aged 1–9 years for treatment and chemoprophylaxis is 4.4–8.8 mg/kg per day, not to exceed 150 mg per day. Although further studies are needed to determine the optimal dosage for children aged 1–9 years, physicians should consider prescribing only 5 mg/kg per day (not to exceed 150 mg per day) to reduce the risk for toxicity. The approved dosage for children aged ≥10 years is 200 mg per day (100 mg twice a day); for children weighing <40 kg, prescribing 5 mg/kg per day, regardless of age, is recommended (*203*).

Rimantadine. Because of resistance in circulating influenza A virus strains, rimantadine is not recommended for antiviral treatment or chemoprophylaxis of influenza A. Rimantadine is FDA-approved for chemoprophylaxis of influenza A virus infections among children aged ≥1 year and for treatment and chemoprophylaxis of influenza A virus infections among adults. Although rimantadine is approved only for chemoprophylaxis of influenza A among children, certain specialists in the management of influenza consider it appropriate for treatment among children (*203*). Use of rimantadine among children aged <1 year has not been evaluated adequately. Rimantadine should be administered in 1 or 2 divided doses at a dosage of 5 mg/kg per day, not to exceed 150 mg per day for children aged 1–9 years. The approved dosage for children aged ≥10 years is 200 mg per day (100 mg twice a day); however, for children weighing <40 kg, prescribing 5 mg/kg per day, regardless of age, is recommended (*204*).

Use of Medications for Symptomatic Relief in Children

Aspirin or aspirin-containing products (e.g. bismuth subsalicylate [Pepto Bismol]) should not be administered to any person aged ≤18 years with suspected influenza because of the risk for Reye's syndrome. For relief of fever, other antipyretic medications (e.g., acetaminophen or non steroidal anti-inflammatory drugs) are recommended. Children aged <4 years should not receive over-the-counter cold medications without a health-care provider being consulted first (*205*).

Persons Aged ≥65 Years

Oseltamivir and Zanamivir. No reduction in dosage for oseltamivir or zanamivir is recommended on the basis of age alone (*116,156*).

Amantadine. 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 (*206,207*).

Rimantadine. 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 (*204*). 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 (*204,205,208*).

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 (*204*).

Pregnant Women

Pregnant women with confirmed or suspected influenza are recommended to receive antiviral treatment, and treatment of fever with acetaminophen (*209*). Pregnancy should not be considered a contraindication to oseltamivir or zanamivir use. Pregnant women are known to be at higher risk for complications from infection with seasonal influenza viruses (*210,211*) and severe disease among pregnant women was reported during past pandemics (*209,212,213*). Multiple studies have demonstrated that pregnant women are at higher risk for influenza complications from 2009 H1N1 virus infection *(12,24,25,68*).

Oseltamivir, zanamivir, rimantadine, and amantadine are "Pregnancy Category C" medications, indicating that data from clinical studies are not adequate to assess the safety of these medications for pregnant women (*116,156*). Although a few adverse events have been reported occasionally in pregnant women who took these medications, no causal relation between the use of these medications and these adverse events has been established (*214, 215*). In addition, fever can cause adverse fetal outcomes, and reducing fever, whether directly by using antipyretics, or indirectly by reducing the duration and severity of symptoms with antiviral medications, might reduce this risk (*209*). One retrospective cohort study found no evidence of an association between oseltamivir use during pregnancy and a variety of adverse events, including preterm birth, premature rupture of membranes, increased duration of hospital stay for mother or neonate, malformations, or fetal weight (*214*).

Oseltamivir is preferred for treatment of pregnant women. Zanamivir might be preferred by some providers because of its limited systemic absorption; however, respiratory complications that might be associated with zanamivir because of its inhaled route of administration need to be considered, especially in women at risk for respiratory problems (*209*). Pregnant women are recommended to receive the same antiviral dosing as nonpregnant persons (*106*).

As with others at high risk for influenza-related complications, treatment of pregnant women with suspected or confirmed influenza virus infection should begin as early as possible after onset of illness. Treatment should not be delayed while waiting for results of diagnostic testing (*28,51*).

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 reported (*116*). However, a limited number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose (*173,214*). 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 (*156*).

Oseltamivir. Serum concentrations of oseltamivir carboxylate, the active metabolite of oseltamivir, increase with declining renal function (*116*). For patients with creatinine clearance of 10–30 mL per minute, 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 (*116,216*). Treatment or chemoprophylaxis dosing recommendations have been proposed for patients undergoing routine renal dialysis treatment but are based on limited pharmacokinetic data (*217,218*).

Amantadine. When used for amantadine-susceptible influenza A virus infection, a reduction in dosage is recommended for patients with creatinine clearance <50 mL/min. Guidelines for amantadine dosage on the basis of creatinine clearance are located in the package insert. Because recommended dosages on the basis of creatinine clearance might provide only an approximation of the optimal dose for a specific patient, such persons should be observed carefully for adverse reactions. If necessary, further reduction in the dose or discontinuation of the drug might be indicated because of side effects. Hemodialysis contributes minimally to amantadine clearance (*219*).

Rimantadine. When used for rimantadine-susceptible influenza A virus infection, a reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance <10 mL/min. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including older persons, should be monitored for adverse effects, and, if necessary, either the dosage should be reduced or the drug should be discontinued. Hemodialysis contributes minimally to rimantadine clearance (*204*).

Persons with Liver Disease

Zanamivir and oseltamivir. Use of zanamivir or oseltamivir has not been studied among persons with liver disease.

Amantadine. No increase in adverse reactions to amantadine has been observed among persons with liver disease. Rare instances of reversible elevation of liver enzymes among patients receiving

amantadine have been reported, although a specific relation between the drug and such changes has not been established (*220*).

Rimantadine. A reduction in dosage to 100 mg/day is recommended for persons with severe hepatic dysfunction (*204*).

Persons with Seizure Disorders

Zanamivir and oseltamivir. Seizure events have been reported during postmarketing use of zanamivir and oseltamivir (*115,156*), although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

Amantadine. An increased incidence of seizures has been reported among patients with a history of seizure disorders who have received amantadine (*221*). Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine.

Rimantadine. Seizures (or seizure-like activity) have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine (*208*). The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been evaluated adequately.

Persons with Immunosuppression

A recent retrospective case-control study demonstrated that oseltamivir was safe and well tolerated when used during the control of an influenza outbreak among hematopoietic stem cell transplant recipients living in a residential facility (*222*).

Adverse Events

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 therapy); and the potential for interaction with other medications.

Zanamivir

Limited data are available about the safety or efficacy of zanamivir for persons with underlying respiratory disease or for persons with complications of acute influenza, and zanamivir is licensed only for use in persons without underlying respiratory or cardiac disease (*156*). In a study of zanamivir treatment of ILI among persons with asthma or chronic obstructive pulmonary disease in which study medication was administered after use of a β2-agonist,13% of patients receiving zanamivir and 14% of patients who received inhaled placebo (powdered lactose vehicle alone) experienced a >20% decline in forced expiratory volume in 1 second (FEV1) after treatment (*156,223*). 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 (*156*). In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Because of the risk for serious adverse events and because efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying pulmonary disease (*156*). Allergic reactions, including oropharyngeal or facial edema, also have been reported during postmarketing surveillance (*156,223*).

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 inhaled placebo (i.e., powdered lactose vehicle alone) (*15,16,142*). 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 (*156*). Zanamivir does not impair the immunologic response to trivalent inactivated vaccine (*224*).

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%) (*91,111,188*). 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 (*21*), and a limited number of adults who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (*116*). Similar types and rates of adverse events were reported in studies of oseltamivir chemoprophylaxis (*116*). Nausea and vomiting might be less severe if oseltamivir is taken with food (*116*). In several reports based on public health responses to school outbreaks of 2009 H1N1, self-reported nausea and vomiting have been more common than reported in clinical studies and might reduce compliance with recommended treatment or chemoprophylaxis regimens among children (*155,189,190*). No published studies have assessed whether oseltamivir impairs the immunologic response to trivalent inactivated influenza vaccine.

Transient neuropsychiatric events (self-injury or delirium) have been reported postmarketing among persons taking oseltamivir; the majority of reports were among Japanese adolescents and adults (*225*). Several recent analyses and reviews have found that oseltamivir is not associated with an increased risk for neuropsychiatric events (*226,227*). FDA advises that persons receiving oseltamivir be monitored closely for abnormal behavior (*116*).

Limited safety data on oseltamivir treatment for seasonal influenza in children aged <1year have not demonstrated any age-related safety concerns, but careful attention to dosing is essential (*200,228–230*). Health-care providers should be aware of the limited data on safety and dosing when considering oseltamivir use for infants, and carefully monitor infants for adverse events. Clinicians and pharmacists should pay careful attention to the potential for dosing errors in young children (*231*).

Reporting of Adverse Events that Occur After Administering Antiviral Medications

Health-care professionals should report any serious adverse event after antiviral medication use promptly to MedWatch, the FDA's adverse event reporting program for medications. Serious adverse events are defined as medical events that involve hospitalization, death, life-threatening illness, disability, or certain other medically important conditions. Any serious adverse event that follows administration of medications should be reported to FDA at http://www.fda.gov/medwatch/report/hcp.htm.

Drug Interactions

Clinical data are limited regarding drug interactions with zanamivir. No known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro and animal study data (*116,232*).

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 (*163*).

No published data from clinical trials are available concerning the safety or efficacy of using combinations of different classes of influenza antiviral drugs. One recent study suggested that use of oseltamivir plus zanamivir was less efficacious than monotherapy with either drug alone (*233*). Providers should consult package inserts for more detailed information about potential drug interactions (available at http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm100228.htm).

Emergency Use Authorization

Licensed vaccines and drugs, or approved therapeutics and medical devices treat, prevent, or mitigate disease. If an emerging public health threat is identified for which no licensed or approved product exists, the Project BioShield Act of 2004 authorizes the FDA Commissioner to issue an EUA so appropriate countermeasures (e.g., distribution of unlicensed antiviral medications) can be taken quickly to protect the safety of the U.S. population. Specifically, these countermeasures can facilitate the diagnosis, treatment, or prevention of serious or life-threatening diseases, or for conditions caused by chemical, biologic, or radiologic agents for which no adequate, approved, or available alternatives exist. CDC in conjunction with NIH provides expert consultation to the FDA Commissioner regarding the appropriateness of EUA requests and supports the distribution of products stored in the Strategic National Stockpile (SNS) formulary (*234*). EUAs in effect during the 2009 H1N1 pandemic have expired because there is no longer a declared emergency.

Additional Information

Each year, ACIP provides general, annually updated information regarding prevention and control of influenza. The following additional guidance on antiviral treatment of influenza and other reports related to controlling and preventing influenza among specific populations (e.g., immunocompromised persons, health-care personnel, hospital patients, pregnant women, children, and travelers) are available:

- CDC. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR 2003;53(No. RR-3).
- CDC. Prevention strategies for seasonal influenza in healthcare settings. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm.
- American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 468: influenza vaccination during pregnancy. Obstet Gynecol 2010;116:1006–7.
- American Academy of Pediatrics. Committee on Infectious Diseases. Policy statement—recommendations for prevention and control of influenza in children, 2010–2011. Available at http://pediatrics.aappublications.org/cgi/reprint/peds.2010-2216v1.
- Food and Drug Administration. Influenza (Flu) Antiviral drugs and related information. Available at http://www.fda.gov/cder/drug/antivirals/influenza/default.htm.
- Food and Drug Administration. Approved drug products with therapeutic equivalence evaluations. Available at http://www.fda.gov/cder/orange/obannual.pdf.
- National Institutes of Health. Registry of federally and privately supported clinical trials conducted in the United States and around the world. Available at http://clinicaltrials.gov.
- Harper SA, Bradley JS, Englund JA, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1003–32. Available at http://www.journals.uchicago.edu/doi/pdf/10.1086/598513.
- World Health Organization. WHO guidelines for pharmacological management of pandemic influenza A (H1N1) 2009 and other influenza viruses. Available at http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf.

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