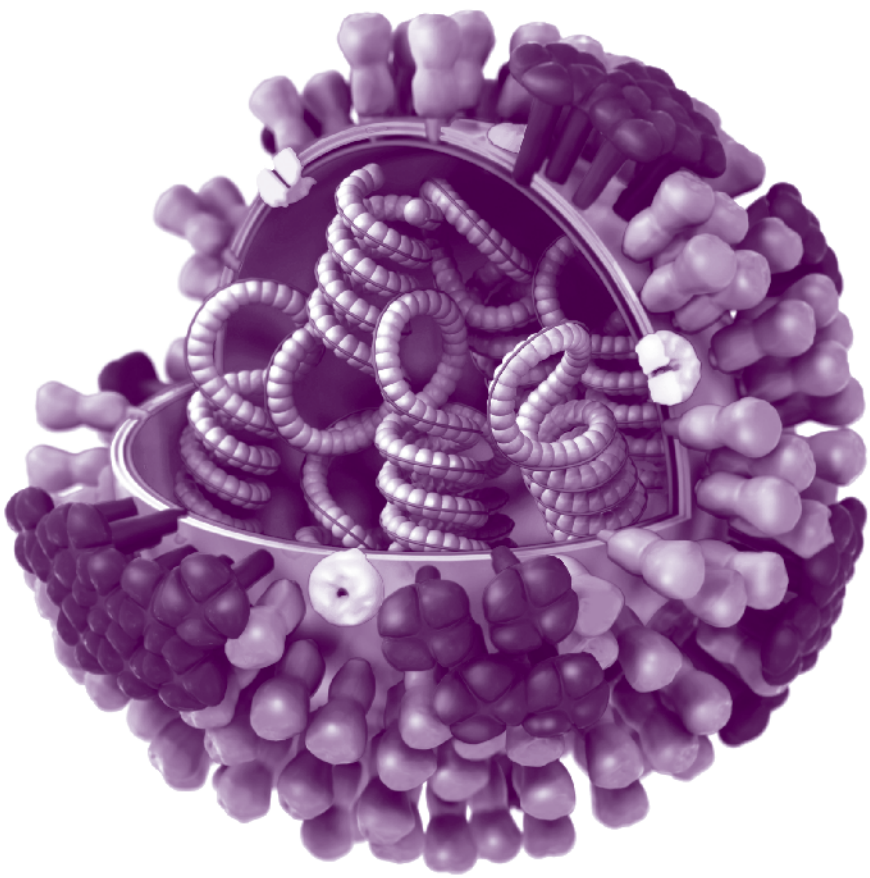
Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 60 / No. 1 January 21, 2011

Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza

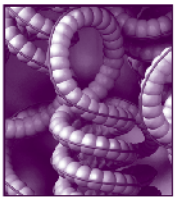
Recommendations of the Advisory Committee on Immunization Practices (ACIP)



Hemagglutinin

Neuraminidase

M2 Ion Channel



RNP

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CONTENTS

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

The *MMWR* series of publications is published by Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.
Suggested Citation: Centers for Disease Control and Prevention. [Title]. MMWR 2011;60(No. RR-#):[inclusive page numbers].

Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Prepared by
Anthony E. Fiore, MD
Alicia Fry, MD
David Shay, MD
Larisa Gubareva, PhD
Joseph S. Bresee, MD
Timothy M. Uyeki, MD
Influenza Division, National Center for Immunization and Respiratory Diseases

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.
Corresponding preparer: Timothy Uyeki, MD, Influenza Division, National Center for Immunization and Respiratory Diseases, CDC, 1600 Clifton Road, N.E., MS A-20, Atlanta, GA 30333. Telephone: 404-639-3747; Fax: 404-639-3866; E-mail: tuyeki@cdc.gov.

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.

Acknowledgments

Assistance in the preparation of this report was provided by Carolyn Bridges, MD, Amanda Zongrone, Influenza Division; Beth Bell, MD, Office of the Director, National Center for Immunization and Respiratory Diseases, CDC.

References

1. Monto AS, Kioumehr F. The Tecumseh study of respiratory illness. IX. Occurrence of influenza in the community, 1966–1971. Am J Epidemiol 1975;102:553–63.
2. Glezen PF, Couch RB. Interpandemic influenza in the Houston area, 1974–76. N Engl J Med 1978;298:587–92.
3. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292:1333–40.
4. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289:179–86.
5. CDC. Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives—12 states, 2009. MMWR 2009;58:1341–4.
6. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med 2009;361:1935–44.
7. Louie JK, Acosta M, Winter K, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 2009;302:1896–902.
8. Morgan OW, Bramley A, Fowlkes A, et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. PLoS ONE 2010;5:e9694.
9. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. JAMA 2005;294:2188–94.
10. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. N Engl J Med 2006;355:31–40.
11. CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR 2010;59(No. RR-8).
12. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010;303:1517–25.
13. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med 1999;341:1336–43.
14. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. N Engl J Med 2000;343:1282–9.
15. Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. N Engl J Med 1997;337:874–80.
16. Monto AS, Fleming DM, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. J Infect Dis 1999;180:254–61.
17. Monto AS, Robinson DP, Herlocher ML, et al. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. JAMA 1999;282:31–5.
18. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA 2001;285:748–54.
19. Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet 2000;355:1845–50.
20. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA 2000;283:1016–24.
21. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001;20:127–33.
22. Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med 2003;163:1667–72.
23. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis 2007;45:1568–75.
24. Creanga AA, Johnson TF, Graitcer SB, et al. Severity of 2009 pandemic influenza A (H1N1) virus infection in pregnant women. Obstet Gynecol 2010;115:717–26.
25. Louie JK, Acosta M, Jamieson DJ, et al. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med 2009;362:27–35.
26. Lee N, Chan PK, Choi KW, et al. Factors associated with early hospital discharge of adult influenza patients. Antivir Ther 2007;12:501–8.
27. Lee N, Cockram CS, Chan PKS, et al. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. Clin Infect Dis 2008;46:1323–4.
28. CDC. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–10 season. Atlanta, GA: US Department of Health and Human Services, CDC; 2009. Available at http://www.cdc.gov/H1N1flu/recommendations.htm.
29. Brankston G, Gitterman L, Hirji Z, et al. Transmission of influenza A in human beings. Lancet Infect Dis 2007;7:257–65.
30. Bell DM. Non-pharmaceutical interventions for pandemic influenza, international measures. Emerg Infect Dis 2006;12:81–7.
31. Moser MR, Bender TR, Margolis HS, et al. An outbreak of influenza aboard a commercial airliner. Am J Epidemiol 1979;110:1–6.
32. Klontz KC, Hynes NA, Gunn RA, et al. An outbreak of influenza A/Taiwan/1/86 (H1N1) infections at a naval base and its association with airplane travel. Am J Epidemiol 1989;129:341–8.
33. Hall CB. The spread of influenza and other respiratory viruses: complexities and conjectures. Clin Infect Dis 2007;45:353–9.
34. Tellier R. Review of aerosol transmission of influenza A virus. Emerg Infect Dis 2006;12:1657–62.
35. Wong BC, Lee N, Li Y, et al. Possible role of aerosol transmission in a hospital outbreak of influenza. Clin Infect Dis 2010;51:1176–83.
36. Cox NJ, Subbarao K. Influenza. Lancet 1999;354:1277–82.
37. Cowling BJ, Fang VJ, Riley S, et al. Estimation of the serial interval of influenza. Epidemiology 2009;20:344–7.
38. Cowling BJ, Chan KH, Fang VJ, et al. Comparative epidemiology of pandemic and seasonal influenza A in households. N Engl J Med 2010;362:2175–84.
39. Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. Am J Epidemiol 2008;167:775–85.
40. Hayden FG, Fritz R, Lobo MC, et al. Local and systemic cytokine responses during experimental human influenza A virus infection. Relation to symptom formation and host defense. J Clin Invest 1998;101:643–9.
41. Hall CB, Douglas RG Jr. Nosocomial influenza infection as a cause of intercurrent fevers in infants. Pediatrics 1975;55:673–7.
42. Giannella M, Alonso M, Viedma DG, et al. Prolonged viral shedding in pandemic influenza A H1N1: clinical significance and viral load analysis in hospitalized patients. Clin Microbiol Infect 2010.
43. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis 2009;200:492–500.
44. Frank AL, Taber LH, Wells CR, et al. Patterns of shedding of myxoviruses and paramyxoviruses in children. J Infect Dis 1981;144:433–41.
45. Klimov AI, Rocha E, Hayden FG, et al. Prolonged shedding of amantadine-resistant influenzae A viruses by immunodeficient patients: detection by polymerase chain reaction-restriction analysis. J Infect Dis 1995;172:1352–5.

46. Englund JA, Champlin RE, Wyde PR, et al. Common emergence of amantadine- and rimantadine-resistant influenza A viruses in symptomatic immunocompromised adults. Clin Infect Dis 1998;26:1418–24.
47. Boivin G, Goyette N, Bernatchez H. Prolonged excretion of amantadine-resistant influenza a virus quasi species after cessation of antiviral therapy in an immunocompromised patient. Clin Infect Dis 2002;34:E23–5.
48. Pinsky BA, Mix S, Rowe J, et al. Long-term shedding of influenza A virus in stool of immunocompromised child. Emerg Infect Dis 2010;16:1165–7.
49. Nicholson KG. Clinical features of influenza. Semin Respir Infect 1992;7:26–37.
50. Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360:2605–15.
51. Bautista E, Chotpitayasunondh T, Gao Z, et al. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med 2010;362:1708–19.
52. Cao B, Li XW, Mao Y, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 2009;361:2507–17.
53. Douglas R Jr. Influenza in man. In: Kilbourne E, ed. Influenza viruses and influenza. New York, NY: Academic Press, Inc.; 1975:395–418.
54. Schrag SJ, Shay DK, Gershman K, et al. Multistate surveillance for laboratory-confirmed, influenza-associated hospitalizations in children: 2003–2004. Pediatr Infect Dis J 2006;25:395–400.
55. Ho YC, Wang JL, Wang JT, et al. Prognostic factors for fatal adult influenza pneumonia. J Infect 2009;58:439–45.
56. Dagan R, Hall CB. Influenza A virus infection imitating bacterial sepsis in early infancy. Pediatr Infect Dis 1984;3:218–21.
57. Iwane MK, Edwards KM, Szilagyi PG, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics 2004;113:1758–64.
58. Chiu SS, Tse CY, Lau YL, et al. Influenza A infection is an important cause of febrile seizures. Pediatrics 2001;108:E63.
59. McCullers JA, Facchini S, Chesney PJ, et al. Influenza B virus encephalitis. Clin Infect Dis 1999;28:898–900.
60. Dawood FS, Fiore A, Kamimoto L, et al. Influenza-associated pneumonia in children hospitalized with laboratory-confirmed influenza, 2003–2008. Pediatr Infect Dis J 2010;29:585–90.
61. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol 2010;177:166–75.
62. Libster R, Bugna J, Coviello S, et al. Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med 2010;362:45–55.
63. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 2009;302:1872–9.
64. Webb SA, Pettila V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 2009;361:1925–34.
65. Lee EH, Wu C, Lee EU, et al. Fatalities associated with the 2009 H1N1 influenza A virus in New York city. Clin Infect Dis 2010;50:1498–504.
66. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol 2010;177:166–75.
67. Ampofo K, Herbener A, Blaschke AJ, et al. Association of 2009 pandemic influenza A (H1N1) infection and increased hospitalization with parapneumonic empyema in children in Utah. Pediatr Infect Dis J 2010;29:905–9.
68. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009;374:451–8.
69. Dawood FS, Fiore A, Kamimoto L, et al. Burden of seasonal influenza hospitalization in children, United States, 2003 to 2008. J Pediatr 2010;157:808–14.
70. Webster RI, Hazelton B, Suleiman J, et al. Severe encephalopathy with swine origin influenza A H1N1 infection in childhood: case reports. Neurology 2010;74:1077–8.
71. Puzelli S, Buonaguro FM, Facchini M, et al. Cardiac tamponade and heart failure due to myopericarditis as a presentation of infection with the pandemic H1N1 2009 influenza A virus. J Clin Microbiol 2010;48:2298–300.
72. Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. Clin Infect Dis 2003;36:299–305.
73. Morishima T, Togashi T, Yokota S, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. Clin Infect Dis 2002;35:512–7.
74. Bratincsak A, El-Said HG, Bradley JS, et al. Fulminant myocarditis associated with pandemic H1N1 influenza A virus in children. J Am Coll Cardiol 2010;55:928–9.
75. Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza. Crit Care Med 2010;38:e91–7.
76. Lyon JB, Remigio C, Milligan T, et al. Acute necrotizing encephalopathy in a child with H1N1 influenza infection. Pediatr Radiol 2010;40:200–5.
77. Lister P, Reynolds F, Parslow R, et al. Swine-origin influenza virus H1N1, seasonal influenza virus, and critical illness in children. Lancet 2009;374:605–7.
78. Hackett S, Hill L, Patel J, et al. Clinical characteristics of paediatric H1N1 admissions in Birmingham, UK. Lancet 2009;374:605.
79. Ekstrand JJ, Herbener A, Rawlings J, et al. Heightened neurologic complications in children with pandemic H1N1 influenza. Ann Neurol 2010;68:762–6..
80. Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. Arch Intern Med 2000;160:3243–7.
81. Ohmit SE, Monto AS. Symptomatic predictors of influenza virus positivity in children during the influenza season. Clin Infect Dis 2006;43:564–8.
82. Boivin G, Hardy I, Tellier G, et al. Predicting influenza infections during epidemics with use of a clinical case definition. Clin Infect Dis 2000;31:1166–9.
83. Govaert TM, Dinant GJ, Aretz K, et al. The predictive value of influenza symptomatology in elderly people. Fam Pract 1998;15:16–22.
84. Walsh EE, Cox CFalsey AR. Clinical features of influenza A virus infection in older hospitalized persons. J Am Geriatr Soc 2002;50:1498–503.
85. v d Hoeven AM, Scholing M, Wever PC, et al. Lack of discriminating signs and symptoms in clinical diagnosis of influenza of patients admitted to the hospital. Infection 2007;35:65–8.
86. Babcock HM, Merz LRFraser VJ. Is influenza an influenza-like illness? Clinical presentation of influenza in hospitalized patients. Infect Control Hosp Epidemiol 2006;27:266–70.
87. Neuzil KM, O'Connor TZ, Gorse GJ, et al. Recognizing influenza in older patients with chronic obstructive pulmonary disease who have received influenza vaccine. Clin Infect Dis 2003;36:169–74.
88. CDC. Influenza-testing and antiviral-agent prescribing practices—Connecticut, Minnesota, New Mexico, and New York, 2006–07 influenza season. MMWR 2008;57:61–5.
89. Katz MA, Lamias MJ, Shay DK, et al. Use of rapid tests and antiviral medications for influenza among primary care providers in the United States. Influenza Other Respi Viruses 2009;3:29–35.
90. Uyeki TM. Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza. Pediatr Infect Dis J 2003;22:164–77.
91. Schmid ML, Kudesia G, Wake S, et al. Prospective comparative study of culture specimens and methods in diagnosing influenza in adults. BMJ 1998;316:275.
92. Ali T, Scott N, Kallas W, et al. Detection of influenza antigen with rapid antibody-based tests after intranasal influenza vaccination (FluMist). Clin Infect Dis 2004;38:760–2.

93. Anonymous. Rapid diagnostic tests for influenza. Med Lett Drugs Ther 1999;41:121–2.
94. Storch GA. Rapid diagnostic tests for influenza. Curr Opin Pediatr 2003;15:77–84.
95. Grijalva CG, Poehling KA, Edwards KM, et al. Accuracy and interpretation of rapid influenza tests in children. Pediatrics 2007;119:e6–11.
96. Uyeki TM, Prasad R, Vukotich C, et al. Low sensitivity of rapid diagnostic test for influenza. Clin Infect Dis 2009;48:e89–92.
97. Steininger C, Redlberger M, Graninger W, et al. Near-patient assays for diagnosis of influenza virus infection in adult patients. Clin Microbiol Infect 2009;15:267–73.
98. Hurt AC, Alexander R, Hibbert J, et al. Performance of six influenza rapid tests in detecting human influenza in clinical specimens. J Clin Virol 2007;39:132–5.
99. Rahman M, Vandermause MF, Kieke BA, et al. Performance of Binax NOW Flu A and B and direct fluorescent assay in comparison with a composite of viral culture or reverse transcription polymerase chain reaction for detection of influenza infection during the 2006 to 2007 season. Diagn Microbiol Infect Dis 2008;62:162–6.
100. Ruest A, Michaud S, Deslandes S, et al. Comparison of the Directigen flu A+B test, the QuickVue influenza test, and clinical case definition to viral culture and reverse transcription-PCR for rapid diagnosis of influenza virus infection. J Clin Microbiol 2003;41:3487–93.
101. Blyth CC, Iredell JR, Dwyer DE. Rapid-test sensitivity for novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;361:2493.
102. Kok J, Blyth CC, Foo H, et al. Comparison of a rapid antigen test with nucleic acid testing during cocirculation of pandemic influenza A/H1N1 2009 and seasonal influenza A/H3N2. J Clin Microbiol 2009;48:290–1.
103. Louie JK, Guevara H, Boston E, et al. Rapid influenza antigen test for diagnosis of pandemic (H1N1) 2009. Emerg Infect Dis 2010;16:824–6.
104. CDC. Interim guidance on infection control measures for 2009 H1N1 influenza in healthcare settings, including protection of healthcare personnel. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at http://www.cdc.gov/h1n1flu/guidelines_infection_control.htm. Accessed December 16, 2010.
105. 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.
106. Infectious Diseases Society of America. Influenza H1N1: frontline questions and expert opinion answers. Arlington, VA: Infectious Diseases Society of America; 2009. Available at http://www.idsociety.org/Content.aspx?id=15743. Accessed December 16, 2010.
107. US Department of Health and Human Services. FDA clears new CDC test to detect human influenza. Washington, DC: US Department of Health and Human Services; 2008.
108. CDC. CDC issues interim recommendations for the use of influenza antiviral medications in the setting of oseltamivir resistance among circulating influenza A (H1N1) viruses, 2008–09 influenza season. Atlanta, GA: US Department of Health and Human Services, CDC; 2008. Available at http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?AlertNum=00279. Accessed December 16, 2010.
109. Focus Diagnostics. Simplexa influenza A(H1N1) 2009. Cypress, CA: Focus Diagnostics; 2010. Available at http://www.fda.gov/downloads/MedicalDevices/Safety/EmergencySituations/UCM195515.pdf. Accessed December 16, 2010.
110. CDC. FluView: week ending May 20, 2010. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at http://www.cdc.gov/flu/weekly. Accessed December 16, 2010.
111. Baz M, Abed Y, Papenburg J, et al. Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. N Engl J Med 2009;361:2296–7.
112. Le QM, Wertheim HF, Tran ND, et al. A community cluster of oseltamivir-resistant cases of 2009 H1N1 influenza. N Engl J Med 2010;362:86–7.
113. CDC. Update: influenza activity—United States, 2009–10 season. MMWR 2010;59:901–8.
114. CDC. Oseltamivir-resistant novel influenza A (H1N1) virus infection in two immunosuppressed patients—Seattle, Washington, 2009. MMWR 2009;58:893–6.
115. CDC. Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis—North Carolina, 2009. MMWR 2009;58:969–72.
116. Roche Laboratories Inc. Tamiflu (oseltamivir phosphate) capsules and oral suspension [package insert]. Nutley, NJ: Roche laboratories, Inc.; 2009.
117. Gubareva LV, Kaiser L, Matrosovich MN, et al. Selection of influenza virus mutants in experimentally infected volunteers treated with oseltamivir. J Infect Dis 2001;183:523–31.
118. Gubareva LV, Matrosovich MN, Brenner MK, et al. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. J Infect Dis 1998;178:1257–62.
119. Barnett JM, Cadman A, Gor D, et al. Zanamivir susceptibility monitoring and characterization of influenza virus clinical isolates obtained during phase II clinical efficacy studies. Antimicrob Agents Chemother 2000;44:78–87.
120. Stephenson I, Democratis J, Lackenby A, et al. Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. Clin Infect Dis 2009;48:389–96.
121. Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 2004;364:759–65.
122. Hatakeyama S, Sugaya N, Ito M, et al. Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. JAMA 2007;297:1435–42.
123. Stephenson I, Democratis J, Lackenby A, et al. neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza a and b in children. Clin Infect Dis 2009;48:389–96.
124. CDC. Update: influenza activity—United States, August 30, 2009–March 27, 2010, and composition of the 2010–11 influenza vaccine. MMWR 2010;59:423–30.
125. Inoue M, Barkham T, Leo YS, et al. Emergence of oseltamivir-resistant pandemic (H1N1) 2009 virus within 48 hours. Emerg Infect Dis 2010;16:1633–6.
126. Gubareva LV, Fry AM. Current challenges in the risk assessment of neuraminidase inhibitor-resistant influenza viruses. J Infect Dis 2010;201:656–8.
127. Ison MG, Gubareva LV, Atmar RL, et al. Recovery of drug-resistant influenza virus from immunocompromised patients: a case series. J Infect Dis 2006;193:760–4.

128. Baz M, Abed Y, McDonald J, et al. Characterization of multidrug-resistant influenza A/H3N2 viruses shed during 1 year by an immunocompromised child. Clin Infect Dis 2006;43:1555–61.
129. Weinstock DM, Gubareva LV, Zuccotti G. Prolonged shedding of multidrug-resistant influenza A virus in an immunocompromised patient. N Engl J Med 2003;348:867–8.
130. van der Vries E, Stelma FF, Boucher CA. Emergence of a multidrug-resistant pandemic influenza A (H1N1) virus. N Engl J Med 2010;363:1381–2.
131. Nguyen HT, Fry AM, Loveless PA, et al. Recovery of a multidrug-resistant strain of pandemic influenza A 2009 (H1N1) virus carrying a dual H275Y/I223R mutation from a child after prolonged treatment with oseltamivir. Clin Infect Dis 2010;51:983–4.
132. World Health Organization. Influenza A (H1N1) virus resistance to oseltamivir. Geneva, Switzerland: World Health Organization; 2009.
133. Dharan NJ, Gubareva LV, Meyer JJ, et al. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. JAMA 2009;301:1034–41.
134. Hauge SH, Dudman S, Borgen K, et al. Oseltamivir-resistant influenza viruses A (H1N1), Norway, 2007–08. Emerg Infect Dis 2009;15:155–62.
135. Kramarz P, Monnet D, Nicoll A, et al. Use of oseltamivir in 12 European countries between 2002 and 2007—lack of association with the appearance of oseltamivir-resistant influenza A(H1N1) viruses. Euro Surveill 2009;14.
136. Meijer A, Lackenby A, Hungnes O, et al. Oseltamivir-resistant influenza virus A (H1N1), Europe, 2007–08 season. Emerg Infect Dis 2009;15:552–60.
137. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005;366:1175–81.
138. Bright RA, Shay DK, Shu B, et al. Adamantane resistance among influenza A viruses isolated early during the 2005–2006 influenza season in the United States. JAMA 2006;295:891–4.
139. Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. Pediatr Infect Dis J 2000;19:410–7.
140. Lalezari J, Campion K, Keene O, et al. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. Arch Intern Med 2001;161:212–7.
141. Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. J Antimicrob Chemother 1999;44(Suppl B):23–9.
142. MIST (Management of Influenza in the Southern Hemisphere Trialists). Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet 1998;352:1877–81.
143. Heinonen S, Silvennoinen H, Lehtinen P, et al. Early oseltamivir treatment of influenza in children 1–3 years of age: a randomized controlled trial. Clin Infect Dis 2010;51:887–94.
144. Sato M, Hosoya M, Kato K, et al. Viral shedding in children with influenza virus infections treated with neuraminidase inhibitors. Pediatr Infect Dis J 2005;24:931–2.
145. Hayden FG, Treanor JJ, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. JAMA 1999;282:1240–6.
146. Monto AS. Antivirals for influenza in healthy adults. Lancet 2006;367:1571–2; author reply 1573.
147. Jefferson T, Demicheli V, Rivetti D, et al. Antivirals for influenza in healthy adults: systematic review. Lancet 2006;367:303–13.
148. Johnston SL, Ferrero F, Garcia ML, et al. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. Pediatr Infect Dis J 2005;24:225–32.
149. Hanshaoworakul W, Simmerman JM, Narueponjirakul U, et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. PLoS ONE 2009;4:e6051.
150. Lee N, Choi KW, Chan PK, et al. Outcomes of adults hospitalised with severe influenza. Thorax 2010;65:510–5.
151. Chemaly RF, Torres HA, Aguilera EA, et al. Neuraminidase inhibitors improve outcome of patients with leukemia and influenza: an observational study. Clin Infect Dis 2007;44:964–7.
152. Yu H, Liao Q, Yuan Y, et al. Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. BMJ 2010;341:c4779.
153. Farias JA, Fernandez A, Monteverde E, et al. Critically ill infants and children with influenza A (H1N1) in pediatric intensive care units in Argentina. Intensive Care Med 2010;36:1015–22.
154. Dominguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. JAMA 2009;302:1880–7.
155. Hayden FG, Jennings L, Robson R, et al. Oral oseltamivir in human experimental influenza B infection. Antivir Ther 2000;5:205–13.
156. Glaxo Wellcome Inc. Relenza (zanimivir for inhalation) [Package insert]. Research Triangle Park, NC: Glaxo Wellcome, Inc.; 2009.
157. Sugaya N, Mitamura K, Yamazaki M, et al. Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. Clin Infect Dis 2007;44:197–202.
158. Hageman JC, Uyeki TM, Francis JS, et al. Severe community-acquired pneumonia due to Staphylococcus aureus, 2003–04 influenza season. Emerg Infect Dis 2006;12:894–9.
159. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl 2):S27–72.
160. Mauad T, Hajjar LA, Callegari GD, et al. Lung pathology in fatal novel human influenza A (H1N1) infection. Am J Respir Crit Care Med 2010;181:72–9.
161. Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of *Staphylococcus aureus* coinfection. Pediatrics 2008;122:805–11.
162. Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. CMAJ 2010;182:357–63.
163. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. Clin Pharmacokinet 1999;37:471–84.
164. Abdel-Ghafar AN, Chotpitayasunondh T, Gao Z, et al. Update on avian influenza A (H5N1) virus infection in humans. N Engl J Med 2008;358:261–73.
165. Wildschut ED, de Hoog M, Ahsman MJ, et al. Plasma concentrations of oseltamivir and oseltamivir carboxylate in critically ill children on extracorporeal membrane oxygenation support. PLoS ONE 2010;5:e10938.

166. Taylor WR, Thinh BN, Anh GT, et al. Oseltamivir is adequately absorbed following nasogastric administration to adult patients with severe H5N1 influenza. PLoS ONE 2008;3:e3410.
167. World Health Organization. Clinical management of human infection with avian influenza A (H5N1) virus. Geneva, Switzerland: World Health Organization; 2007.
168. Tramontana AR, George B, Hurt AC, et al. Oseltamivir resistance in adult oncology and hematology patients infected with pandemic (H1N1) 2009 virus, Australia. Emerg Infect Dis 2010;16:1068–75.
169. Gaur AH, Bagga B, Barman S, et al. Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza. N Engl J Med 2010;362:88–9.
170. Kidd IM, Down J, Nastouli E, et al. H1N1 pneumonitis treated with intravenous zanamivir. Lancet 2009;374:1036.
171. Hayden F. Developing new antiviral agents for influenza treatment: what does the future hold? Clin Infect Dis 2009;48(Suppl 1):S3–13.
172. Yun NE, Linde NS, Zacks MA, et al. Injectable peramivir mitigates disease and promotes survival in ferrets and mice infected with the highly virulent influenza virus, A/Vietnam/1203/04 (H5N1). Virology 2008;374:198–209.
173. Calfee DP, Peng AW, Cass LM, et al. Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. Antimicrob Agents Chemother 1999;43:1616–20.
174. Dulek DE, Williams JV, Creech CB, et al. Use of intravenous zanamivir after development of oseltamivir resistance in a critically ill immunosuppressed child infected with 2009 pandemic influenza A (H1N1) virus. Clin Infect Dis 2010;50:1493–6.
175. Ison MG, Gnann JW Jr, Nagy-Agren S, et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. Antivir Ther 2003;8:183–90.
176. Kiatboonsri S, Kiatboonsri CTheerawit P. Fatal respiratory events caused by zanamivir nebulization. Clin Infect Dis 2009;50:620.
177. National Institutes of Allergy and Infectious Diseases and Biomedical Advanced Research and Development Authority. NIAID influenza antiviral development workshop: new generation, March 26–27, 2009 [Conference summary]. Available at http://www3.niaid.nih.gov/topics/Flu/PDF/fluantiviral09.pdf. Accessed December 16, 2010.
178. Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. J Infect Dis 2002;186:1582–8.
179. Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999–2000. J Am Geriatr Soc 2002;50:608–16.
180. Lee VJ, Yap J, Tay JK, et al. Seroconversion and asymptomatic infections during oseltamivir prophylaxis against Influenza A H1N1 2009. BMC Infect Dis 2010;10:164.
181. Khazeni N, Bravata DM, Holty JE, et al. Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. Ann Intern Med 2009;151:464–73.
182. Strong M, Burrows J, Stedman E, et al. Adverse drug effects following oseltamivir mass treatment and prophylaxis in a school outbreak of 2009 pandemic influenza A(H1N1) in June 2009, Sheffield, United Kingdom. Euro Surveill 2010;15:pii/19565.
183. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev 2010;2:CD001265.
184. World Health Organization. Update on oseltamivir-resistant influenza A (H1N1) 2009 influenza virus: January 2010. Wkly Epidemiol Rec 2010;85:37–40.
185. Peters PH Jr, Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc 2001;49:1025–31.
186. Schilling M, Povinelli L, Krause P, et al. Efficacy of zanamivir for chemoprophylaxis of nursing home influenza outbreaks. Vaccine 1998;16:1771–4.
187. Lee C, Loeb M, Phillips A, et al. Zanamivir use during transmission of amantadine-resistant influenza A in a nursing home. Infect Control Hosp Epidemiol 2000;21:700–4.
188. LaForce C, Man CY, Henderson FW, et al. Efficacy and safety of inhaled zanamivir in the prevention of influenza in community-dwelling, high-risk adult and adolescent subjects: a 28-day, multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther 2007;29:1579–90; discussion 1577–8.
189. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 2004;39:1300–6.
190. Kitching A, Roche A, Balasegaram S, et al. Oseltamivir adherence and side effects among children in three London schools affected by influenza A(H1N1)v, May 2009—an internet-based cross-sectional survey. Euro Surveill 2009;14:19287.
191. CDC. Update: influenza activity—United States, 2009–10 season. MMWR 2010;59:901–8.
192. Gomolin IH, Leib HB, Arden NH, et al. Control of influenza outbreaks in the nursing home: guidelines for diagnosis and management. J Am Geriatr Soc 1995;43:71–4.
193. Garner JS. Guideline for isolation precautions in hospitals. The Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1996;17:53–80.
194. Bradley SF. Prevention of influenza in long-term-care facilities. Long-Term-Care Committee of the Society for Healthcare Epidemiology of America. Infect Control Hosp Epidemiol 1999;20:629–37.
195. Arden NH, Patriarca PA, Fasano MB, et al. The roles of vaccination and amantadine prophylaxis in controlling an outbreak of influenza A (H3N2) in a nursing home. Arch Intern Med 1988;148:865–8.
196. Hota SMcGeer A. Antivirals and the control of influenza outbreaks. Clin Infect Dis 2007;45:1362–8.
197. Kimberlin DW, Escude J, Gantner J, et al. Targeted antiviral prophylaxis with oseltamivir in a summer camp setting. Arch Pediatr Adolesc Med 2010;164:323–7.
198. American Academy of Pediatrics. Influenza. In Pickering LK, ed. Red book: 2009 report of the Committee on Infectious Diseases; Elk Grove Village, IL: American Academy of Pediatrics; 2009.
199. Food and Drug Administration. Termination of declarations of emergency justifying emergency use authorization (EUA) of certain antiviral drugs—zanamivir, oseltamivir phosphate, and peramivir. Silver Spring, MD: US Department of Health and Human Services, FDA; 2010. Available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM216494.pdf. Accessed December 16, 2010.
200. Kimberlin DW, Shalabi M, Abzug MJ, et al. Safety of oseltamivir compared with the adamantanes in children less than 12 months of age. Pediatr Infect Dis J 2009;29:195–8.
201. World Health Organization. WHO guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other influenza viruses. Geneva, Switzerland: World Health Organization; 2010.
202. Acosta EP, Jester P, Gal P, et al. Oseltamivir dosing for influenza infection in premature neonates. J Infect Dis 2010;303:563–6.

203. American Academy of Pediatrics. Influenza. In: Pickering LK, ed. Red book: 2003 report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2006.
204. Forest Pharmaceuticals. Flumadine syrup (rimantadine hydrochloride syrup) [Package insert]. St. Louis, MO: Forest Pharmaceuticals; 2001.
205. Food and Drug Administration. FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2008. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm. Accessed December 16, 2010.
206. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2004;53(No. RR-6).
207. Keyser LA, Karl M, Nafziger AN, et al. Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of influenza A in elderly nursing home patients. Arch Intern Med 2000;160:1485–8.
208. Soo W. Adverse effects of rimantadine: summary from clinical trials. J Respir Dis 1989;10(Suppl):S26–31.
209. Rasmussen SA, Jamieson DJBresee JS. Pandemic influenza and pregnant women. Emerg Infect Dis 2008;14:95–100.
210. Dodds L, McNeil SA, Fell DB, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ 2007;176:463–8.
211. Callaghan WM, Chu SY, Jamieson DJ. Deaths from seasonal influenza among pregnant women in the United States, 1998–2005. Obstet Gynecol 2010;115:919–23.
212. Harris J. Influenza occurring in pregnant women: a statistical study of thirteen hundred and fifty cases. JAMA 1919;72:978–80.
213. Hartert TV, Neuzil KM, Shintani AK, et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. Am J Obstet Gynecol 2003;189:1705–12.
214. Greer LG, Sheffield JS, Rogers VL, et al. Maternal and neonatal outcomes after antepartum treatment of influenza with antiviral medications. Obstet Gynecol 2010;115:711–6.
215. Cass LM, Efthymiopoulos C, Bey A. Pharmacokinetics of of zanamivir after intravenous, oral, inhaled or intranasal administration to healthy volunteers. Clin Pharmacokinet 1999;36(Suppl 1):1–11.
216. Karie S, Launay-Vacher V, Janus N, et al. Pharmacokinetics and dosage adjustment of oseltamivir and zanamivir in patients with renal failure. Nephrol Dial Transplant 2006;21:3606–8.
217. Robson R, Buttimore A, Lynn K, et al. The pharmacokinetics and tolerability of oseltamivir suspension in patients on haemodialysis and continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2006;21:2556–62.
218. Schreuder MF, van der Flier M, Knops NB, et al. Oseltamivir dosing in children undergoing hemodialysis. Clin Infect Dis 2010;50:1427–8.
219. Soung LS, Ing TS, Daugirdas JT, et al. Amantadine hydrochloride pharmacokinetics in hemodialysis patients. Ann Intern Med 1980;93:46–9.
220. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2005;54(No. RR-8).
221. Atkinson WL, Arden NH, Patriarca PA, et al. Amantadine prophylaxis during an institutional outbreak of type A (H1N1) influenza. Arch Intern Med 1986;146:1751–6.
222. Vu D, Peck AJ, Nichols WG, et al. Safety and tolerability of oseltamivir prophylaxis in hematopoietic stem cell transplant recipients: a retrospective case-control study. Clin Infect Dis 2007;45:187–93.
223. Gravenstein S, Johnston SL, Loeschel E, et al. Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. Drug Saf 2001;24:1113–25.
224. Webster A, Boyce M, Edmundson S, et al. Coadministration of orally inhaled zanamivir with inactivated trivalent influenza vaccine does not adversely affect the production of antihaemagglutinin antibodies in the serum of healthy volunteers. Clin Pharmacokinet 1999;36 Suppl 1:51–8.
225. Anonymous. New concerns about oseltamivir. Lancet 2007;369:1056.
226. Blumentals WA, Song X. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. MedGenMed 2007;9:23.
227. Toovey S, Rayner C, Prinssen E, et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. Drug Saf 2008;31:1097–114.
228. Tamura D, Miura T, Kikuchi Y. Oseltamivir phosphate in infants under 1 year of age with influenza infection. Pediatr Int 2005;47:484.
229. Shalabi M, Abughali N, Abzug M, et al., Safety of oseltamivir vs. amantadine of rimantadine in children under 1 year of age [Abstract]. Presented at the 45th annual meeting of the Infectious Diseases Society of America, October 4–7, 2007; San Diego, California.
230. Okamoto S, Kamiya I, Kishida K, et al. Experience with oseltamivir for infants younger than 1 year old in Japan. Pediatr Infect Dis J 2005;24:575–6.
231. Budnitz DS, Lewis LL, Shehab N, et al. CDC and FDA response to risk of confusion in dosing Tamiflu oral suspension. N Engl J Med 2009;361:1913–4.
232. Daniel MJ, Barnett JMPearson BA. The low potential for drug interactions with zanamivir. Clin Pharmacokinet 1999;36 Suppl 1:41–50.
233. Duval X, van der Werf S, Blanchon T, et al. Efficacy of oseltamivir-zanamivir combination compared to each monotherapy for seasonal influenza: a randomized placebo-controlled trial. PLoS Med 2010;7:e1000362.
234. Food and Drug Administration. Administrative procedures for emergency use authorization of medical products. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2005. Available at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm061226.htm. Accessed December 16, 2010.

Advisory Committee on Immunization Practices

Membership List, June 2010

Chair: Carol Baker, MD, Baylor College of Medicine, Houston, Texas.

Executive Secretary: Larry Pickering, MD, National Center for Immunization and Respiratory Diseases, CDC, Atlanta, Georgia.

Members: Lance Chilton, MD, University of New Mexico, Albuquerque, New Mexico; Paul Cieslak, MD, Oregon Public Health Division, Portland, Oregon; Kristen Ehresmann, MPH, Minnesota Department of Health, St. Paul, Minnesota; Janet Englund, MD, University of Washington and Children's Hospital and Regional Medical Center, Seattle, Washington; Franklyn Judson, MD, University of Colorado Health Sciences Center, Denver, Colorado; Wendy Keitel, MD, Baylor College of Medicine, Houston, Texas; Susan Lett, MD, Massachusetts Department of Public Health, Boston, Massachusetts; Michael Marcy, MD, UCLA Center for Vaccine Research, Torrance, California; Cody Meissner, MD, Tufts Medical Center, Boston, Massachusetts; Kathleen Neuzil, MD, University of Washington, Seattle, Washington; Sara Rosenbaum, JD, Georgetown University, District of Columbia; Mark Sawyer, MD, University of California-San Diego, California; Ciro Valent Sumaya, MD, Texas A&M Health Science Center, College Station, Texas; Jonathan Temte, MD, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

Ex Officio Members: James E. Cheek, MD, Indian Health Service, Albuquerque, New Mexico; Wayne Hachey, DO, Department of Defense, Falls Church, Virginia; Ted Cieslak, MD, Department of Defense, Atlanta, Georgia; Geoffrey S. Evans, MD, Health Resources and Services Administration, Rockville, Maryland; Bruce Gellin, MD, National Vaccine Program Office, Washington, District of Columbia; Linda Murphy, Centers for Medicare and Medicaid Services, Baltimore, Maryland; George T. Curlin, MD, National Institutes of Health, Bethesda, Maryland; Norman Baylor, PhD, Food and Drug Administration, Bethesda, Maryland; Linda Kinsinger, MD, Department of Veterans Affairs, Durham, North Carolina.

Liaison Representatives: American Academy of Family Physicians, Doug Campos-Outcalt, MD, Phoenix, Arizona; American Academy of Pediatrics, Joseph Bocchini, MD, Shreveport, Louisiana, David Kimberlin, MD, Birmingham, Alabama; American College Health Association, James C. Turner, MD, Charlottesville, Virginia; American College of Obstetricians and Gynecologists, Stanley Gall, MD, Louisville, Kentucky; American College of Physicians, Gregory Poland, MD, Rochester, Minnesota; American Geriatrics Society, Kenneth Schmader, MD, Durham, North Carolina; America's Health Insurance Plans, Mark Netoskie, MD, MBA, Houston, Texas; American Medical Association, Litjen Tan, PhD, Chicago, Illinois; American Osteopathic Association, Stanley Grogg, DO, Tulsa, Oklahoma; American Pharmacists Association, Stephan L. Foster, PharmD, Memphis, Tennessee; Association for Prevention Teaching and Research, W. Paul McKinney, MD, Louisville, Kentucky; Biotechnology Industry Organization, Clement Lewin, PhD, Cambridge, Massachusetts; Canadian National Advisory Committee on Immunization, Joanne Langley, MD, Halifax, Nova Scotia, Canada; Council of State and Territorial Epidemiologists, Christine Hahn, MD, Boise, Idaho; Department of Health, United Kingdom David M. Salisbury, MD, London, United Kingdom; Healthcare Infection Control Practices Advisory Committee, Alexis Elward, MD, St Louis, Missouri; Infectious Diseases Society of America, Samuel L. Katz, MD, Durham, North Carolina; National Association of County and City Health Officials, Jeff Duchin, MD, Seattle, Washington; National Association of Pediatric Nurse Practitioners, Patricia Stinchfield, MPH, St Paul, Minnesota; National Foundation for Infectious Diseases, William Schaffner, MD, Nashville, Tennessee; National Immunization Council and Child Health Program, Mexico, Vesta Richardson, MD, Mexico City, Mexico; National Medical Association, Patricia Whitley-Williams, MD, New Brunswick, New Jersey; National Vaccine Advisory Committee, Guthrie Birkhead, MD, Albany, New York; Pharmaceutical Research and Manufacturers of America, Damian A. Braga, Swiftwater, Pennsylvania, Peter Paradiso, PhD, Collegeville, Pennsylvania; Society for Adolescent Medicine, Amy Middleman, MD, Houston, Texas; Society for Healthcare Epidemiology of America, Harry Keyserling, MD, Atlanta, Georgia.

ACIP Influenza Vaccine Work Group

Chair: Wendy Keitel, MD, Houston, Texas.

Members: William Atkinson, MD, Atlanta, Georgia; Carol Baker, MD, Houston, Texas; Beth Bell, MD, Atlanta, Georgia, Nancy Bennett, MD, Rochester, New York; Henry Bernstein, DO, Lebanon, New Hampshire; Joseph Bresee, MD, Atlanta, Georgia; Carolyn Bridges, MD, Atlanta, Georgia; Karen Broder, MD, Atlanta, Georgia; Doug Campos-Outcalt, MD, Phoenix, Arizona; Fred Cassels, MD, Rockville, Maryland; Lance Chilton, MD, Albuquerque, New Mexico; David Cho, MD, District of Columbia; Nancy Cox, PhD, Atlanta, Georgia; Therese Cvetkovich, MD, Rockville, Maryland; Sandra Dos Santos Chaves, MD, Atlanta, GA; Jeff Duchin, MD, Seattle, Washington; Janet Englund, MD, Seattle, Washington; Anthony Fiore, MD, Atlanta, Georgia; Sandra Fryhofer, MD, Atlanta, Georgia; Stanley Gall, MD, Louisville, Kentucky; Paul Gargiullo, PhD, Atlanta, Georgia; Steven Gordon, MD, Cleveland, Ohio; Wayne Hachey, DO, Falls Church, Virginia; John Iskander, MD, Atlanta Georgia; Wendy Keitel, MD, Houston, Texas; Elyse Olshen Kharbanda, MD, New York, NY; David Lakey, MD, Austin, Texas; Susan Lett, MD, Boston, Massachusetts; Tamara Lewis, MD, Salt Lake City, Utah; Cynthia Nolletti, MD, Rockville, Maryland; Gregory Poland, MD, Rochester, Minnesota; William Schaffner, MD, Nashville, Tennessee; Robert Schechter, MD, Sacramento, California; Kenneth Schmader, MD, Durham, North Carolina; David Shay, MD, Atlanta, Georgia; Nadine Sicard, MD, Ottawa, Canada; Patricia Stinchfield, St. Paul, Minnesota; Ray Strikas, MD, District of Columbia; Litjen Tan, PhD, Chicago, Illinois; Mary Vernon-Smiley, MD Atlanta, Georgia; Timothy Uyeki, MD, Atlanta, Georgia; Amanda Zongrone, Atlanta, Georgia.

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format. To receive an electronic copy each week, visit MMWR's free subscription page at *http://www.cdc.gov/mmwr/mmwrsubscribe.html*. Paper copy subscriptions are available through the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Address all inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop E-90, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333 or to *mmwrq@cdc.gov.*

☆ U.S. Government Printing Office: 2011-723-011/21020 Region IV ISSN: 1546-0738