Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports | August 8, 2008 / Vol. 57 / No. RR-7

Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

The *MMWR* series of publications is published by the Coordinating Center for Health Information and Service, 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 2008;57(No. RR-#):[inclusive page numbers].

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Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008

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Summary

This report updates the 2007 recommendations by CDC's Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccine and antiviral agents (CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2007;56[No. RR-6]). The 2008 recommendations include new and updated information. Principal updates and changes include 1) a new recommendation that annual vaccination be administered to all children aged 5–18 years, beginning in the 2008–09 influenza season, if feasible, but no later than the 2009–10 influenza season; 2) a recommendation that annual vaccination of all children aged 6 months through 4 years (59 months) continue to be a primary focus of vaccination efforts because these children are at higher risk for influenza complications compared with older children; 3) a new recommendation that either trivalent inactivated influenza vaccine or live, attenuated influenza vaccine (LAIV) be used when vaccinating healthy persons aged 2 through 49 years (the previous recommendation was to administer LAIV to person aged 5–49 years); 4) a recommendation that vaccines containing the 2008–09 trivalent vaccine virus strains A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens be used; and, 5) new information on antiviral resistance among influenza viruses in the United States. Persons for whom vaccination is recommended are listed in boxes 1 and 2. These recommendations also include a summary of safety data for U.S. licensed influenza vaccines. This report and other information are available at CDC's influenza website (http://www.cdc.gov/flu), including any updates or supplements to these recommendations that might be required during the 2008–09 influenza season. Vaccination and health-care providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information.

Introduction

In the United States, annual epidemics of influenza occur typically during the late fall through early spring seasons. Influenza viruses can cause disease among persons in any age group, but rates of infection are highest among children (*1–3*). 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 (*1,4,5*). An annual average of approximately 36,000 deaths during 1990–1999 and 226,000 hospitalizations during 1979–2001 have been associated with influenza epidemics (*6,7*).

Annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications. Influenza vaccine can be administered to any person aged ≥6 months (who does not have contraindications to vaccination) to reduce the likelihood of becoming ill with influenza or of transmitting influenza to others. Trivalent inactivated influenza vaccine (TIV) can be used for any person aged

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≥6 months, including those with high-risk conditions (Boxes 1 and 2). Live, attenuated influenza vaccine (LAIV) may be used for healthy, nonpregnant persons aged 2–49 years. If vaccine supply is limited, priority for vaccination is typically assigned to persons in specific groups and of specific ages who are, or are contacts of, persons at higher risk for influenza complications. Because the safety or effectiveness of LAIV has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications, these persons should only be vaccinated with TIV. Influenza viruses undergo frequent antigenic change (i.e., antigenic drift), and persons recommended for vaccination must receive an annual vaccination against the influenza viruses forecasted to be in circulation. Although vaccination coverage has increased in recent years for many groups targeted for routine vaccination, coverage remains low among most of these groups, and strategies to improve vaccination coverage, including use of reminder/recall systems and standing orders programs, should be implemented or expanded.

Antiviral medications are an adjunct to vaccination and are effective when administered as treatment and when used for chemoprophylaxis after an exposure to influenza virus. Oseltamivir and zanamivir are the only antiviral medications recommended for use in the United States. Amantadine or rimantidine should not be used for the treatment or prevention of influenza in the United States until evidence of susceptibility to these antiviral medications has been reestablished among circulating influenza A viruses.

BOX 1. Summary of influenza vaccination recommendations, 2008: children and adolescents aged 6 months–18 years

Vaccination of all children aged 6 months–18 years should begin before or during the 2008–09 influenza season if feasible, but no later than during the 2009–10 influenza season. Vaccination of all children aged 5–18 years is a new ACIP recommendation.

Children and adolescents at high risk for influenza complications should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all children and adolescents. Recommendations for these children have not changed. Children and adolescents at higher risk for influenza complication are those:

- aged 6 months–4 years;
- who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus);
- who are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus);
- who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- who are receiving long-term aspirin therapy who therefore might be at risk for experiencing Reye syndrome after influenza virus infection;
- who are residents of chronic-care facilities; and,
- who will be pregnant during the influenza season.

Note: Children aged <6 months should not receive influenza vaccination. Household and other close contacts (e.g., daycare providers) of children aged <6 months, including older children and adolescents, should be vaccinated.

BOX 2. Summary of influenza vaccination recommendations, 2008: adults

Annual recommendations for adults have not changed. Annual vaccination against influenza is recommended for any adult who wants to reduce the risk for becoming ill with influenza or of transmitting it to others. Vaccination also is recommended for all adults in the following groups, because these persons are either at high risk for influenza complications, or are close contacts of persons at higher risk:

- persons aged ≥50 years;
- women who will be pregnant during the influenza season;
- persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus);
- persons who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus);
- persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration;
- residents of nursing homes and other chronic-care facilities;
- health-care personnel;
- household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months; and,
- household contacts and caregivers of persons with medical conditions that put them at high risk for severe complications from influenza.

Methods

CDC's Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Vaccine Working 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 ACIP consideration of the full committee, members of the working group consider a variety of issues, including burden of influenza illness, vaccine effectiveness, safety and coverage in groups recommended for vaccination, feasibility, cost-effectiveness, and anticipated vaccine supply. Working group members also request periodic updates on vaccine and antiviral production, supply, safety and efficacy from vaccinologists, epidemiologists, and manufacturers. State and local vaccination program representatives are consulted. Influenza surveillance and antiviral resistance data were obtained from CDC's Influenza Division. The Vaccines and Related Biological Products Advisory Committee provides advice on vaccine strain selection to the Food and Drug Administration (FDA), which selects the viral strains to be used in the annual trivalent influenza vaccines.

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 might be considered. Among studies discussed or cited, those of greatest scientific quality and those that measured influenza-specific outcomes are the most influential. For example, population-based estimates that use outcomes associated with laboratory-confirmed influenza virus infection outcomes contribute the most specific data for estimates of influenza burden. The best evidence for vaccine or antiviral efficacy and effectiveness comes from randomized controlled trials that assess laboratory-confirmed influenza infections as an outcome measure and consider factors such as timing and intensity of influenza circulation and degree of match between vaccine strains and wild circulating strains (*8,9*). Randomized, placebo-controlled trials cannot be performed ethically in populations for which vaccination already is recommended, but observational studies that assess outcomes associated with laboratory-confirmed influenza infection can provide important vaccine or antiviral effectiveness data. Randomized, placebo-controlled clinical trials are the best source of vaccine and antiviral safety data for common adverse events; however, such studies do not have the power to identify rare but potentially serious adverse events. The frequency of rare adverse events that might be associated with vaccination or antiviral treatment is best assessed by retrospective reviews of computerized medical records from large linked clinical databases, and by reviewing medical charts of persons who are identified as having a potential adverse event after vaccination (*10,11*). Vaccine coverage data from a nationally representative, randomly selected population that includes verification of vaccination through health-care record review is superior to coverage data derived from limited populations or without verification of vaccination but is rarely available for older children or adults (*12*). Finally, studies that assess vaccination program practices that improve vaccination coverage are most influential in formulating recommendations if the study design includes a nonintervention comparison group. 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 February 2008. 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 July 1, 2008. Further updates, if needed, will be posted at CDC's influenza website (http://www.cdc.gov/flu).

Primary Changes and Updates in the Recommendations

The 2008 recommendations include five principal changes or updates:

- Beginning with the 2008–09 influenza season, annual vaccination of all children aged 5–18 years is recommended. Annual vaccination of all children aged 5–18 years should begin in September or as soon as vaccine is available for the 2008–09 influenza season, if feasible, but annual vaccination of all children aged 5–18 years should begin no later than during the 2009–10 influenza season.
- Annual vaccination of all children aged 6 months–4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue. Children and adolescents at high risk for influenza complications should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all children.
- Either TIV or LAIV can be used when vaccinating healthy persons aged 2–49 years. Children aged 6 months–8 years should receive 2 doses of vaccine if they have not been

*A list of members appears on page 59 of this report.

vaccinated previously at any time with either LAIV or TIV (doses separated by ≥4 weeks); 2 doses are required for protection in these children. Children aged 6 months–8 years who received only 1 dose in their first year of vaccination should receive 2 doses the following year. LAIV should not be administered to children aged <5 years with possible reactive airways disease, such as those who have had recurrent wheezing or a recent wheezing episode. Children with possible reactive airways disease, persons at higher risk for influenza complications because of underlying medical conditions, children aged 6–23 months, and persons aged >49 years should receive TIV.

- The 2008–09 trivalent vaccine virus strains are A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens.
- Oseltamivir-resistant influenza A (H1N1) strains have been identified in the United States and some other countries. However, oseltamivir or zanamivir continue to be the recommended antivirals for treatment of influenza because other influenza virus strains remain sensitive to oseltamivir, and resistance levels to other antiviral medications remain high.

Background and Epidemiology

Biology of Influenza

Influenza A and B are the two types of influenza viruses that cause epidemic human disease. Influenza A viruses are categorized into subtypes on the basis of two surface antigens: hemagglutinin and neuraminidase. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have circulated globally. Influenza A (H1N2) viruses that probably emerged after genetic reassortment between human A (H3N2) and A (H1N1) viruses also have been identified in some influenza seasons. Both influenza A subtypes and B viruses are further separated into groups on the basis of antigenic similarities. New influenza virus variants result from frequent antigenic change (i.e., antigenic drift) resulting from point mutations that occur during viral replication (*13*).

Currently circulating influenza B viruses are separated into two distinct genetic lineages (Yamagata and Victoria) but are not categorized into subtypes. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses. Influenza B viruses from both lineages have circulated in most recent influenza seasons (*13*).

Immunity to the surface antigens, particularly the hemagglutinin, reduces the likelihood of infection (*14*). Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype of influenza virus. Furthermore, antibody to one antigenic type or subtype of influenza virus might not protect against infection with a new antigenic variant of the same type or subtype (*15*). Frequent emergence of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and is the reason for annually reassessing the need to change one or more of the recommended strains for influenza vaccines.

More dramatic changes, or antigenic shifts, occur less frequently. Antigenic shift occurs when a new subtype of influenza A virus appears and can result in the emergence of a novel influenza A virus with the potential to cause a pandemic. New influenza A subtypes have the potential to cause a pandemic when they are able to cause human illness and demonstrate efficient human-to-human transmission and there is little or no previously existing immunity among humans (*13*).

Clinical Signs and Symptoms of Influenza

Influenza viruses are 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) (*16*). Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets do not remain suspended in the air and generally travel only a short distance (≤1 meter) through the air. Contact with respiratory-droplet contaminated surfaces is another possible source of transmission. Airborne transmission (via small-particle residue [≤5µm] of evaporated droplets that might remain suspended in the air for long periods of time) also is thought to be possible, although data supporting airborne transmission are limited (*16–21*). The typical incubation period for influenza is 1–4 days (average: 2 days) (*13*). Adults shed influenza virus from the day before symptoms begin through 5–10 days after illness onset (*22,23*). However, the amount of virus shed, and presumably infectivity, decreases rapidly by 3–5 days after onset in an experimental human infection model (*24,25*). Young children also might shed virus several days before illness onset, and children can be infectious for ≥10 days after onset of symptoms (*26*). Severely immunocompromised persons can shed virus for weeks or months (*27–30*).

Uncomplicated influenza illness 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) (*31*). Among children, otitis media, nausea, and vomiting also are commonly reported with influenza illness (*32,33*). Uncomplicated influenza illness typically resolves after 3–7 days for the majority of persons,

although cough and malaise can persist for >2 weeks. However, influenza virus infections can cause primary influenza viral pneumonia; exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease); lead to secondary bacterial pneumonia, sinusitis, or otitis media; or contribute to coinfections with other viral or bacterial pathogens (*34–36*). Young children with influenza virus infection might have initial symptoms mimicking bacterial sepsis with high fevers (*35–38*), and febrile seizures have been reported in 6%–20% of children hospitalized with influenza virus infection (*32,35,39*). Population-based studies among hospitalized children with laboratory-confirmed 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 (*35,37*). Among 1,308 hospitalized children in one study, 80% were aged <5 years, and 27% were aged <6 months (*35*). Influenza virus infection also has been uncommonly associated with encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye syndrome (*32,34,40,41*).

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 predictive value of clinical definitions vary, depending on the prevalence of other respiratory pathogens and the level of influenza activity (*42*). 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 definition of influenza (acute onset of cough and fever) for laboratory-confirmed influenza infection have varied (range: 79%–88%) (*43,44*).

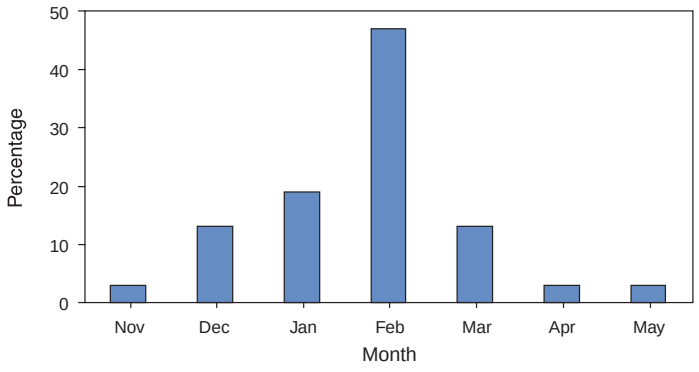
Young children are less likely to report typical influenza symptoms (e.g., fever and cough). In studies conducted among children aged 5–12 years, the positive predictive value of fever and cough together was 71%–83%, compared with 64% among children aged <5 years (*45*). In one large, population-based surveillance study in which all children with fever or symptoms of acute respiratory tract infection were tested for influenza, 70% of hospitalized children aged <6 months with laboratory-confirmed influenza were reported to have fever and cough, compared with 91% of hospitalized children aged 6 months–5 years. Among children who subsequently were shown to have laboratory-confirmed influenza infections, only 28% of those hospitalized and 17% of those treated as outpatients had a discharge diagnosis of influenza (*38*).

Clinical 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 (*46*). Among 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 infection (*47*). In addition, the absence of symptoms of influenza-like illness (ILI) does not effectively rule out influenza; among hospitalized adults with laboratory-confirmed infection in two studies, 44%–51% had typical ILI symptoms (*48,49*). A study of 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% (*50*). 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.

Health-Care Use, Hospitalizations, and Deaths Attributed to Influenza

In the United States, annual epidemics of influenza typically occur during the fall or winter months, but the peak of influenza activity can occur as late as April or May (Figure 1). Influenza-related complications requiring urgent medical care, including hospitalizations or deaths, can result from the direct effects of influenza virus infection, from complications associated with age or pregnancy, or from complications of underlying cardiopulmonary conditions or other chronic diseases. Studies that have measured rates of a clinical outcome without a laboratory confirmation of influenza virus infection (e.g., respiratory illness requiring hospitalization during influenza season) to assess the effect of influenza can be difficult to interpret because of circulation of other respiratory pathogens (e.g., respiratory syncytial virus) during the same time as influenza viruses (*51–53*).

FIGURE 1. Peak influenza activity, by month — United States, 1976–77 through 2007–08 influenza seasons



During seasonal influenza epidemics from 1979–1980 through 2000–2001, the estimated annual overall number of influenza-associated hospitalizations in the United States ranged from approximately 55,000 to 431,000 per annual epidemic (mean: 226,000) (*7*). The estimated annual number of deaths attributed to influenza from the 1990–91 influenza season through 1998–99 ranged from 17,000 to 51,000 per epidemic (mean: 36,000) (*6*). In the United States, the estimated number of influenza-associated deaths increased during 1990–1999. This increase was attributed in part to the substantial increase in the number of persons aged ≥65 years who were at increased risk for death from influenza complications (*6*). In one study, an average of approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976–1990, compared with an average of approximately 36,000 deaths per season during 1990–1999 (*6*). In addition, influenza A (H3N2) viruses, which have been associated with higher mortality (*54*), predominated in 90% of influenza seasons during 1990–1999, compared with 57% of seasons during 1976–1990 (*6*).

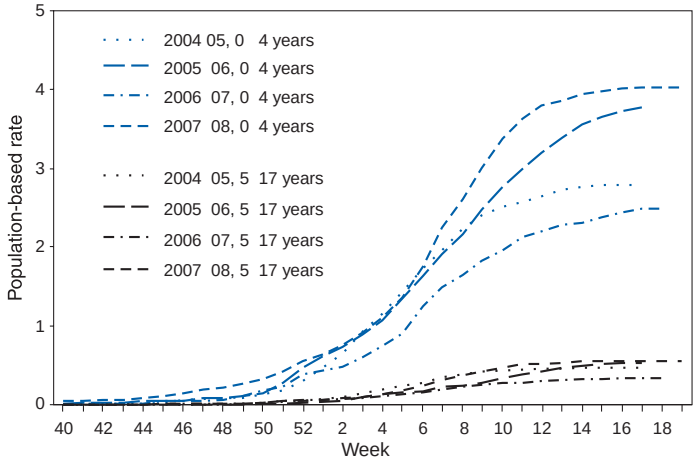
Influenza viruses cause disease among persons in all age groups (*1–5*). Rates of infection are highest among children, but the risks for complications, hospitalizations, and deaths from influenza are higher among persons aged ≥65 years, young children, and persons of any age who have medical conditions that place them at increased risk for complications from influenza (*1,4,5,55–58*). Estimated rates of influenza-associated hospitalizations and deaths varied substantially by age group in studies conducted during different influenza epidemics. During 1990–1999, estimated average rates of influenza-associated pulmonary and circulatory deaths per 100,000 persons were 0.4–0.6 among persons aged 0–49 years, 7.5 among persons aged 50–64 years, and 98.3 among persons aged ≥65 years (*6*).

Children

Among children aged <5 years, influenza-related illness is a common cause of visits to medical practices and emergency departments. During two influenza seasons (2002–03 and 2003–04), the percentage of visits among children aged <5 years with acute respiratory illness or fever caused by laboratory-confirmed influenza ranged from 10%–19% of medical office visits to 6%–29% of emergency departments visits during the influenza season. Using these data, the rate of visits to medical clinics for influenza was estimated to be 50–95 per 1,000 children, and to emergency departments 6–27 per 1,000 children (*38*). Retrospective studies using medical records data have demonstrated similar rates of illness among children aged <5 years during other influenza seasons (*33,56,59*). During the influenza season, an estimated 7–12 additional outpatient visits and 5–7 additional antibiotic prescriptions per 100 children aged <15 years has been documented when compared with periods when influenza viruses are not circulating, with rates decreasing with increasing age of the child (*59*). During 1993–2004 in the Boston area, the rate of emergency department visits for respiratory illness that was attributed to influenza virus based on viral surveillance data among children aged ≤7 years during the winter respiratory illness season ranged from 22.0 per 1000 children aged 6–23 months to 5.4 per 1000 children aged 5–7 years (*60*).

Rates of influenza-associated hospitalization are substantially higher among infants and young children than among older children when influenza viruses are in circulation (Figure 2) and are similar to rates for other groups considered at high risk for influenza-related complications (*61–66*), including persons aged ≥65 years (*59,63*). During 1979–2001, the estimated rate of influenza-associated hospitalizations, using a national sample of hospital discharges of influenza-associated hospitalizations in the United States among children aged <5 years, was 108 hospitalizations per 100,000 person-years (*7*). Recent population-based studies that measured hospitalization rates for laboratory-confirmed influenza in young children documented hospitalization rates that are similar to or higher than rates derived from studies that analyzed hospital discharge data (*33,35,36,38,65*). Annual hospitalization rates for laboratory-confirmed influenza decrease with increasing age, ranging from 240–720 per 100,000 children aged <6 months to approximately 20 per 100,000 children aged 2–5 years (*38*). Hospitalization rates for children aged <5 years

FIGURE 2. Cumulative hospitalization rates* for laboratory-confirmed influenza among children aged 0–4 and 5–17 years, by selected influenza seasons — United States



Source: Emerging Infections Program.
* Per 10,000 children.

with high-risk medical conditions are approximately 250–500 per 100,000 children (*56,58,67*).

Influenza-associated deaths are uncommon among children. An estimated annual average of 92 influenza-related deaths (0.4 deaths per 100,000 persons) occurred among children aged <5 years during the 1990s, compared with 32,651 deaths (98.3 per 100,000 persons) among adults aged ≥65 years (*6*). Of 153 laboratory-confirmed influenza-related pediatric deaths reported during the 2003–04 influenza season, 96 (63%) deaths occurred among children aged <5 years and 61 (40%) among children aged <2 years. Among the 149 children who died and for whom information on underlying health status was available, 100 (67%) did not have an underlying medical condition that was an indication for vaccination at that time (*68*). In California during the 2003–04 and 2004–05 influenza seasons, 51% of children with laboratory-confirmed influenza who died and 40% of those who required admission to an intensive care unit had no underlying medical conditions (*69*). These data indicate that although deaths are more common among children with risk factors for influenza complications, the majority of pediatric deaths occur among children of all age groups with no known high-risk conditions. The annual number of deaths among children reported to CDC for the past four influenza seasons has ranged from 84 during 2004–05 to 84 during 2007–08 (CDC, unpublished data, 2008).

Death associated with laboratory-confirmed influenza virus infection among children (defined as persons aged <18 years) is a nationally reportable condition. Deaths among children that have been attributed to co-infection with influenza and *Staphylococcus aureus*, particularly methicillin resistant *S. aureus* (MRSA), have increased during the preceding four influenza seasons (*70*; CDC, unpublished data, 2008). The reason for this increase is not established but might reflect an increasing prevalence within the general population of colonization with MRSA strains, some of which carry certain virulence factors (*71,72*).

Adults

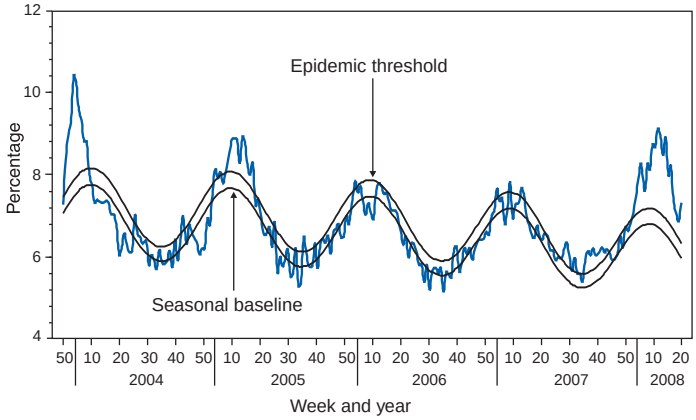
Hospitalization rates during the influenza season are substantially increased for persons aged ≥65 years. One retrospective analysis based on data from managed-care organizations collected during 1996–2000 estimated that the risk during influenza season among persons aged ≥65 years with underlying conditions that put them at risk for influenza-related complications (i.e., one or more of the conditions listed as indications for vaccination) was approximately 560 influenza-associated hospitalizations per 100,000 persons, compared with approximately 190 per 100,000 healthy elderly persons. Persons aged 50–64 years with underlying medical conditions also were at substantially increased risk for hospitalizations during influenza season, compared with healthy adults aged 50–64 years. No increased risk for influenza-associated hospitalizations was demonstrated among healthy adults aged 50–64 years or among those aged 19–49 years, regardless of underlying medical conditions (*64*).

Influenza is an important contributor to the annual increase in deaths attributed to pneumonia and influenza that is observed during the winter months (Figure 3). During 1976–2001, an estimated yearly average of 32,651 (90%) influenza-related deaths occurred among adults aged ≥65 years (*6*). Risk for influenza-associated death was highest among the oldest elderly, with persons aged ≥85 years 16 times more likely to die from an influenza-associated illness than persons aged 65–69 years (*6*).

The duration of influenza symptoms is prolonged and the severity of influenza illness increased among persons with human immunodeficiency virus (HIV) infection (*73–77*). A retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program determined that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than it was either before or after influenza was circulating. The risk for hospitalization was higher for HIV-infected women than it was for women with other underlying medical conditions (*78*). Another study estimated that the risk for influenza-related death was 94–146 deaths per 100,000 persons with acquired immunodeficiency syndrome (AIDS), compared with 0.9–1.0 deaths per 100,000 persons aged 25–54 years and 64–70 deaths per 100,000 persons aged ≥65 years in the general population (*79*).

Influenza-associated excess deaths among pregnant women were reported during the pandemics of 1918–1919 and 1957–1958 (*80–83*). Case reports and several epidemiologic studies

FIGURE 3. Percentage of all deaths attributed to pneumonia and influenza in the 122 cities mortality reporting system — United States, 2004–2008



also indicate that pregnancy increases the risk for influenza complications (*84–89*) for the mother. The majority of studies that have attempted to assess the effect of influenza on pregnant women have measured changes in excess hospitalizations for respiratory illness during influenza season but not laboratory-confirmed influenza hospitalizations. Pregnant women have an increased number of medical visits for respiratory illnesses during influenza season compared with nonpregnant women (*90*). Hospitalized pregnant women with respiratory illness during influenza season have increased lengths of stay compared with hospitalized pregnant women without respiratory illness. Rates of hospitalization for respiratory illness were twice as common during influenza season (*91*). A retrospective cohort study of approximately 134,000 pregnant women conducted in Nova Scotia during 1990–2002 compared medical record data for pregnant women to data from the same women during the year before pregnancy. Among pregnant women, 0.4% were hospitalized and 25% visited a clinician during pregnancy for a respiratory illness. The rate of third-trimester hospital admissions during the influenza season was five times higher than the rate during the influenza season in the year before pregnancy and more than twice as high as the rate during the noninfluenza season. An excess of 1,210 hospital admissions in the third trimester per 100,000 pregnant women with comorbidities and 68 admissions per 100,000 women without comorbidities was reported (*92*). In one study, pregnant women with respiratory hospitalizations did not have an increase in adverse perinatal outcomes or delivery complications (*93*); however, another study indicated an increase in delivery complications (*91*). However, infants born to women with laboratory-confirmed influenza during pregnancy do not have higher rates of low birth weight, congenital abnormalities, or low Apgar scores compared with infants born to uninfected women (*88,94*).

Options for Controlling Influenza

The most effective strategy for preventing influenza is annual vaccination. Strategies that focus on providing routine vaccination to persons at higher risk for influenza complications have long been recommended, although coverage among the majority of these groups remains low. Routine vaccination of certain persons (e.g., children, contacts of persons at risk for influenza complications, and HCP) who serve as a source of influenza virus transmission might provide additional protection to persons at risk for influenza complications and reduce the overall influenza burden, but coverage levels among these persons needs to be increased before effects on transmission can be reliably measured. Antiviral drugs used for chemoprophylaxis or treatment of influenza are adjuncts to vaccine but are not substitutes for annual vaccination. However, antiviral drugs might be underused among those hospitalized with influenza (*95*). Nonpharmacologic interventions (e.g., advising frequent handwashing and improved respiratory hygiene) are reasonable and inexpensive; these strategies have been demonstrated to reduce respiratory diseases (*96,97*) but have not been studied adequately to determine if they reduce transmission of influenza virus. Similarly, few data are available to assess the effects of community-level respiratory disease mitigation strategies (e.g., closing schools, avoiding mass gatherings, or using respiratory protection) on reducing influenza virus transmission during typical seasonal influenza epidemics (*98,99*).

Influenza Vaccine Efficacy, Effectiveness, and Safety

Evaluating Influenza Vaccine Efficacy and Effectiveness Studies

The efficacy (i.e., prevention of illness among vaccinated persons in controlled trials) and effectiveness (i.e., prevention of illness in vaccinated populations) of influenza vaccines depend in part on the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation (see Effectiveness of Influenza Vaccination when Circulating Influenza Virus Strains Differ from Vaccine Strains), and the outcome being measured. Influenza vaccine efficacy and effectiveness studies have used multiple possible outcome measures, including the prevention of medically attended acute respiratory illness (MAARI), prevention of laboratory-confirmed influenza virus illness, prevention of influenza or pneumonia-associated hospitalizations or deaths, or prevention of seroconversion to circulating influenza virus strains. Efficacy or effectiveness for more specific outcomes such as laboratory-confirmed influenza typically will be higher than for less specific outcomes such as MAARI because the causes of MAARI include infections with other pathogens that influenza vaccination would not be expected to prevent (*100*). Observational studies that compare less-specific outcomes among vaccinated populations to those among unvaccinated populations are subject to biases that are difficult to control for during analyses. For example, an observational study that determines that influenza vaccination reduces overall mortality might be biased if healthier persons in the study are more likely to be vaccinated (*101,102*). Randomized controlled trials that measure laboratory-confirmed influenza virus infections as the outcome

are the most persuasive evidence of vaccine efficacy, but such trials cannot be conducted ethically among groups recommended to receive vaccine annually.

Influenza Vaccine Composition

Both LAIV and TIV contain strains of influenza viruses that are antigenically equivalent to the annually recommended strains: one influenza A (H3N2) virus, one influenza A (H1N1) virus, and one influenza B virus. Each year, one or more virus strains in the vaccine might be changed on the basis of global surveillance for influenza viruses and the emergence and spread of new strains. All three vaccine virus strains were changed for the recommended vaccine for the 2008–09 influenza season, compared with the 2007–08 season (see Recommendations for Using TIV and LAIV During the 2008–09 Influenza Season). Viruses for both types of currently licensed vaccines are grown in eggs. Both vaccines are administered annually to provide optimal protection against influenza virus infection (Table 1). Both TIV and LAIV are widely available in the United States. Although both types of vaccines are expected to be effective, the vaccines differ in several respects (Table 1).

Major Differences Between TIV and LAIV

During the preparation of TIV, the vaccine viruses are made noninfectious (i.e., inactivated or killed) (*103*). Only subvirion and purified surface antigen preparations of TIV (often referred to as "split" and subunit vaccines, respectively) are available in the United States. TIV contains killed viruses and thus cannot cause influenza. LAIV contains live, attenuated viruses that have the potential to cause mild signs or symptoms such as runny nose, nasal congestion, fever or sore throat. LAIV is administered intranasally by sprayer, whereas TIV is administered intramuscularly by injection. LAIV is licensed for use among nonpregnant persons aged 2–49 years; safety has not been established in persons with underlying medical conditions that confer a higher risk of influenza complications. TIV is licensed for use among persons aged ≥6 months, including those who are healthy and those with chronic medical conditions (Table 1).

Correlates of Protection after Vaccination

Immune correlates of protection against influenza infection after vaccination include serum hemagglutination inhibition antibody and neutralizing antibody (*14,104*). Increased levels of antibody induced by vaccination decrease the risk for illness caused by strains that are antigenically similar to those strains of the same type or subtype included in the vaccine (*105–108*). The majority of healthy children and adults have high titers of antibody after vaccination (*106,109*). Although immune correlates such as achievement of certain antibody titers after vaccination correlate well with immunity on a population level, the significance of reaching or failing to reach a certain antibody threshold is not well understood on the individual level. Other immunologic correlates of protection that might best indicate clinical protection after receipt of an intranasal vaccine such as LAIV (e.g., mucosal antibody) are more difficult to measure (*103,110*).

Immunogenicity, Efficacy, and Effectiveness of TIV

Children

Children aged ≥6 months typically have protective levels of anti-influenza antibody against specific influenza virus strains after receiving the recommended number of doses of influenza vaccine (*104,109,111–116*). In most seasons, one or more vaccine antigens are changed compared to the previous season. In consecutive years when vaccine antigens change, children aged <9 years who received only 1 dose of vaccine in their first year of vaccination are less likely to have protective antibody responses when administered only a single dose during their second year of vaccination, compared with children who received 2 doses in their first year of vaccination (*117–119*).

When the vaccine antigens do not change from one season to the next, priming children aged 6–23 months with a single dose of vaccine in the spring followed by a dose in the fall engenders similar antibody responses compared with a regimen of 2 doses in the fall (*120*). However, one study conducted during a season when the vaccine antigens did not change compared with the previous season estimated 62% effectiveness against ILI for healthy children who had received only 1 dose in the previous influenza season and only 1 dose in the study season, compared with 82% for those who received 2 doses separated by >4 weeks during the study season (*121*).

The antibody response among children at higher risk for influenza-related complications (e.g., children with chronic medical conditions) might be lower than those typically reported among healthy children (*122,123*). However, antibody responses among children with asthma are similar to those of healthy children and are not substantially altered during asthma exacerbations requiring short-term prednisone treatment (*124*).

Vaccine effectiveness studies also have indicated that 2 doses are needed to provide adequate protection during the first season that young children are vaccinated. Among children aged

TABLE 1. Live, attenuated influenza vaccine (LAIV) compared with inactivated influenza vaccine (TIV) for seasonal influenza, United States formulations.

Factor	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live-attenuated virus	Killed virus
No. of included virus strains	Three (two influenza A, one influenza B)	Three (two influenza A, one influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration	Annually*	Annually*
Approved age	Persons aged 2–49 yrs†	Persons aged ≥6 months
Interval between 2 doses recommended for children aged ≥6 months–8 years who are receiving influenza vaccine for the first time	4 weeks	4 weeks
Can be administered to persons with medical risk factors for influenza-related complications†	No	Yes
Can be administered to children with asthma or children aged 2–4 years with wheezing during the preceding year§	No	Yes
Can be administered to family members or close contacts of immunosuppressed persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunosuppressed persons requiring a protected environment (e.g., hematopoietic stem cell transplant recipient)	No	Yes
Can be administered to family members or close contacts of persons at high risk but not severely immunosuppressed	Yes	Yes
Can be simultaneously administered with other vaccines	Yes¶	Yes**
If not simultaneously administered, can be administered within 4 weeks of another live vaccine	Prudent to space 4 weeks apart	Yes
If not simultaneously administered, can be administered within 4 weeks of an inactivated vaccine	Yes	Yes

* Children aged 6 months–8 years who have never received influenza vaccine before should receive 2 doses. Those who only receive 1 dose in their first year of vaccination should receive 2 doses in the following year, spaced 4 weeks apart.

† Persons at high risk for complications of influenza infection because of underlying medical conditions should not receive LAIV. Persons at higher risk for complications of influenza infection because of underlying medical conditions include adults and children with chronic disorders of the pulmonary or cardiovascular systems; adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunnosuppression; children and adolescents receiving long-term aspirin therapy (at risk for developing Reye syndrome after wild-type influenza infection); persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration; pregnant women; and residents of nursing homes and other chronic-care facilities that house persons with chronic medical conditions.

§ Clinicians and vaccination programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2–4 years, and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health-care providers should consult the medical record, when available, to identify children aged 2–4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2–4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months, should not receive FluMist.

¶ Live attenuated influenza vaccine coadministration has been evaluated systematically only among children aged 12–15 months who received measles, mumps and rubella vaccine or varicella vaccine.

** Inactivated influenza vaccine coadministration has been evaluated systematically only among adults who received pneumococcal polysaccharide or zoster vaccine.

<5 years who have never received influenza vaccine previously or who received only 1 dose of influenza vaccine in their first year of vaccination, vaccine effectiveness is lower compared with children who receive 2 doses in their first year of being vaccinated. Two recent, large retrospective studies of young children who had received only 1 dose of TIV in their first year of being vaccinated determined that no decrease was observed in ILI-related office visits compared with unvaccinated children (*121,125*). Similar results were reported in a case-control study of children aged 6–59 months (*126*). These results, along with the immunogenicity data indicating that antibody responses are significantly higher when young chil-

dren are given 2 doses, are the basis for the recommendation that all children aged <9 years who are being vaccinated for the first time should receive 2 vaccine doses separated by at least 4 weeks.

Certain studies have demonstrated vaccine efficacy or effectiveness among children aged ≥6 months, although estimates have varied. In a randomized trial conducted during five influenza seasons (1985–1990) in the United States among children aged 1–15 years, annual vaccination reduced laboratory-confirmed influenza A substantially (77%–91%) (*106*). A limited 1-year placebo-controlled study reported vaccine efficacy against laboratory-confirmed influenza illness of 56% among healthy children aged 3–9 years and 100% among healthy children and adolescents aged 10–18 years (*127*). A randomized, double-blind, placebo-controlled trial conducted during two influenza seasons among children aged 6–24 months indicated that efficacy was 66% against culture-confirmed influenza illness during 1999–2000, but did not significantly reduce culture-confirmed influenza illness during 2000–2001 (*128*). In a nonrandomized controlled trial among children aged 2–6 years and 7–14 years who had asthma, vaccine efficacy was 54% and 78% against laboratory-confirmed influenza type A infection and 22% and 60% against laboratory-confirmed influenza type B infection, respectively. Vaccinated children aged 2–6 years with asthma did not have substantially fewer type B influenza virus infections compared with the control group in this study (*129*). Vaccination also might provide protection against asthma exacerbations (*130*); however, other studies of children with asthma have not demonstrated decreased exacerbations (*131*). Because of the recognized influenza-related disease burden among children with other chronic diseases or immunosuppression and the long-standing recommendation for vaccination of these children, randomized placebo-controlled studies to study efficacy in these children have not been conducted because of ethical considerations.

A retrospective study conducted among approximately 30,000 children aged 6 months–8 years during an influenza season (2003–04) with a suboptimal vaccine match indicated vaccine effectiveness of 51% against medically attended, clinically diagnosed pneumonia or influenza (i.e., no laboratory confirmation of influenza) among fully vaccinated children, and 49% among approximately 5,000 children aged 6–23 months (*125*). Another retrospective study of similar size conducted during the same influenza season in Denver but limited to healthy children aged 6–21 months estimated clinical effectiveness of 2 TIV doses to be 87% against pneumonia or influenza-related office visits (*121*). Among children, TIV effectiveness might increase with age (*106,132*).

TIV has been demonstrated to reduce acute otitis media in some studies. Two studies have reported that TIV decreases the risk for influenza-associated otitis media by approximately 30% among children with mean ages of 20 and 27 months, respectively (*133,134*). However, a large study conducted among children with a mean age of 14 months indicated that TIV was not effective against acute otitis media (*128*). Influenza vaccine effectiveness against acute otitis media, which is caused by a variety of pathogens and is not typically diagnosed using influenza virus culture, would be expected to be relatively low when assessing a nonspecific clinical outcome.

Adults Aged <65 Years

One dose of TIV is highly immunogenic in healthy adults aged <65 years. Limited or no increase in antibody response is reported among adults when a second dose is administered during the same season (*135–139*). When the vaccine and circulating viruses are antigenically similar, TIV prevents laboratory-confirmed influenza illness among approximately 70%–90% of healthy adults aged <65 years in randomized controlled trials (*139–142*). Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including use of antibiotics, when the vaccine and circulating viruses are well-matched (*139–141,143–145*). Efficacy or effectiveness against laboratory-confirmed influenza illness was 50%–77% in studies conducted during different influenza seasons when the vaccine strains were antigenically dissimilar to the majority of circulating strains (*139,141,145–147*). However, effectiveness among healthy adults against influenza-related hospitalization, measured in the most recent of these studies, was 90% (*147*).

In certain studies, persons with certain chronic diseases have lower serum antibody responses after vaccination compared with healthy young adults and can remain susceptible to influenza virus infection and influenza-related upper respiratory tract illness (*148–150*). Vaccine effectiveness among adults aged <65 years who are at higher risk for influenza complications is typically lower than that reported for healthy adults. In a case-control study conducted during 2003–2004, when the vaccine was a suboptimal antigenic match to many circulating virus strains, effectiveness for prevention of laboratory-confirmed influenza illness among adults aged 50–64 years with high risk conditions was 48%, compared with 60% for healthy adults (*147*). Effectiveness against hospitalization among adults aged 50–64 years with high-risk conditions was 36%, compared with 90% effectiveness among healthy adults in that age range (*147*). A randomized controlled trial among adults in Thailand with chronic obstructive pulmonary disease (median age: 68 years) indicated a vaccine effectiveness of 76% in preventing laboratory-confirmed influenza during

a season when viruses were well-matched to vaccine viruses. Effectiveness did not decrease with increasing severity of underlying lung disease (*151*).

Studies using less specific outcomes, without laboratory confirmation of influenza virus infection, typically have demonstrated substantial reductions in hospitalizations or deaths among adults with risk factors for influenza complications. In a case-control study conducted in Denmark among adults with underlying medical conditions aged <65 years during 1999–2000, vaccination reduced deaths attributable to any cause 78% and reduced hospitalizations attributable to respiratory infections or cardiopulmonary diseases 87% (*152*). A benefit was reported after the first vaccination and increased with subsequent vaccinations in subsequent years (*153*). Among patients with diabetes mellitus, vaccination was associated with a 56% reduction in any complication, a 54% reduction in hospitalizations, and a 58% reduction in deaths (*154*). Certain experts have noted that the substantial effects on morbidity and mortality among those who received influenza vaccination in these observational studies should be interpreted with caution because of the difficulties in ensuring that those who received vaccination had similar baseline health status as those who did not (*101,102*). One meta-analysis of published studies did not determine sufficient evidence to conclude that persons with asthma benefit from vaccination (*155*). However, a meta-analysis that examined effectiveness among persons with chronic obstructive pulmonary disease identified evidence of benefit from vaccination (*156*).

Immunocompromised Persons

TIV produces adequate antibody concentrations against influenza among vaccinated HIV-infected persons who have minimal AIDS-related symptoms and normal or near-normal CD4+ T-lymphocyte cell counts (*157–159*). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, TIV might not induce protective antibody titers (*159,160*); a second dose of vaccine does not improve the immune response in these persons (*160,161*). A randomized, placebo-controlled trial determined that TIV was highly effective in preventing symptomatic, laboratory-confirmed influenza virus infection among HIV-infected persons with a mean of 400 CD4+ T-lymphocyte cells/mm3; however, a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study (*161*). A nonrandomized study of HIV-infected persons determined that influenza vaccination was most effective among persons with >100 CD4+ cells and among those with <30,000 viral copies of HIV type-1/mL (*77*).

On the basis of certain small studies, immunogenicity for persons with solid organ transplants varies according to transplant type. Among persons with kidney or heart transplants, the proportion who developed seroprotective antibody concentrations was similar or slightly reduced compared with healthy persons (*162–164*). However, a study among persons with liver transplants indicated reduced immunologic responses to influenza vaccination (*165–167*), especially if vaccination occurred within the 4 months after the transplant procedure (*165*).

Pregnant Women and Neonates

Pregnant women have protective levels of anti-influenza antibodies after vaccination (*168,169*). Passive transfer of anti-influenza antibodies that might provide protection from vaccinated women to neonates has been reported (*168,170–172*). A retrospective, clinic-based study conducted during 1998–2003 documented a nonsignificant trend towards fewer episodes of MAARI during one influenza season among vaccinated pregnant women compared with unvaccinated pregnant women and substantially fewer episodes of MAARI during the peak influenza season (*169*). However, a retrospective study conducted during 1997–2002 that used clinical records data did not indicate a reduction in ILI among vaccinated pregnant women or their infants (*173*). In another study conducted during 1995–2001, medical visits for respiratory illness among the infants were not substantially reduced (*174*). However, studies of influenza vaccine effectiveness among pregnant women have not included specific outcomes such as laboratory-confirmed influenza in women or their infants.

Older Adults

Adults aged ≥65 years typically have a diminished immune response to influenza vaccination compared with young healthy adults, suggesting that immunity might be of shorter duration (although still extending through one influenza season) (*175,176*). However, a review of the published literature concluded that no clear evidence existed that immunity declined more rapidly in the elderly (*177*). Infections among the vaccinated elderly might be associated with an age-related reduction in ability to respond to vaccination rather than reduced duration of immunity (*149–150*).

The only randomized controlled trial among community-dwelling persons aged ≥60 years reported a vaccine efficacy of 58% against influenza respiratory illness during a season when the vaccine strains were considered to be well-matched to circulating strains, but indicated that efficacy was lower among those aged ≥70 years (*178*). Influenza vaccine effectiveness in preventing MAARI among the elderly in nursing homes has been estimated at 20%–40% (*179,180*), and reported outbreaks among well-vaccinated nursing home populations have suggested that vaccination might not have any significant

effectiveness when circulating strains are drifted from vaccine strains (*181,182*). In contrast, some studies have indicated that vaccination can be up to 80% effective in preventing influenza-related death (*179,183–185*). Among elderly persons not living in nursing homes or similar chronic-care facilities, influenza vaccine is 27%–70% effective in preventing hospitalization for pneumonia and influenza (*186–188*). Influenza vaccination reduces the frequency of secondary complications and reduces the risk for influenza-related hospitalization and death among community-dwelling adults aged ≥65 years with and without high-risk medical conditions (e.g., heart disease and diabetes) (*187–192*). However, studies demonstrating large reductions in hospitalizations and deaths among the vaccinated elderly have been conducted using medical record databases and have not measured reductions in laboratory-confirmed influenza illness. These studies have been challenged because of concerns that they have not adequately controlled for differences in the propensity for healthier persons to be more likely than less healthy persons to receive vaccination (*101,102,183,193–195*).

TIV Dosage, Administration, and Storage

The composition of TIV varies according to manufacturer, and package inserts should be consulted. TIV formulations in multidose vials contain the vaccine preservative thimerosal; preservative-free single dose preparations also are available. TIV should be stored at 35°F–46°F (2°C–8°C) and should not be frozen. TIV that has been frozen should be discarded. Dosage recommendations and schedules vary according to age group (Table 2). Vaccine prepared for a previous influenza season should not be administered to provide protection for any subsequent season.

The intramuscular route is recommended for TIV. Adults and older children should be vaccinated in the deltoid muscle. A needle length of ≥1 inch (>25 mm) should be considered for persons in these age groups because needles of <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children (*196*). When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of 7/8–1.25 inches is recommended (*197*).

TABLE 2. Approved influenza vaccines for different age groups — United States, 2008–09 season

Vaccine	Trade name	Manufacturer	Presentation	Mercury content (mcg Hg/0.5 mL dose)	Age group	No. of doses	Route
TIV*	Fluzone	sanofi pasteur	0.25 mL pre-filled syringe	0	6–35 mos	1 or 2†	Intramuscular§
			0.5 mL pre-filled syringe	0	≥36 mos	1 or 2†	Intramuscular§
			0.5 mL vial	0	≥36 mos	1 or 2†	Intramuscular§
			5.0 mL multi-dose vial	25	≥6 mos	1 or 2†	Intramuscular§
TIV*	Fluvirin	Novartis Vaccine	5.0 mL multi-dose vial	24.5	≥4 yrs	1 or 2†	Intramuscular§
			0.5 mL pre-filled syringe	<1.0	≥4 yrs	1 or 2†	Intramuscular§
TIV*	Fluarix	GlaxoSmithKline	0.5 mL pre-filled syringe	<1.0	≥18 yrs	1	Intramuscular§
TIV*	FluLuval	GlaxoSmithKline	5.0 mL multi-dose vial	25	≥18 years	1	Intramuscular§
TIV*	Afluria	CSL Biotherapies	0.5 mL pre-filled syringe	0	≥18 years	1	
			5.0 mL multi-dose vial	25	≥18 years	1	Intramuscular§
LAIV¶	FluMist**	MedImmune	0.2 mL sprayer	0	2–49 yrs	1 or 2††	Intranasal

* Trivalent inactivated vaccine (TIV). A 0.5-mL dose contains 15 mcg each of A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens.

† Two doses administered at least 1 month apart are recommended for children aged 6 months–8 years who are receiving TIV for the first time and those who only received 1 dose in their first year of vaccination should receive 2 doses in the following year.

§ For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

¶ Live attenuated influenza vaccine (LAIV). A 0.2-mL dose contains $10^{6.5–7.5}$ fluorescent focal units of live attenuated influenza virus reassortants of each of the three strains for the 2008–09 influenza season: A/Brisbane/59/2007(H1N1), A/Brisbane/10/2007(H3N2), and B/Florida/4/2006.

** FluMist is shipped refrigerated and stored in the refrigerator at 2°C to 8°C after arrival in the vaccination clinic. The dose is 0.2 mL divided equally between each nostril. Health-care providers should consult the medical record, when available, to identify children aged 2–4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2–4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months, should not receive FluMist.

†† Two doses administered at least 4 weeks apart are recommended for children aged 2–8 years who are receiving LAIV for the first time, and those who only received 1 dose in their first year of vaccination should receive 2 doses in the following year.

Infants and young children should be vaccinated in the anterolateral aspect of the thigh. A needle length of 7/8–1 inch should be used for children aged <12 months.

Adverse Events after Receipt of TIV

Children

Studies support the safety of annual TIV in children and adolescents. The largest published postlicensure population-based study assessed TIV safety in 215,600 children aged <18 years and 8,476 children aged 6–23 months enrolled in one of five health maintenance organizations (HMOs) during 1993–1999. This study indicated no increase in biologically plausible, medically attended events during the 2 weeks after inactivated influenza vaccination, compared with control periods 3–4 weeks before and after vaccination (*198*). A retrospective study using medical records data from approximately 45,000 children aged 6–23 months provided additional evidence supporting overall safety of TIV in this age group. Vaccination was not associated with statistically significant increases in any medically attended outcome, and 13 diagnoses, including acute upper respiratory illness, otitis media and asthma, were significantly less common (*199*).

In a study of 791 healthy children aged 1–15 years, post-vaccination fever was noted among 11.5% of those aged 1–5 years, 4.6% among those aged 6–10 years, and 5.1% among those aged 11–15 years (*106*). Fever, malaise, myalgia, and other systemic symptoms that can occur after vaccination with inactivated vaccine most often affect persons who have had no previous exposure to the influenza virus antigens in the vaccine (e.g., young children) (*200,201*). These reactions begin 6–12 hours after vaccination and can persist for 1–2 days. Data about potential adverse events among children after influenza vaccination are available from the Vaccine Adverse Event Reporting System (VAERS). A recently published review of VAERS reports submitted after administration of TIV to children aged 6–23 months documented that the most frequently reported adverse events were fever, rash, injection-site reactions, and seizures; the majority of the limited number of reported seizures appeared to be febrile (*202*). Because of the limitations of passive reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, usually is not possible using VAERS data alone.

Adults

In placebo-controlled studies among adults, the most frequent side effect of vaccination was soreness at the vaccination site (affecting 10%–64% of patients) that lasted <2 days (*203,204*). These local reactions typically were mild and rarely interfered with the recipients' ability to conduct usual daily activities. Placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of TIV is not associated with higher rates for systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections (*139,155, 203–205*).

Pregnant Women and Neonates

FDA has classified TIV as a "Pregnancy Category C" medication, indicating that animal reproduction studies have not been conducted to support a labeling change. Available data indicate that influenza vaccine does not cause fetal harm when administered to a pregnant woman or affect reproductive capacity. One study of approximately 2,000 pregnant women who received TIV during pregnancy demonstrated no adverse fetal effects and no adverse effects during infancy or early childhood (*206*). A matched case-control study of 252 pregnant women who received TIV within the 6 months before delivery determined no adverse events after vaccination among pregnant women and no difference in pregnancy outcomes compared with 826 pregnant women who were not vaccinated (*169*). During 2000–2003, an estimated 2 million pregnant women were vaccinated, and only 20 adverse events among women who received TIV were reported to VAERS during this time, including nine injection-site reactions and eight systemic reactions (e.g., fever, headache, and myalgias). In addition, three miscarriages were reported, but these were not known to be causally related to vaccination (*207*). Similar results have been reported in certain smaller studies (*168,170,208*), and a recent international review of data on the safety of TIV concluded that no evidence exists to suggest harm to the fetus (*209*).

Persons with Chronic Medical Conditions

In a randomized cross-over study of children and adults with asthma, no increase in asthma exacerbations was reported for either age group (*210*), and a second study indicated no increase in wheezing among vaccinated asthmatic children (*130*). One study (*123*) reported that 20%–28% of children with asthma aged 9 months–18 years had local pain and swelling at the site of influenza vaccination, and another study (*113*) reported that 23% of children aged 6 months–4 years with chronic heart or lung disease had local reactions. A blinded, randomized, cross-over study of 1,952 adults and children with asthma demonstrated that only self-reported "body aches" were reported more frequently after TIV (25%) than placebo-injection (21%) (*210*). However, a placebo-controlled trial of TIV indicated no difference in local reactions among 53 children aged 6 months–6 years with high-risk medical conditions or among 305 healthy children aged 3–12 years (*114*).

Among children with high-risk medical conditions, one study of 52 children aged 6 months–3 years reported fever among 27% and irritability and insomnia among 25% (*113*); and a study among 33 children aged 6–18 months reported that one child had irritability and one had a fever and seizure after vaccination (*211*). No placebo comparison group was used in these studies.

Immunocompromised Persons

Data demonstrating safety of TIV for HIV-infected persons are limited, but no evidence exists that vaccination has a clinically important impact on HIV infection or immunocompetence. One study demonstrated a transient (i.e., 2–4 week) increase in HIV RNA (ribonucleic acid) levels in one HIV-infected person after influenza virus infection (*212*). Studies have demonstrated a transient increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration (*159,213*). However, more recent and better-designed studies have not documented a substantial increase in the replication of HIV (*214–217*). CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated to change substantially after influenza vaccination among HIV-infected persons compared with unvaccinated HIV-infected persons (*159,218*). Limited information is available about the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza virus infection or influenza vaccination (*73,219*).

Data are similarly limited for persons with other immunocompromising conditions. In small studies, vaccination did not affect allograft function or cause rejection episodes in recipients of kidney transplants (*162,164*), heart transplants (*163*), or liver transplants (*165*).

Hypersensitivity

Immediate and presumably allergic reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) occur rarely after influenza vaccination (*220,221*). These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Manufacturers use a variety of different compounds to inactivate influenza viruses and add antibiotics to prevent bacterial contamination. Package inserts should be consulted for additional information.

Persons who have had hives or swelling of the lips or tongue, or who have experienced acute respiratory distress or who collapse after eating eggs, should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had occupational asthma related to egg exposure or other allergic responses to egg protein, also might be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician before vaccination should be considered (*222–224*).

Hypersensitivity reactions to other vaccine components can occur but are rare. Although exposure to vaccines containing thimerosal can lead to hypersensitivity, the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity (*225,226*). When reported, hypersensitivity to thimerosal typically has consisted of local delayed hypersensitivity reactions (*225*).

Guillain-Barré Syndrome and TIV

The annual incidence of Guillain-Barré Syndrome (GBS) is 10–20 cases per 1 million adults (*227*). Substantial evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni* gastrointestinal infections and upper respiratory tract infections, are associated with GBS (*228–230*). The 1976 swine influenza vaccine was associated with an increased frequency of GBS (*231,232*), estimated at one additional case of GBS per 100,000 persons vaccinated. The risk for influenza vaccine-associated GBS was higher among persons aged ≥25 years than among persons aged <25 years (*233*). However, obtaining strong epidemiologic evidence for a possible small increase in risk for a rare condition with multiple causes is difficult, and no evidence exists for a consistent causal relation between subsequent vaccines prepared from other influenza viruses and GBS.

None of the studies conducted using influenza vaccines other than the 1976 swine influenza vaccine have demonstrated a substantial increase in GBS associated with influenza vaccines. During three of four influenza seasons studied during 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were not statistically significant in any of these studies (*234–236*). However, in a study of the 1992–93 and 1993–94 seasons, the overall relative risk for GBS was 1.7 (CI = 1.0–2.8; p = 0.04) during the 6 weeks after vaccination, representing approximately one additional case of GBS per 1 million persons vaccinated; the combined number of GBS cases peaked 2 weeks after vaccination (*231*). Results of a study that examined health-care data from Ontario, Canada,

during 1992–2004 demonstrated a small but statistically significant temporal association between receiving influenza vaccination and subsequent hospital admission for GBS. However, no increase in cases of GBS at the population level was reported after introduction of a mass public influenza vaccination program in Ontario beginning in 2000 (*237*). Data from VAERS have documented decreased reporting of GBS occurring after vaccination across age groups over time, despite overall increased reporting of other, non-GBS conditions occurring after administration of influenza vaccine (*203*). Cases of GBS after influenza virus infection have been reported, but no other epidemiologic studies have documented such an association (*238,239*). Recently published data from the United Kingdom's General Practice Research Database (GPRD) found influenza vaccine to be protective against GBS, although it is unclear if this was associated with protection against influenza or confounding because of a "healthy vaccinee" (e.g., healthier persons might be more likely to be vaccinated and are lower risk for GBS) (*240*). A separate GPRD analysis found no association between vaccination and GBS over a 9 year period; only three cases of GBS occurred within 6 weeks after influenza vaccine (*241*).

If GBS is a side effect of influenza vaccines other than 1976 swine influenza vaccine, the estimated risk for GBS (on the basis of the few studies that have demonstrated an association between vaccination and GBS) is low (i.e., approximately one additional case per 1 million persons vaccinated). The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh these estimates of risk for vaccine-associated GBS. No evidence indicates that the case fatality ratio for GBS differs among vaccinated persons and those not vaccinated.

Use of TIV among Patients with a History of GBS

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history (*227*). Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown. However, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccination might be prudent as a precaution. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. Although data are limited, the established benefits of influenza vaccination might outweigh the risks for many persons who have a history of GBS and who are also at high risk for severe complications from influenza.

Vaccine Preservative (Thimerosal) in Multidose Vials of TIV

Thimerosal, a mercury-containing anti-bacterial compound, has been used as a preservative in vaccines since the 1930s (*242*) and is used in multidose vial preparations of TIV to reduce the likelihood of bacterial contamination. No scientific evidence indicates that thimerosal in vaccines, including influenza vaccines, is a cause of adverse events other than occasion local hypersensitivity reactions in vaccine recipients. In addition, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received vaccine during pregnancy. Evidence is accumulating that supports the absence of substantial risk for neurodevelopment disorders or other harm resulting from exposure to thimerosal-containing vaccines (*243–250*). However, continuing public concern about exposure to mercury in vaccines was viewed as a potential barrier to achieving higher vaccine coverage levels and reducing the burden of vaccine-preventable diseases. Therefore, the U.S. Public Health Service and other organizations recommended that efforts be made to eliminate or reduce the thimerosal content in vaccines as part of a strategy to reduce mercury exposures from all sources (*243,245,247*). Since mid-2001, vaccines routinely recommended for infants aged <6 months in the United States have been manufactured either without or with greatly reduced (trace) amounts of thimerosal. As a result, a substantial reduction in the total mercury exposure from vaccines for infants and children already has been achieved (*197*). ACIP and other federal agencies and professional medical organizations continue to support efforts to provide thimerosal preservative–free vaccine options.

The benefits of influenza vaccination for all recommended groups, including pregnant women and young children, outweigh concerns on the basis of a theoretical risk from thimerosal exposure through vaccination. The risks for severe illness from influenza virus infection are elevated among both young children and pregnant women, and vaccination has been demonstrated to reduce the risk for severe influenza illness and subsequent medical complications. In contrast, no scientifically conclusive evidence has demonstrated harm from exposure to vaccine containing thimerosal preservative. For these reasons, persons recommended to receive TIV may receive any age- and risk factor–appropriate vaccine preparation, depending on availability. An analysis of VAERS reports found

no difference in the safety profile of preservative-containing compared with preservative-free TIV vaccines in infants aged 6–23 months (*202*).

Nonetheless, certain states have enacted legislation banning the administration of vaccines containing mercury; the provisions defining mercury content vary (*251*). LAIV and many of the single dose vial or syringe preparations of TIV are thimerosal-free, and the number of influenza vaccine doses that do not contain thimerosal as a preservative is expected to increase (Table 2). However, these laws might present a barrier to vaccination unless influenza vaccines that do not contain thimerosal as a preservative are easily available in those states.

The U.S. vaccine supply for infants and pregnant women is in a period of transition during which the availability of thimerosal-reduced or thimerosal-free vaccine intended for these groups is being expanded by manufacturers as a feasible means of further reducing an infant's cumulative exposure to mercury. Other environmental sources of mercury exposure are more difficult or impossible to avoid or eliminate (*243*).

LAIV Dosage, Administration, and Storage

Each dose of LAIV contains the same three vaccine antigens used in TIV. However, the antigens are constituted as live, attenuated, cold-adapted, temperature-sensitive vaccine viruses. Additional components of LAIV include egg allantoic fluid, monosodium glutamate, sucrose, phosphate, and glutamate buffer; and hydrolyzed porcine gelatin. LAIV does not contain thimerosal. LAIV is made from attenuated viruses that are only able to replicate efficiently at temperatures present in the nasal mucosa. LAIV does not cause systemic symptoms of influenza in vaccine recipients, although a minority of recipients experience nasal congestion, which is probably a result of either effects of intranasal vaccine administration or local viral replication or fever (*252*).

LAIV is intended for intranasal administration only and should not be administered by the intramuscular, intradermal, or intravenous route. LAIV is not licensed for vaccination of children aged <2 years or adults aged >49 years. LAIV is supplied in a prefilled, single-use sprayer containing 0.2 mL of vaccine. Approximately 0.1 mL (i.e., half of the total sprayer contents) is sprayed into the first nostril while the recipient is in the upright position. An attached dose-divider clip is removed from the sprayer to administer the second half of the dose into the other nostril. LAIV is shipped to end users at 35°F–46°F (2°C–8°C). LAIV should be stored at 35°F–46°F (2°C–8°C) on receipt and can remain at that temperature until the expiration date is reached (*252*). Vaccine prepared for a previous influenza season should not be administered to provide protection for any subsequent season.

Shedding, Transmission, and Stability of Vaccine Viruses

Available data indicate that both children and adults vaccinated with LAIV can shed vaccine viruses after vaccination, although in lower amounts than occur typically with shedding of wild-type influenza viruses. In rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons. However, serious illnesses have not been reported among unvaccinated persons who have been infected inadvertently with vaccine viruses.

One study of children aged 8–36 months in a child care center assessed transmissibility of vaccine viruses from 98 vaccinated to 99 unvaccinated subjects; 80% of vaccine recipients shed one or more virus strains (mean duration: 7.6 days). One influenza type B vaccine strain isolate was recovered from a placebo recipient and was confirmed to be vaccine-type virus. The type B isolate retained the cold-adapted, temperature-sensitive, attenuated phenotype, and it possessed the same genetic sequence as a virus shed from a vaccine recipient who was in the same play group. The placebo recipient from whom the influenza type B vaccine strain was isolated had symptoms of a mild upper respiratory illness but did not experience any serious clinical events. The estimated probability of acquiring vaccine virus after close contact with a single LAIV recipient in this child care population was 0.6%–2.4% (*253*).

Studies assessing whether vaccine viruses are shed have been based on viral cultures or PCR detection of vaccine viruses in nasal aspirates from persons who have received LAIV. One study of 20 healthy vaccinated adults aged 18–49 years demonstrated that the majority of shedding occurred within the first 3 days after vaccination, although the vaccine virus was detected in one subject on day 7 after vaccine receipt. Duration or type of symptoms associated with receipt of LAIV did not correlate with detection of vaccine viruses in nasal aspirates (*254*). Another study in 14 healthy adults aged 18–49 years indicated that 50% of these adults had viral antigen detected by direct immunofluorescence or rapid antigen tests within 7 days of vaccination. The majority of samples with detectable virus were collected on day 2 or 3 (*255*). Vaccine strain virus was detected from nasal secretions in one (2%) of 57 HIV-infected adults who received LAIV, none of 54 HIV-negative participants (*256*), and three (13%) of 23 HIV-infected children compared with seven (28%) of 25 children who were not HIV-infected (*257*). No participants in these studies had detectable virus beyond 10 days after receipt of

LAIV. The possibility of person-to-person transmission of vaccine viruses was not assessed in these studies (*254–257*).

In clinical trials, viruses isolated from vaccine recipients have been phenotypically stable. In one study, nasal and throat swab specimens were collected from 17 study participants for 2 weeks after vaccine receipt (*258*). Virus isolates were analyzed by multiple genetic techniques. All isolates retained the LAIV genotype after replication in the human host, and all retained the cold-adapted and temperature-sensitive phenotypes. A study conducted in a child-care setting demonstrated that limited genetic change occurred in the LAIV strains following replication in the vaccine recipients (*259*).

Immunogenicity, Efficacy, and Effectiveness of LAIV

LAIV virus strains replicate primarily in nasopharyngeal epithelial cells. The protective mechanisms induced by vaccination with LAIV are not understood completely but appear to involve both serum and nasal secretory antibodies. The immunogenicity of the approved LAIV has been assessed in multiple studies conducted among children and adults (*106,260–266*). No single laboratory measurement closely correlates with protective immunity induced by LAIV (*261*).

Healthy Children

A randomized, double-blind, placebo-controlled trial among 1,602 healthy children aged 15–71 months assessed the efficacy of LAIV against culture-confirmed influenza during two seasons (*267,268*). This trial included a subset of children aged 60–71 months who received 2 doses in the first season. In season one (1996–97), when vaccine and circulating virus strains were well-matched, efficacy against culture-confirmed influenza was 94% for participants who received 2 doses of LAIV separated by ≥6 weeks, and 89% for those who received 1 dose. In season two, when the A (H3N2) component in the vaccine was not well-matched with circulating virus strains, efficacy (1 dose) was 86%, for an overall efficacy over two influenza seasons of 92%. Receipt of LAIV also resulted in 21% fewer febrile illnesses and a significant decrease in acute otitis media requiring antibiotics (*267,269*). Other randomized, placebo-controlled trials demonstrating the efficacy of LAIV in young children against culture-confirmed influenza include a study conducted among children aged 6–35 months attending child care centers during consecutive influenza seasons (*270*), in which 85%–89% efficacy was observed, and a study conducted among children aged 12–36 months living in Asia during consecutive influenza seasons, in which 64%-70% efficacy was documented (*271*). In one community-based, nonrandomized open-label study, reductions in MAARI were observed among children who received 1 dose of LAIV during the 1990–00 and 2000–01 influenza seasons even though antigenically drifted influenza A/H1N1 and B viruses were circulating during that season (*272*). LAIV efficacy in preventing laboratory confirmed influenza has also been demonstrated in studies comparing the efficacy of LAIV with TIV rather than with a placebo (see Comparisons of LAIV and TIV Efficacy or Effectiveness).

Healthy Adults

A randomized, double-blind, placebo-controlled trial of LAIV effectiveness among 4,561 healthy working adults aged 18–64 years assessed multiple endpoints, including reductions in self-reported respiratory tract illness without laboratory confirmation, work loss, health-care visits, and medication use during influenza outbreak periods (*273*). The study was conducted during the 1997–98 influenza season, when the vaccine and circulating A (H3N2) strains were not well-matched. The frequency of febrile illnesses was not significantly decreased among LAIV recipients compared with those who received placebo. However, vaccine recipients had significantly fewer severe febrile illnesses (19% reduction) and febrile upper respiratory tract illnesses (24% reduction), and significant reductions in days of illness, days of work lost, days with health-care–provider visits, and use of prescription antibiotics and over-the-counter medications (*273*). Efficacy against culture-confirmed influenza in a randomized, placebo-controlled study was 57%, although efficacy in this study was not demonstrated to be significantly greater than placebo (*155*).

Adverse Events after Receipt of LAIV

Healthy Children Aged 2–18 Years

In a subset of healthy children aged 60–71 months from one clinical trial (*233*), certain signs and symptoms were reported more often after the first dose among LAIV recipients (n = 214) than among placebo recipients (n = 95), including runny nose (48% and 44%, respectively); headache (18% and 12%, respectively); vomiting (5% and 3%, respectively); and myalgias (6% and 4%, respectively). However, these differences were not statistically significant. In other trials, signs and symptoms reported after LAIV administration have included runny nose or nasal congestion (20%–75%), headache (2%–46%), fever (0–26%), vomiting (3%–13%), abdominal pain (2%), and myalgias (0–21%) (*106,260,263, 265,270,273–276*). These symptoms were associated more often with the first dose and were self-limited.

In a randomized trial published in 2007, LAIV and TIV were compared among children aged 6–59 months (*277*). Children with medically diagnosed or treated wheezing within

42 days before enrollment, or a history of severe asthma, were excluded from this study. Among children aged 24–59 months who received LAIV, the rate of medically significant wheezing, using a pre-specified definition, was not greater compared with those who received TIV (*277*); wheezing was observed more frequently among younger LAIV recipients in this study (see Persons at Higher Risk from Influenza-Related Complications). In a previous randomized placebo-controlled safety trial among children aged 12 months–17 years without a history of asthma by parental report, an elevated risk for asthma events (RR = 4.06, CI = 1.29–17.86) was documented among 728 children aged 18–35 months who received LAIV. Of the 16 children with asthma-related events in this study, seven had a history of asthma on the basis of subsequent medical record review. None required hospitalization, and elevated risks for asthma were not observed in other age groups (*276*).

Another study was conducted among >11,000 children aged 18 months–18 years in which 18,780 doses of vaccine were administered for 4 years. For children aged 18 months–4 years, no increase was reported in asthma visits 0–15 days after vaccination compared with the prevaccination period. A significant increase in asthma events was reported 15–42 days after vaccination, but only in vaccine year 1 (*278*).

Initial data from VAERS during 2007–2008, following ACIP recommendation for LAIV use in children aged 2–4 years, do not suggest a concern for wheezing after LAIV in young children. However data also suggest uptake of LAIV is limited and continued safety monitoring for wheezing events after LAIV is indicated (CDC, unpublished data, 2008).

Adults Aged 19–49 Years

Among adults, runny nose or nasal congestion (28%–78%), headache (16%–44%), and sore throat (15%–27%) have been reported more often among vaccine recipients than placebo recipients (*252,279*). In one clinical trial among a subset of healthy adults aged 18–49 years, signs and symptoms reported more frequently among LAIV recipients (n = 2,548) than placebo recipients (n = 1,290) within 7 days after each dose included cough (14% and 11%, respectively); runny nose (45% and 27%, respectively); sore throat (28% and 17%, respectively); chills (9% and 6%, respectively); and tiredness/weakness (26% and 22%, respectively) (*279*).

Persons at Higher Risk for Influenza-Related Complications

Limited data assessing the safety of LAIV use for certain groups at higher risk for influenza-related complications are available. In one study of 54 HIV-infected persons aged 18–58 years and with CD4 counts ≥200 cells/mm3 who received LAIV, no serious adverse events were reported during a 1-month follow-up period (*256*). Similarly, one study demonstrated no significant difference in the frequency of adverse events or viral shedding among HIV-infected children aged 1–8 years on effective antiretroviral therapy who were administered LAIV, compared with HIV-uninfected children receiving LAIV (*257*). LAIV was well-tolerated among adults aged ≥65 years with chronic medical conditions (*280*). These findings suggest that persons at risk for influenza complications who have inadvertent exposure to LAIV would not have significant adverse events or prolonged viral shedding and that persons who have contact with persons at higher risk for influenza-related complications may receive LAIV.

Serious Adverse Events

Serious adverse events after administration of LAIV requiring medical attention among healthy children aged 5–17 years or healthy adults aged 18–49 years occurred at a rate of <1% (*252*). Surveillance will continue for adverse events, including those that might not have been detected in previous studies. Reviews of reports to VAERS after vaccination of approximately 2.5 million persons during the 2003–04 and 2004–05 influenza seasons did not indicate any new safety concerns (*281*). Health-care professionals should report all clinically significant adverse events occurring after LAIV administration promptly to VAERS after LAIV administration.

Comparisons of LAIV and TIV Efficacy or Effectiveness

Both TIV and LAIV have been demonstrated to be effective in children and adults, but data directly comparing the efficacy or effectiveness of these two types of influenza vaccines are limited. Studies comparing the efficacy of TIV to that of LAIV have been conducted in a variety of settings and populations using several different outcomes. One randomized, double-blind, placebo-controlled challenge study among 92 healthy adults aged 18–41 years assessed the efficacy of both LAIV and TIV in preventing influenza infection when challenged with wild-type strains that were antigenically similar to vaccine strains (*282*). The overall efficacy in preventing laboratory-documented influenza from all three influenza strains combined was 85% and 71%, respectively, when challenged 28 days after vaccination by viruses to which study participants were susceptible before vaccination. The difference in efficacy between the two vaccines was not statistically significant in this limited study. No additional challenges to assess efficacy at time points later than 28 days were conducted. In a randomized, double-blind, placebo-controlled trial, conducted among young adults during an influenza season when the majority of circulating H3N2 viruses were antigenically

drifted from that season's vaccine viruses, the efficacy of LAIV and TIV against culture-confirmed influenza was 57% and 77%, respectively. The difference in efficacy was not statistically significant and was based largely on a difference in efficacy against influenza B (*155*).

A randomized controlled clinical trial conducted among children aged 6–71 months during the 2004–05 influenza season demonstrated a 55% reduction in cases of culture-confirmed influenza among children who received LAIV compared with those who received TIV (*277*). In this study, LAIV efficacy was higher compared with TIV against antigenically drifted viruses as well as well-matched viruses (*277*). An open-label, nonrandomized, community-based influenza vaccine trial conducted during an influenza season when circulating H3N2 strains were poorly matched with strains contained in the vaccine also indicated that LAIV, but not TIV, was effective against antigenically drifted H3N2 strains during that influenza season. In this study, children aged 5–18 years who received LAIV had significant protection against laboratory-confirmed influenza (37%) and pneumonia and influenza events (50%) (*278*).

Although LAIV is not licensed for use in persons with risk factors for influenza complications, certain studies have compared the efficacy of LAIV to TIV in these groups. LAIV provided 32% increased protection in preventing culture-confirmed influenza compared with TIV in one study conducted among children aged ≥6 years and adolescents with asthma (*283*) and 52% increased protection compared with TIV among children aged 6–71 months with recurrent respiratory tract infections (*284*).

Effectiveness of Vaccination for Decreasing Transmission to Contacts

Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce ILI and complications among persons at high risk. Influenza virus infection and ILI are common among HCP (*285–287*). Influenza outbreaks have been attributed to low vaccination rates among HCP in hospitals and long-term–care facilities (*288–290*). One serosurvey demonstrated that 23% of HCP had serologic evidence of influenza virus infection during a single influenza season; the majority had mild illness or subclinical infection (*285*). Observational studies have demonstrated that vaccination of HCP is associated with decreased deaths among nursing home patients (*291,292*). In one cluster-randomized controlled trial that included 2,604 residents of 44 nursing homes, significant decreases in mortality, ILI, and medical visits for ILI care were demonstrated among residents in nursing homes in which staff were offered influenza vaccination (coverage rate: 48%), compared with nursing homes in which staff were not provided with vaccination (coverage rate: 6%) (*293*). A review concluded that vaccination of HCP in settings in which patients were also vaccinated provided significant reductions in deaths among elderly patients from all causes and deaths from pneumonia (*294*).

Epidemiologic studies of community outbreaks of influenza demonstrate that school-age children typically have the highest influenza illness attack rates, suggesting routine universal vaccination of children might reduce transmission to their household contacts and possibly others in the community. Results from certain studies have indicated that the benefits of vaccinating children might extend to protection of their adult contacts and to persons at risk for influenza complications in the community. However, these data are limited and studies have not used laboratory-confirmed influenza as an outcome measure. A single-blinded, randomized controlled study conducted during as part of a 1996–1997 vaccine effectiveness study demonstrated that vaccinating preschool-aged children with TIV reduced influenza-related morbidity among some household contacts (*295*). A randomized, placebo-controlled trial among children with recurrent respiratory tract infections demonstrated that members of families with children who had received LAIV were significantly less likely to have respiratory tract infections and reported significantly fewer workdays lost, compared with families with children who received placebo (*296*). In nonrandomized community-based studies, administration of LAIV has been demonstrated to reduce MAARI (*297,298*) and ILI-related economic and medical consequences (e.g., workdays lost and number of health-care provider visits) among contacts of vaccine recipients (*298*). Households with children attending schools in which school-based LAIV vaccination programs had been established reported less ILI and fewer physician visits during peak influenza season, compared with households with children in schools in which no LAIV vaccination had been offered. However a decrease in the overall rate of school absenteeism was not reported in communities in which LAIV vaccination was offered (*298*). These community-based studies have not used laboratory-confirmed influenza as an outcome.

Some studies have also documented reductions in influenza illness among persons living in communities where focused programs for vaccinating children have been conducted. A community-based observational study conducted during the 1968 pandemic using a univalent inactivated vaccine reported that a vaccination program targeting school-aged children (coverage rate: 86%) in one community reduced influenza rates within the community among all age groups compared with another community in which aggressive vaccination was not conducted among school-aged children (*299*). An observa-

tional study conducted in Russia demonstrated reductions in ILI among the community-dwelling elderly after implementation of a vaccination program using TIV for children aged 3–6 years (57% coverage achieved) and children and adolescents aged 7–17 years (72% coverage achieved) (*300*). In a nonrandomized community-based study conducted over three influenza seasons, 8%–18% reductions in the incidence of MAARI during the influenza season among adults aged ≥35 years were observed in communities in which LAIV was offered to all children aged ≥18 months (estimated coverage rate: 20%–25%) compared with communities with such vaccination programs (*297*). In a subsequent influenza season, the same investigators documented a 9% reduction in MAARI rates during the influenza season among persons aged 35–44 years in intervention communities, where coverage was estimated at 31% among school children, compared with control communities. However, MAARI rates among persons aged ≥45 years were lower in the intervention communities regardless of the presence of influenza in the community, suggesting that lower rates could not be attributed to vaccination of school children against influenza (*301*).

Effectiveness of Influenza Vaccination when Circulating Influenza Virus Strains Differ from Vaccine Strains

Manufacturing trivalent influenza virus vaccines is a challenging process that takes 6–8 months to complete. This manufacturing timeframe requires that influenza vaccine strains for influenza vaccines used in the United States must be selected in February of each year by the FDA to allow time for manufacturers to prepare vaccines for the next influenza season. Vaccine strain selections are based on global viral surveillance data that is used to identify trends in antigenic changes among circulating influenza viruses and the availability of suitable vaccine virus candidates.

Vaccination can provide reduced but substantial cross-protection against drifted strains in some seasons, including reductions in severe outcomes such as hospitalization. Usually one or more circulating viruses with antigenic changes compared with the vaccine strains are identified in each influenza season. However, assessment of the clinical effectiveness of influenza vaccines cannot be determined solely by laboratory evaluation of the degree of antigenic match between vaccine and circulating strains. In some influenza seasons, circulating influenza viruses with significant antigenic differences predominate and, compared with seasons when vaccine and circulating strains are well-matched, reductions in vaccine effectiveness are sometimes observed (*126,139,145, 147,191*). However, even during years when vaccine strains were not antigenically well matched to circulating strains, substantial protection has been observed against severe outcomes, presumably because of vaccine-induced cross-reacting antibodies (*139,145,147,273*). For example, in one study conducted during an influenza season (2003–04) when the predominant circulating strain was an influenza A (H3N2) virus that was antigenically different from that season's vaccine strain, effectiveness among persons aged 50–64 years against laboratory-confirmed influenza illness was 60% among healthy persons and 48% among persons with medical conditions that increase risk for influenza complications (*147*). An interim, within-season analysis during the 2007–08 influenza season indicated that vaccine effectiveness was 44% overall, 54% among healthy persons aged 5–49 years, and 58% against influenza A, despite the finding that viruses circulating in the study area were predominately a drifted influenza A H3N2 and a influenza B strain from a different lineage compared with vaccine strains (*302*). Among children, both TIV and LAIV provide protection against infection even in seasons when vaccines and circulating strains are not well matched. Vaccine effectiveness against ILI was 49%–69% in two observational studies, and 49% against medically attended, laboratory-confirmed influenza in a case-control study conducted among young children during the 2003–04 influenza season, when a drifted influenza A H3N2 strain predominated, based on viral surveillance data (*121,125*). However, continued improvements in collecting representative circulating viruses and use surveillance data to forecast antigenic drift are needed. Shortening manufacturing time to increase the time to identify good vaccine candidate strains from among the most recent circulating strains also is important. Data from multiple seasons and collected in a consistent manner are needed to better understand vaccine effectiveness during seasons when circulating and vaccine virus strains are not well-matched.

Cost-Effectiveness of Influenza Vaccination

Economic studies of influenza vaccination are difficult to compare because they have used different measures of both costs and benefits (e.g., cost-only, cost-effectiveness, cost-benefit, or cost-utility). However, most studies find that vaccination reduces or minimizes health care, societal, and individual costs, or the productivity losses and absenteeism associated with influenza illness. One national study estimated the annual economic burden of seasonal influenza in the United States (using 2003 population and dollars) to be $87.1 billion, including $10.4 billion in direct medical costs (*303*).

Studies of influenza vaccination in the United States among persons aged ≥65 years have documented substantial reduc-

tions in hospitalizations and deaths and overall societal cost savings (*186,187*). Studies comparing adults in different age groups also find that vaccination is economically beneficial. One study that compared the economic impact of vaccination among persons aged ≥65 years with those aged 15–64 years indicated that vaccination resulted in a net savings per quality-adjusted life year (QALY) and that the Medicare program saved costs of treating illness by paying for vaccination (*304*). A study of a larger population comparing persons aged 50–64 years with those aged ≥65 years estimated the cost-effectiveness of influenza vaccination to be $28,000 per QALY saved (in 2000 dollars) in persons aged 50–64 years compared with $980 per QALY saved among persons aged ≥65 years (*305*).

Economic analyses among adults aged <65 years have reported mixed results regarding influenza vaccination. Two studies in the United States found that vaccination can reduce both direct medical costs and indirect costs from work absenteeism and reduced productivity (*306,307*). However, another United States study indicated no productivity and absentee savings in a strategy to vaccinate healthy working adults, although vaccination was still estimated to be cost-effective (*139*).

Cost analyses have documented the considerable cost burden of illness among children. In a study of 727 children at a medical center during 2000–2004, the mean total cost of hospitalization for influenza-related illness was $13,159 ($39,792 for patients admitted to an intensive care unit and $7,030 for patients cared for exclusively on the wards) (*308*). Strategies that focus on vaccinating children with medical conditions that confer a higher risk for influenza complications are more cost-effective than a strategy of vaccinating all children (*309*). An analysis that compared the costs of vaccinating children of varying ages with TIV and LAIV indicated that costs per QALY saved increased with age for both vaccines. In 2003 dollars per QALY saved, costs for routine vaccination using TIV were $12,000 for healthy children aged 6–23 months and $119,000 for healthy adolescents aged 12–17 years, compared with $9,000 and $109,000 using LAIV, respectively (*310*). Economic evaluations of vaccinating children have demonstrated a wide range of cost estimates, but have generally found this strategy to be either cost-saving or cost-beneficial (*311–314*).

Economic analyses are sensitive to the vaccination venue, with vaccination in medical care settings incurring higher projected costs. In a published model, the mean cost (year 2004 values) of vaccination was lower in mass vaccination ($17.04) and pharmacy ($11.57) settings than in scheduled doctor's office visits ($28.67) (*315*). Vaccination in nonmedical settings was projected to be cost saving for healthy adults aged ≥50 years and for high-risk adults of all ages. For healthy adults aged 18–49 years, preventing an episode of influenza would cost $90 if vaccination were delivered in a pharmacy setting, $210 in a mass vaccination setting, and $870 during a scheduled doctor's office visit (*315*). Medicare payment rates in recent years have been less than the costs associated with providing vaccination in a medical practice (*316*).

Vaccination Coverage Levels

Continued annual monitoring is needed to determine the effects on vaccination coverage of vaccine supply delays and shortages, changes in influenza vaccination recommendations and target groups for vaccination, reimbursement rates for vaccine and vaccine administration, and other factors related to vaccination coverage among adults and children. One of the national health objectives for 2010 includes achieving an influenza vaccination coverage level of 90% for persons aged ≥65 years and among nursing home residents (*317,318*); new strategies to improve coverage are needed to achieve these objectives (*319,320*). Increasing vaccination coverage among persons who have high-risk conditions and are aged <65 years, including children at high risk, is the highest priority for expanding influenza vaccine use.

On the basis of the 2006 final data set and the 2007 early release data from the National Health Interview Survey (NHIS), estimated national influenza vaccine coverage during the 2005–06 and 2006–07 influenza seasons among persons aged ≥65 years and 50–64 years increased slightly from 32% and 65%, respectively to 36% and 66% (Table 3) and appear to be approaching coverage levels observed before the 2004–05 vaccine shortage year. In 2005–06 and 2006–07, estimated vaccination coverage levels among adults with high-risk conditions aged 18–49 years were 23% and 26%, respectively, substantially lower than the *Healthy People 2000* and *Healthy People 2010* objectives of 60% (Table 3) (*317,318*).

Opportunities to vaccinate persons at risk for influenza complications (e.g., during hospitalizations for other causes) often are missed. In a study of hospitalized Medicare patients, only 31.6% were vaccinated before admission, 1.9% during admission, and 10.6% after admission (*321*). A study in New York City during 2001–2005 among 7,063 children aged 6–23 months indicated that 2-dose vaccine coverage increased from 1.6% to 23.7%. Although the average number of medical visits during which an opportunity to be vaccinated decreased during the course of the study from 2.9 to 2.0 per child, 55% of all visits during the final year of the study still represented a missed vaccination opportunity (*322*). Using standing orders in hospitals increases vaccination rates among hospitalized persons (*323*). In one survey, the strongest pre-

TABLE 3. Influenza vaccination* coverage levels for the 2005–06 and 2006–07 influenza seasons, among population groups — National Health Interview Survey (NHIS), United States, 2006 and 2007, and National Immunization Survey (NIS), 2006

	2005–06 season			2006–07 season		
	Crude sample	Influenza vaccination level		Crude sample	Influenza vaccination level	
Population Group	size†	%	(95% CI§)	size	%	(95% CI)
Persons with an age indication						
Aged 6–23 mos (NIS¶)	13,546	32.2	(30.9–33.5)		NA	
Aged 2–4 yrs	611	26.4	(22.2–31.0)	853	37.9	(34.2–41.7)
Aged 50–64 yrs	2,843	31.6	(29.5–33.8)	3,746	36.0	(34.0–38.0)
Aged ≥65 yrs	2,328	64.5	(62.6–66.8)	3,086	65.6	(63.3–67.9)
Persons with high-risk conditions**						
Aged 5–17 yrs	376	22.1	(17.1–28.2)	387	33.0	(26.2–40.7)
Aged 18–49 yrs	937	23.4	(20.2–26.9)	1,186	25.5	(22.4–28.9)
Aged 50–64 yrs	878	44.3	(40.2–48.5)	1,117	46.1	(42.8–49.4)
Aged 18–64 yrs	1,815	33.4	(30.5–36.5)	2,303	35.3	(33.0–37.7)
Persons without high-risk conditions						
Aged 5–17 yrs	2,679	12.4	(10.9–14.1)	3,307	17.5	(15.9–19.2)
Aged 18–49 yrs	6,275	13.4	(12.4–14.6)	7,905	15.3	(14.2–16.4)
Aged 50–64 yrs	1,956	26.0	(23.7–28.4)	2,619	31.8	(29.5–34.1)
Pregnant women††	126	12.3	(7.2–20.4)	177	13.4	(8.5–20.5)
Health-care workers§§	833	41.8	(37.4–46.3)		NA¶¶	
Household contacts of persons at high risk, including children aged <5 years***						
Aged 5–17 yrs	840	16.3	(13.4–19.7)	449	26.0	(21.5–31.1)
Aged 18–49 yrs	1621	14.4	(12.5–16.5)	2,038	17.0	(15.0–19.4)

* Answered yes to this question, "During the past 12 months, have you had a flu shot (flu spray)," and answered the follow-up question "What was the month and year of your most recent shot (spray)," which were asked during a face-to-face interview conducted any day during March–August.

† The population sizes by sub groups can be found at http://www.cdc.gov/flu/professionals/vaccination/pdf/targetpopchart.pdf.

§ Confidence interval.

¶ NIS uses provider-verified vaccination status to improve the accuracy of the estimate. The NIS estimate for the 2006–07 season will be available summer or fall 2007. The NHIS coverage estimates based on parental report were 39.5% (95% CI: 32.8–46.7; n=295) for the 2005–06 season and 46.4% (95% CI: 39.7–53.2; n=368) for the 2006–07 season.

** Adults categorized as being at high risk for influenza-related complications self-reported one or more of the following: 1) ever being told by a physician they had diabetes, emphysema, coronary heart disease, angina, heart attack, or other heart condition; 2) having a diagnosis of cancer during the previous 12 months (excluding nonmelanoma skin cancer) or ever being told by a physician they have lymphoma, leukemia, or blood cancer during the previous 12 months (Post coding for a cancer diagnosis was not yet completed at the time of this publication so this diagnosis was not include in the 2006–07 season data.); 3) being told by a physician they have chronic bronchitis or weak or failing kidneys; or 4) reporting an asthma episode or attack during the preceding 12 months. For children aged <18 years, high risk conditions included ever having been told by a physician of having diabetes, cystic fibrosis, sickle cell anemia, congenital heart disease, other heart disease, or neuromuscular conditions (seizures, cerebral palsy, and muscular dystrophy), or having an asthma episode or attack during the preceding 12 months.

†† Aged 18–44 years, pregnant at the time of the survey and without high-risk conditions.

§§ Adults were classified as health-care workers if they were currently employed in a health-care occupation or in a health-care–industry setting, on the basis of standard occupation and industry categories recoded in groups by CDC's National Center for Health Statistics.

¶¶ Data not yet available.

*** Interviewed sample child or adult in each household containing at least one of the following: a child aged <5 years, an adult aged ≥65 years, or any person aged 5–17 years at high risk (see previous footnote**). To obtain information on household composition and high-risk status of household members, the sampled adult, child, and person files from NHIS were merged. Interviewed adults who were health-care workers or who had high-risk conditions were excluded. Information could not be assessed regarding high-risk status of other adults aged 18–64 years in the household, thus, certain adults 18–64 years who live with an adult aged 18–64 years at high risk were not included in the analysis. Also note that although the recommendation for vaccination of children aged 2–4 years was not in place during the 2005–06 season. Children aged 2–4 years in these calculations were considered to have an indication for vaccination to facilitate comparison of coverage date for subsequent years.

dictor of receiving vaccination was the survey respondent's belief that he or she was in a high-risk group. However, many persons in high-risk groups did not know that they were in a group recommended for vaccination (*324*).

Reducing racial and ethnic health disparities, including disparities in influenza vaccination coverage, is an overarching national goal that is not being met (*317*). Estimated vaccination coverage levels in 2007 among persons aged ≥65 years were 70% for non-Hispanic whites, 58% for non-Hispanic blacks, and 54% for Hispanics (*325*). Among Medicare beneficiaries, other key factors that contribute to disparities in coverage include variations in the propensity of patients to actively seek vaccination and variations in the likelihood that providers recommend vaccination (*326,327*). One study estimated that eliminating these disparities in vaccination coverage would have an impact on mortality similar to the impact of eliminating deaths attributable to kidney disease among blacks or liver disease among Hispanics (*328*).

Reported vaccination levels are low among children at increased risk for influenza complications. Coverage among children aged 2–17 years with asthma for the 2004–05 influenza season was estimated to be 29% (*329*). One study reported 79% vaccination coverage among children attending a cystic fibrosis treatment center (*330*). During the first season for which ACIP recommended that all children aged 6 months–23 months receive vaccination, 33% received one or more dose of influenza vaccination, and 18% received 2 doses if they were unvaccinated previously (*331*). Among children enrolled in HMOs who had received a first dose during 2001–2004, second dose coverage varied from 29% to 44% among children aged 6–23 months and from 12% to 24% among children aged 2–8 years (*332*). A rapid analysis of influenza vaccination coverage levels among members of an HMO in Northern California demonstrated that during 2004–2005, the first year of the recommendation for vaccination of children aged 6–23 months, 1-dose coverage was 57% (*333*). During the 2005–06 influenza season, the second season for which ACIP recommended that all children aged 6 months–23 months receive vaccination, coverage remained low and did not increase substantially from the 2004–05 season. Data collected in 2006 by the National Immunization Survey indicated that for the 2005–06 season, 32% of children aged 6–23 months received at least 1 dose of influenza vaccine and 21% were fully vaccinated (i.e., received 1 or 2 doses depending on previous vaccination history); however, results varied substantially among states (*334*). As has been reported for older adults, a physician recommendation for vaccination and the perception that having a child be vaccinated "is a smart idea" were associated positively with likelihood of vaccination of children aged 6–23 months (*335*). Similarly, children with asthma were more likely to be vaccinated if their parents recalled a physician recommendation to be vaccinated or believed that the vaccine worked well (*336*). Implementation of a reminder/recall system in a pediatric clinic increased the percentage of children with asthma or reactive airways disease receiving vaccination from 5% to 32% (*337*).

Although annual vaccination is recommended for HCP and is a high priority for reducing morbidity associated with influenza in health-care settings and for expanding influenza vaccine use (*338–340*), national survey data demonstrated a vaccination coverage level of only 42% among HCP during the 2005–06 season (Table 3). Vaccination of HCP has been associated with reduced work absenteeism (*286*) and with fewer deaths among nursing home patients (*292,293*) and elderly hospitalized patients (*294*). Factors associated with a higher rate of influenza vaccination among HCP include older age, being a hospital employee, having employer provided health-care insurance, having had pneumococcal or hepatitis B vaccination in the past, or having visited a health-care professional during the preceding year. Non-Hispanic black HCP were less likely than non-Hispanic white HCP to be vaccinated (*341*). Beliefs that are frequently cited by HCP who decline vaccination include doubts about the risk for influenza and the need for vaccination, concerns about vaccine effectiveness and side effects, and dislike of injections (*342*).

Vaccine coverage among pregnant women has not increased significantly during the preceding decade. (*343*). Only 12% and 13% of pregnant women participating in the 2006 and 2007 NHIS reported vaccination during the 2005–06 and 2006–07 seasons, respectively, excluding pregnant women who reported diabetes, heart disease, lung disease, and other selected high-risk conditions (Table 3). In a study of influenza vaccine acceptance by pregnant women, 71% of those who were offered the vaccine chose to be vaccinated (*344*). However, a 1999 survey of obstetricians and gynecologists determined that only 39% administered influenza vaccine to obstetric patients in their practices, although 86% agreed that pregnant women's risk for influenza-related morbidity and mortality increases during the last two trimesters (*345*).

Influenza vaccination coverage in all groups recommended for vaccination remains suboptimal. Despite the timing of the peak of influenza disease, administration of vaccine decreases substantially after November. According to results from the NHIS regarding the two most recent influenza seasons for which these data are available, approximately 84% of all influenza vaccination were administered during September–November. Among persons aged ≥65 years, the percentage of September–November vaccinations was 92% (*346*). Because many persons recommended for vaccination remain unvaccinated at the end of November, CDC encourages public health partners and health-care providers to conduct vaccination clinics and other activities that promote influenza vaccination annually during National Influenza Vaccination Week and throughout the remainder of the influenza season.

Self-report of influenza vaccination among adults, compared with determining vaccination status from the medical record, is a sensitive and specific source of information (*347*). Patient self-reports should be accepted as evidence of influenza vaccination in clinical practice (*347*). However, information on the validity of parents' reports of pediatric influenza vaccination is not yet available.

Recommendations for Using TIV and LAIV During the 2008–09 Influenza Season

Both TIV and LAIV prepared for the 2008–09 season will include A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens. These viruses will be used because they are representative of influenza viruses that are forecasted to be circulating in the United States during the 2008–09 influenza season and have favorable growth properties in eggs.

TIV and LAIV can be used to reduce the risk for influenza virus infection and its complications. Vaccination providers should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected.

Healthy, nonpregnant persons aged 2–49 years can choose to receive either vaccine. Some TIV formulations are FDA-licensed for use in persons as young as age 6 months (see Recommended Vaccines for Different Age Groups). TIV is licensed for use in persons with high-risk conditions. LAIV is FDA-licensed for use only for persons aged 2–49 years. In addition, FDA has indicated that the safety of LAIV has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications. All children aged 6 months–8 years who have not been vaccinated previously at any time with at least 1 dose of either LAIV or TIV should receive 2 doses of age-appropriate vaccine in the same season, with a single dose during subsequent seasons.

Target Groups for Vaccination

Influenza vaccine should be provided to all persons who want to reduce the risk of becoming ill with influenza or of transmitting it to others. However, emphasis on providing routine vaccination annually to certain groups at higher risk for influenza infection or complications is advised, including all children aged 6 months–18 years, all persons aged ≥50 years, and other adults at risk for medical complications from influenza or more likely to require medical care should receive influenza vaccine annually. In addition, all persons who live with or care for persons at high risk for influenza-related complications, including contacts of children aged <6 months, should receive influenza vaccine annually (Boxes 1 and 2). Approximately 83% of the United States population is included in one or more of these target groups; however, <40% of the U.S. population received an influenza vaccination during 2007–2008.

Children Aged 6 Months–18 Years

Beginning with the 2008–09 influenza season, annual vaccination for all children aged 6 months–18 years is recommended. Annual vaccination of all children aged 6 months–4 years (59 months) and older children with conditions that place them at increased risk for complications from influenza should continue. Children and adolescents at high risk for influenza complications should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all children. Annual vaccination of all children aged 5–18 years should begin in September 2008 or as soon as vaccine is available for the 2008–09 influenza season, if feasible. Annual vaccination of all children aged 5–18 years should begin no later than during the 2009–10 influenza season.

Healthy children aged 2–18 years can receive either LAIV or TIV. Children aged 6–23 months, those aged 2–4 years who have evidence of possible reactive airways disease (see Considerations When Using LAIV) or who have medical conditions that put them at higher risk for influenza complications should receive TIV. All children aged 6 months–8 years who have not received vaccination against influenza previously should receive 2 doses of vaccine the first year they are vaccinated.

Persons at Risk for Medical Complications

Vaccination to prevent influenza is particularly important for the following persons who are at increased risk for severe complications from influenza, or at higher risk for influenza-associated clinic, emergency department, or hospital visits. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to these persons:

- all children aged 6 months–4 years (59 months);
- all persons aged ≥50 years;
- children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- women who will be pregnant during the influenza season;
- adults and children who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus);
- adults and children who have immunosuppression (including immunosuppression caused by medications or by HIV);
- adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise

respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration; and
- residents of nursing homes and other chronic-care facilities.

Persons Who Live With or Care for Persons at High Risk for Influenza-Related Complications

To prevent transmission to persons identified above, vaccination with TIV or LAIV (unless contraindicated) also is recommended for the following persons. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to these persons:
- HCP;
- healthy household contacts (including children) and caregivers of children aged ≤59 months (i.e., aged <5 years) and adults aged ≥50 years; and
- healthy household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

Additional Information About Vaccination of Specific Populations

Children Aged 6 Months–18 Years

Beginning with the 2008–09 influenza season, all children aged 6 months–18 years should be vaccinated against influenza annually. The expansion of vaccination to include all children aged 5–18 years should begin in 2008 if feasible, but no later than the 2009–10 influenza season. In 2004, ACIP recommended routine vaccination for all children aged 6–23 months, and in 2006, ACIP expanded the recommendation to include all children aged 24–59 months. The committee's recommendation to expand routine influenza vaccination to include all school-age children and adolescents aged 5–18 years is based on 1) accumulated evidence that influenza vaccine is effective and safe for school-aged children (see "Influenza Vaccine Efficacy, Effectiveness, and Safety"), 2) increased evidence that influenza has substantial adverse impacts among school-aged children and their contacts (e.g., school absenteeism, increased antibiotic use, medical care visits, and parental work loss) (see "Health-Care Use, Hospitalizations, and Deaths Attributed to Influenza"), and, 3) an expectation that a simplified age-based influenza vaccine recommendation for all school-age children and adolescents will improve vaccine coverage levels among the approximately 50% of school-aged children who already had a risk- or contact-based indication for annual influenza vaccination.

Children typically have the highest attack rates during community outbreaks of influenza and serve as a major source of transmission within communities (*1,2*). If sufficient vaccination coverage among children can be achieved, evidence for additional benefits, such as the indirect effect of reducing influenza among persons who have close contact with children and reducing overall transmission within communities, might occur. Achieving and sustaining community-level reductions in influenza will require mobilization of community resources and development of sustainable annual vaccination campaigns to assist health-care providers and vaccination programs in providing influenza vaccination services to children of all ages. In many areas, innovative community-based efforts, which might include mass vaccination programs in school or other community settings, will be needed to supplement vaccination services provided in health-care providers' offices or public health clinics. In nonrandomized community-based controlled trials, reductions in ILI-related symptoms and medical visits among household contacts have been demonstrated in communities where vaccination programs among school-aged children were established, compared with communities without such vaccination programs (*299–301*). Rates of school absences associated with ILI also were significantly reduced in some studies. In addition, reducing influenza transmission among children through vaccination has reduced rates for self-reported ILI among household contacts and among unvaccinated children (*297,298*).

Reducing influenza-related illness among children who are at high risk for influenza complications should continue to be a primary focus of influenza-prevention efforts. Children who should be vaccinated because they are at high risk for influenza complications include all children aged 6–59 months, children with certain medical conditions, children who are contacts of children aged <5 years (60 months) or persons aged ≥50 years, and children who are contacts of persons at high risk for influenza complications because of medical conditions. Influenza vaccines are not licensed by FDA for use among children aged <6 months. Because these infants are at higher risk for influenza complications compared with other child age groups, prevention efforts that focus on vaccinating household contacts and out-of-home caregivers to reduce the risk for influenza in these infants is a high priority.

All children aged 6 months–8 years who have not received vaccination against influenza previously should receive 2 doses of vaccine the first influenza season that they are vaccinated. The second dose should be administered 4 or more weeks after the initial dose. For example, children aged 6 months–8 years who were vaccinated for the first time during the 2007–08 influenza season but only received 1 dose during that season should receive 2 doses of the 2008–09 influenza vaccine. All other children aged 6 months–8 years who have previously received 1 or more doses of influenza vaccine at

any time should receive 1 dose of the 2008–09 influenza vaccine. Children aged 6 months–8 years who only received a single vaccination during a season before 2007–08 should receive 1 dose of the 2008–09 influenza vaccine. If possible, both doses should be administered before onset of influenza season. However, vaccination, including the second dose, is recommended even after influenza virus begins to circulate in a community.

HCP and Other Persons Who Can Transmit Influenza to Those at High Risk

Healthy persons who are infected with influenza virus, including those with subclinical infection, can transmit influenza virus to persons at higher risk for complications from influenza. In addition to HCP, groups that can transmit influenza to high-risk persons and that should be vaccinated include

- employees of assisted living and other residences for persons in groups at high risk;
- persons who provide home care to persons in groups at high risk; and
- household contacts (including children) of persons in groups at high risk.

In addition, because children aged <5 years are at increased risk for influenza-related hospitalization (*7,37,58,63,348*) compared with older children, vaccination is recommended for their household contacts and out-of-home caregivers. Because influenza vaccines have not been licensed by FDA for use among children aged <6 months, emphasis should be placed on vaccinating contacts of children aged <6 months. When vaccine supply is limited, priority for vaccination should be given to contacts of children aged <6 months.

Healthy HCP and persons aged 2–49 years who are contacts of persons in these groups and who are not contacts of severely immunosuppressed persons (see Close Contacts of Immunocompromised Persons) should receive either LAIV or TIV when indicated or requested. All other persons, including pregnant women, should receive TIV.

All HCP, as well as those in training for health-care professions, should be vaccinated annually against influenza. Persons working in health-care settings who should be vaccinated include physicians, nurses, and other workers in both hospital and outpatient-care settings, medical emergency-response workers (e.g., paramedics and emergency medical technicians), employees of nursing home and chronic-care facilities who have contact with patients or residents, and students in these professions who will have contact with patients (*339,340,349*).

Facilities that employ HCP should provide vaccine to workers by using approaches that have been demonstrated to be effective in increasing vaccination coverage. Health-care administrators should consider the level of vaccination coverage among HCP to be one measure of a patient safety quality program and consider obtaining signed declinations from personnel who decline influenza vaccination for reasons other than medical contraindications (*340*). Influenza vaccination rates among HCP within facilities should be regularly measured and reported, and ward-, unit-, and specialty-specific coverage rates should be provided to staff and administration (*340*). Studies have demonstrated that organized campaigns can attain higher rates of vaccination among HCP with moderate effort and by using strategies that increase vaccine acceptance (*338,340,350*).

Efforts to increase vaccination coverage among HCP are supported by various national accrediting and professional organizations and in certain states by statute. The Joint Commission on Accreditation of Health-Care Organizations has approved an infection-control standard that requires accredited organizations to offer influenza vaccinations to staff, including volunteers and licensed independent practitioners with close patient contact. The standard became an accreditation requirement beginning January 1, 2007 (*351*). In addition, the Infectious Diseases Society of America recommended mandatory vaccination for HCP, with a provision for declination of vaccination based on religious or medical reasons (*352*). Fifteen states have regulations regarding vaccination of HCP in long-term–care facilities (*353*), six states require that health-care facilities offer influenza vaccination to HCP, and four states require that HCP either receive influenza vaccination or indicate a religious, medical, or philosophical reason for not being vaccinated (*354,355*).

Close Contacts of Immunocompromised Persons

Immunocompromised persons are at risk for influenza complications but might have insufficient responses to vaccination. Close contacts of immunocompromised persons, including HCP, should be vaccinated to reduce the risk for influenza transmission. TIV is preferred for vaccinating household members, HCP, and others who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during those periods in which the immunosuppressed person requires care in a protective environment (typically defined as a specialized patient-care area with a positive airflow relative to the corridor, high-efficiency particulate air filtration, and frequent air changes) (*340,356*).

LAIV transmission from a recently vaccinated person causing clinically important illness in an immunocompromised contact has not been reported. The rationale for avoiding use of LAIV among HCP or other close contacts of severely immunocompromised patients is the theoretical risk that a live, attenuated vaccine virus could be transmitted to the severely immunosuppressed person. As a precautionary measure, HCP who receive LAIV should avoid providing care for severely immunosuppressed patients for 7 days after vaccination. Hospital visitors who have received LAIV should avoid contact with severely immunosuppressed persons in protected environments for 7 days after vaccination but should not be restricted from visiting less severely immunosuppressed patients.

No preference is indicated for TIV use by persons who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with diabetes, persons with asthma who take corticosteroids, persons who have recently received chemotherapy or radiation but who are not being cared for in a protective environment as defined above, or persons infected with HIV) or for TIV use by HCP or other healthy nonpregnant persons aged 2–49 years in close contact with persons in all other groups at high risk.

Pregnant Women

Pregnant women are at risk for influenza complications, and all women who are pregnant or will be pregnant during influenza season should be vaccinated. The American College of Obstetricians and Gynecologists and the American Academy of Family Physicians also have recommended routine vaccination of all pregnant women (*357*). No preference is indicated for use of TIV that does not contain thimerosal as a preservative (see Vaccine Preservative [Thimerosal] in Multidose Vials of TIV) for any group recommended for vaccination, including pregnant women. LAIV is not licensed for use in pregnant women. However, pregnant women do not need to avoid contact with persons recently vaccinated with LAIV.

Breastfeeding Mothers

Vaccination is recommended for all persons, including breastfeeding women, who are contacts of infants or children aged ≤59 months (i.e., <5 years), because infants and young children are at high risk for influenza complications and are more likely to require medical care or hospitalization if infected. Breastfeeding does not affect the immune response adversely and is not a contraindication for vaccination (*197*). Women who are breastfeeding can receive either TIV or LAIV unless contraindicated because of other medical conditions.

Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the temperate regions of the Southern Hemisphere, influenza activity occurs typically during April–September. In temperate climate zones of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large tourist groups (e.g., on cruise ships) that include persons from areas of the world in which influenza viruses are circulating (*358,359*). In the tropics, influenza occurs throughout the year. In a study among Swiss travelers to tropical and subtropical countries, influenza was the most frequently acquired vaccine-preventable disease (*360*).

Any traveler who wants to reduce the risk for influenza infection should consider influenza vaccination, preferably at least 2 weeks before departure. In particular, persons at high risk for complications of influenza and who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to

- travel to the tropics,
- travel with organized tourist groups at any time of year, or
- travel to the Southern Hemisphere during April–September.

No information is available about the benefits of revaccinating persons before summer travel who already were vaccinated during the preceding fall. Persons at high risk who receive the previous season's vaccine before travel should be revaccinated with the current vaccine the following fall or winter. Persons at higher risk for influenza complications should consult with their health-care practitioner to discuss the risk for influenza or other travel-related diseases before embarking on travel during the summer.

General Population

Vaccination is recommended for any person who wishes to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected. Healthy, nonpregnant persons aged 2–49 years might choose to receive either TIV or LAIV. All other persons aged ≥6 months should receive TIV. Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories or correctional facilities) should be encouraged to receive vaccine to minimize morbidity and the disruption of routine activities during epidemics (*361,362*).

Recommended Vaccines for Different Age Groups

When vaccinating children aged 6–35 months with TIV, health-care providers should use TIV that has been licensed by the FDA for this age group (i.e., TIV manufactured by Sanofi Pasteur ([FluZone]). TIV from Novartis (Fluvirin) is FDA-approved in the United States for use among persons aged ≥4 years. TIV from GlaxoSmithKline (Fluarix and FluLaval) or CSL Biotherapies (Afluria) is labeled for use in persons aged ≥18 years because data to demonstrate efficacy among younger persons have not been provided to FDA. LAIV from MedImmune (FluMist) is licensed for use by healthy nonpregnant persons aged 2–49 years (Table 1). A vaccine dose does not need to be repeated if inadvertently administered to a person who does not have an age indication for the vaccine formulation given. Expanded age and risk group indications for licensed vaccines are likely over the next several years, and vaccination providers should be alert to these changes. In addition, several new vaccine formulations are being evaluated in immunogenicity and efficacy trials; when licensed, these new products will increase the influenza vaccine supply and provide additional vaccine choices for practitioners and their patients.

Influenza Vaccines and Use of Influenza Antiviral Medications

Administration of TIV and influenza antivirals during the same medical visit is acceptable. The effect on safety and effectiveness of LAIV coadministration with influenza antiviral medications has not been studied. However, because influenza antivirals reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after receipt of LAIV. Persons receiving antivirals within the period 2 days before to 14 days after vaccination with LAIV should be revaccinated at a later date (*197,252*).

Persons Who Should Not Be Vaccinated with TIV

TIV should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine. Prophylactic use of antiviral agents is an option for preventing influenza among such persons. Information about vaccine components is located in package inserts from each manufacturer. Persons with moderate to severe acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate use of influenza vaccine. GBS within 6 weeks following a previous dose of TIV is considered to be a precaution for use of TIV.

Considerations When Using LAIV

LAIV is an option for vaccination of healthy, nonpregnant persons aged 2–49 years, including HCP and other close contacts of high-risk persons (excepting severely immunocompromised persons who require care in a protected environment). No preference is indicated for LAIV or TIV when considering vaccination of healthy, nonpregnant persons aged 2–49 years. Use of the term "healthy" in this recommendation refers to persons who do not have any of the underlying medical conditions that confer high risk for severe complications (see Persons Who Should Not Be Vaccinated with LAIV). However, during periods when inactivated vaccine is in short supply, use of LAIV is encouraged when feasible for eligible persons (including HCP) because use of LAIV by these persons might increase availability of TIV for persons in groups targeted for vaccination, but who cannot receive LAIV. Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response in children, its ease of administration, and the possibly increased acceptability of an intranasal rather than intramuscular route of administration.

If the vaccine recipient sneezes after administration, the dose should not be repeated. However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness, or TIV should be administered instead. No data exist about concomitant use of nasal corticosteroids or other intranasal medications (*252*).

Although FDA licensure of LAIV excludes children aged 2–4 years with a history of asthma or recurrent wheezing, the precise risk, if any, of wheezing caused by LAIV among these children is unknown because experience with LAIV among these young children is limited. Young children might not have a history of recurrent wheezing if their exposure to respiratory viruses has been limited because of their age. Certain children might have a history of wheezing with respiratory illnesses but have not had asthma diagnosed. The following screening recommendations should be used to assist persons who administer influenza vaccines in providing the appropriate vaccine for children aged 2–4 years.

Clinicians and vaccination programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2–4 years, and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health-care providers should consult the medical record, when

available, to identify children aged 2–4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2–4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months should not receive LAIV. TIV is available for use in children with asthma or possible reactive airways diseases (*363*).

LAIV can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infection with or without fever). However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness.

Persons Who Should Not Be Vaccinated with LAIV

The effectiveness or safety of LAIV is not known for the following groups, and these persons should not be vaccinated with LAIV:

- persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs.
- persons aged <2 years or those aged ≥50 years;
- persons with any of the underlying medical conditions that serve as an indication for routine influenza vaccination, including asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; other underlying medical conditions, including such metabolic diseases as diabetes, renal dysfunction, and hemoglobinopathies; or known or suspected immunodeficiency diseases or immunosuppressed states;
- children aged 2–4 years whose parents or caregivers report that a health-care provider has told them during the preceding 12 months that their child had wheezing or asthma, or whose medical record indicates a wheezing episode has occurred during the preceding 12 months;
- children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza virus infection);
- persons with a history of GBS after influenza vaccination; or
- pregnant women.

Personnel Who Can Administer LAIV

Low-level introduction of vaccine viruses into the environment probably is unavoidable when administering LAIV. The risk for acquiring vaccine viruses from the environment is unknown but is probably low. Severely immunosuppressed persons should not administer LAIV. However, other persons at higher risk for influenza complications can administer LAIV. These include persons with underlying medical conditions placing them at higher risk or who are likely to be at risk, including pregnant women, persons with asthma, and persons aged ≥50 years.

Concurrent Administration of Influenza Vaccine with Other Vaccines

Use of LAIV concurrently with measles, mumps, rubella (MMR) alone and MMR and varicella vaccine among children aged 12–15 months has been studied, and no interference with the immunogenicity to antigens in any of the vaccines was observed (*252,364*). Among adults aged ≥50 years, the safety and immunogenicity of zoster vaccine and TIV was similar whether administered simultaneously or spaced 4 weeks apart (*365*). In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent (*197*). Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. Inactivated or live vaccines can be administered simultaneously with LAIV. However, after administration of a live vaccine, at least 4 weeks should pass before another live vaccine is administered.

Recommendations for Vaccination Administration and Vaccination Programs

Although influenza vaccination levels increased substantially during the 1990s, little progress has been made toward achieving national health objectives, and further improvements in vaccine coverage levels are needed. Strategies to improve vaccination levels, including using reminder/recall systems and standing orders programs (*325,366,367*), should be implemented whenever feasible. Vaccination coverage can be increased by administering vaccine before and during the influenza season to persons during hospitalizations or routine health-care visits. Vaccinations can be provided in alternative settings (e.g., pharmacies, grocery stores, workplaces, or other locations in the community), thereby making special visits to physicians' offices or clinics unnecessary. Coordinated campaigns such as the National Influenza Vaccination Week

(December 8–14, 2008) provide opportunities to refocus public attention on the benefits, safety, and availability of influenza vaccination throughout the influenza season. When educating patients about potential adverse events, clinicians should emphasize that 1) TIV contains noninfectious killed viruses and cannot cause influenza, 2) LAIV contains weakened influenza viruses that cannot replicate outside the upper respiratory tract and are unlikely to infect others, and 3) concomitant symptoms or respiratory disease unrelated to vaccination with either TIV or LAIV can occur after vaccination.

Information About the Vaccines for Children Program

The Vaccines for Children (VFC) program supplies vaccine to all states, territories, and the District of Columbia for use by participating providers. These vaccines are to be provided to eligible children without vaccine cost to the patient or the provider, although the provider might charge a vaccine administration fee. All routine childhood vaccines recommended by ACIP are available through this program, including influenza vaccines. The program saves parents and providers out-of-pocket expenses for vaccine purchases and provides cost savings to states through CDC's vaccine contracts. The program results in lower vaccine prices and ensures that all states pay the same contract prices. Detailed information about the VFC program is available at http://www.cdc.gov/vaccines/programs/vfc/default.htm.

Influenza Vaccine Supply Considerations

The annual supply of influenza vaccine and the timing of its distribution cannot be guaranteed in any year. During the 2007–08 influenza season, 113 million doses of influenza vaccine were distributed in the United States. Total production of influenza vaccine for the United States is anticipated to be >130 million doses for the 2008–09 season, depending on demand and production yields. However, influenza vaccine distribution delays or vaccine shortages remain possible in part because of the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains and various other manufacturing and regulatory issues. To ensure optimal use of available doses of influenza vaccine, health-care providers, those planning organized campaigns, and state and local public health agencies should develop plans for expanding outreach and infrastructure to vaccinate more persons in targeted groups and others who wish to reduce their risk for influenza and develop contingency plans for the timing and prioritization of administering influenza vaccine if the supply of vaccine is delayed or reduced.

If supplies of TIV are not adequate, vaccination should be carried out in accordance with local circumstances of supply and demand based on the judgment of state and local health officials and health-care providers. Guidance for tiered use of TIV during prolonged distribution delays or supply shortfalls is available at http://www.cdc.gov/flu/professionals/vaccination/vax_priority.htm and will be modified as needed in the event of shortage. CDC and other public health agencies will assess the vaccine supply on a continuing basis throughout the manufacturing period and will inform both providers and the general public if any indication exists of a substantial delay or an inadequate supply.

Because LAIV is only recommended for use in healthy nonpregnant persons aged 2–49 years, no recommendations for prioritization of LAIV use are made. Either LAIV or TIV when considering vaccination of healthy, nonpregnant persons aged 2–49 years. However, during shortages of TIV, LAIV should be used preferentially when feasible for all healthy nonpregnant persons aged 2–49 years (including HCP) who desire or are recommended for vaccination to increase the availability of inactivated vaccine for persons at high risk.

Timing of Vaccination

Vaccination efforts should be structured to ensure the vaccination of as many persons as possible over the course of several months, with emphasis on vaccinating before influenza activity in the community begins. Even if vaccine distribution begins before October, distribution probably will not be completed until December or January. The following recommendations reflect this phased distribution of vaccine.

In any given year, the optimal time to vaccinate patients cannot be precisely determined because influenza seasons vary in their timing and duration, and more than one outbreak might occur in a single community in a single year. In the United States, localized outbreaks that indicate the start of seasonal influenza activity can occur as early as October. However, in >80% of influenza seasons since 1976, peak influenza activity (which is often close to the midpoint of influenza activity for the season) has not occurred until January or later, and in >60% of seasons, the peak was in February or later (Figure 1). In general, health-care providers should begin offering vaccination soon after vaccine becomes available and if possible by October. To avoid missed opportunities for vaccination, providers should offer vaccination during routine health-care visits or during hospitalizations whenever vaccine is available.

Vaccination efforts should continue throughout the season, because the duration of the influenza season varies, and influenza might not appear in certain communities until February

or March. Providers should offer influenza vaccine routinely, and organized vaccination campaigns should continue throughout the influenza season, including after influenza activity has begun in the community. Vaccine administered in December or later, even if influenza activity has already begun, is likely to be beneficial in the majority of influenza seasons. The majority of adults have antibody protection against influenza virus infection within 2 weeks after vaccination (*368,369*).

All children aged 6 months–8 years who have not received vaccination against influenza previously should receive their first dose as soon after vaccine becomes available as is feasible. This practice increases the opportunity for both doses to be administered before or shortly after the onset of influenza activity.

Persons and institutions planning substantial organized vaccination campaigns (e.g., health departments, occupational health clinics, and community vaccinators) should consider scheduling these events after at least mid-October because the availability of vaccine in any location cannot be ensured consistently in early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable. These vaccination clinics should be scheduled through December, and later if feasible, with attention to settings that serve children aged 6–59 months, pregnant women, other persons aged <50 years at increased risk for influenza-related complications, persons aged ≥50 years, HCP, and persons who are household contacts of children aged ≤59 months or other persons at high risk. Planners are encouraged to develop the capacity and flexibility to schedule at least one vaccination clinic in December. Guidelines for planning large-scale vaccination clinics are available at http://www.cdc.gov/flu/professionals/vaccination/vax_clinic.htm.

During a vaccine shortage or delay, substantial proportions of TIV doses may not be released and distributed until November and December or later. When the vaccine is substantially delayed or disease activity has not subsided, providers should consider offering vaccination clinics into January and beyond as long as vaccine supplies are available. Campaigns using LAIV also can extend into January and beyond.

Strategies for Implementing Vaccination Recommendations in Health-Care Settings

Successful vaccination programs combine publicity and education for HCP and other potential vaccine recipients, a plan for identifying persons recommended for vaccination, use of reminder/recall systems, assessment of practice-level vaccination rates with feedback to staff, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine, including use of standing orders programs (*367,370*). The use of standing orders programs by long-term–care facilities (e.g., nursing homes and skilled nursing facilities), hospitals, and home health agencies ensures that vaccination is offered. Standing orders programs for influenza vaccination should be conducted under the supervision of a licensed practitioner according to a physician-approved facility or agency policy by HCP trained to screen patients for contraindications to vaccination, administer vaccine, and monitor for adverse events. CMS has removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to Medicare and Medicaid patients in hospitals, long-term–care facilities, and home health agencies (*371*). To the extent allowed by local and state law, these facilities and agencies can implement standing orders for influenza and pneumococcal vaccination of Medicare- and Medicaid-eligible patients. Payment for influenza vaccine under Medicare Part B is available (*372,373*). Other settings (e.g., outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, and adult workplaces) are encouraged to introduce standing orders programs (*374*). In addition, physician reminders (e.g., flagging charts) and patient reminders are recognized strategies for increasing rates of influenza vaccination. Persons for whom influenza vaccine is recommended can be identified and vaccinated in the settings described in the following sections.

Outpatient Facilities Providing Ongoing Care

Staff in facilities providing ongoing medical care (e.g., physicians' offices, public health clinics, employee health clinics, hemodialysis centers, hospital specialty-care clinics, and outpatient rehabilitation programs) should identify and label the medical records of patients who should receive vaccination. Vaccine should be offered during visits throughout the influenza season. The offer of vaccination and its receipt or refusal should be documented in the medical record. Patients for whom vaccination is recommended and who do not have regularly scheduled visits during the fall should be reminded by mail, telephone, or other means of the need for vaccination.

Outpatient Facilities Providing Episodic or Acute Care

Acute health-care facilities (e.g., emergency departments and walk-in clinics) should offer vaccinations throughout the influenza season to persons for whom vaccination is recommended or provide written information regarding why, where, and how to obtain the vaccine. This written information should be available in languages appropriate for the populations served by the facility.

Nursing Homes and Other Residential Long-Term–Care Facilities

Vaccination should be provided routinely to all residents of chronic-care facilities. If possible, all residents should be vaccinated at one time before influenza season. In the majority of seasons, TIV will become available to long-term–care facilities in October or November, and vaccination should commence as soon as vaccine is available. As soon as possible after admission to the facility, the benefits and risks of vaccination should be discussed and education materials provided. Signed consent is not required (*375*). Residents admitted after completion of the vaccination program at the facility should be vaccinated at the time of admission through March.

Since October 2005, the Centers for Medicare and Medicaid Services (CMS) has required nursing homes participating in the Medicare and Medicaid programs to offer all residents influenza and pneumococcal vaccines and to document the results. According to the requirements, each resident is to be vaccinated unless contraindicated medically, the resident or a legal representative refuses vaccination, or the vaccine is not available because of shortage. This information is to be reported as part of the CMS Minimum Data Set, which tracks nursing home health parameters (*372,376*).

Acute-Care Hospitals

Hospitals should serve as a key setting for identifying persons at increased risk for influenza complications. Unvaccinated persons of all ages (including children) with high-risk conditions and persons aged 6 months–18 years or ≥50 years who are hospitalized at any time during the period when vaccine is available should be offered and strongly encouraged to receive influenza vaccine before they are discharged. Standing orders to offer influenza vaccination to all hospitalized persons should be considered.

Visiting Nurses and Others Providing Home Care to Persons at High Risk

Nursing-care plans should identify patients for whom vaccination is recommended, and vaccine should be administered in the home, if necessary as soon as influenza vaccine is available and throughout the influenza season. Caregivers and other persons in the household (including children) should be referred for vaccination.

Other Facilities Providing Services to Persons Aged ≥50 Years

Facilities providing services to persons aged ≥50 years (e.g., assisted living housing, retirement communities, and recreation centers) should offer unvaccinated residents, attendees, and staff annual on-site vaccination before the start of the influenza season. Continuing to offer vaccination throughout the fall and winter months is appropriate. Efforts to vaccinate newly admitted patients or new employees also should be continued, both to prevent illness and to avoid having these persons serve as a source of new influenza infections. Staff education should emphasize the need for influenza vaccine.

Health-Care Personnel

Health-care facilities should offer influenza vaccinations to all HCP, including night, weekend, and temporary staff. Particular emphasis should be placed on providing vaccinations to workers who provide direct care for persons at high risk for influenza complications. Efforts should be made to educate HCP regarding the benefits of vaccination and the potential health consequences of influenza illness for their patients, themselves, and their family members. All HCP should be provided convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs (*340,350,351*).

Future Directions for Research and Recommendations Related to Influenza Vaccine

Although available influenza vaccines are effective and safe, additional research is needed to improve prevention efforts. Most mortality from influenza occurs among person aged ≥65 years (*6*), and more immunogenic influenza vaccines are needed for this age group and other risk groups at high risk for mortality. Additional research is also needed to understand potential biases in estimating the benefits of vaccination among older adults in reducing hospitalizations and deaths (*101,193,377*). Additional studies of the relative cost-effectiveness and cost utility of influenza vaccination among children and adults, especially those aged <65 years, are needed and should be designed to account for year-to-year variations in influenza attack rates, illness severity, hospitalization costs and rates, and vaccine effectiveness when evaluating the long-term costs and benefits of annual vaccination (*378*). Additional data on indirect effects of vaccination are also needed to quantify the benefits of influenza vaccination of HCP in protecting their patients (*294*) and the benefits of vaccinating children to reduce influenza complications among those at risk. Because of expansions in ACIP recommendations for vaccination will lead to more persons being vaccinated, much larger research networks are needed that can identify and assess the causality of very rare events that occur after vaccination, including GBS. These research networks could also provide a platform for effectiveness and safety studies in the event

of a pandemic. Research on potential biologic or genetic risk factors for GBS also is needed. In addition, a better understanding of how to motivate persons at risk to seek annual influenza vaccination is needed.

ACIP continues to review new vaccination strategies to protect against influenza, including the possibility of expanding routine influenza vaccination recommendations toward universal vaccination or other approaches that will help reduce or prevent the transmission of influenza and reduce the burden of severe disease (*379–384*). The expansion of annual vaccination recommendations to include all children aged 6 months–18 years will require a substantial increase in resources for epidemiologic research to develop long term studies capable of assessing the possible effects on community-level transmission. Additional planning to improve surveillance systems capable of monitoring effectiveness, safety and vaccine coverage, and further development of implementation strategies will also be necessary. In addition, as noted by the National Vaccine Advisory Committee, strengthening the U.S. influenza vaccination system will require improving vaccine financing and demand and implementing systems to help better understand the burden of influenza in the United States (*385*). Vaccination programs capable of delivering annual influenza vaccination to a broad range of the population could potentially serve as a resilient and sustainable platform for delivering vaccines and monitoring outcomes for other urgently required public health interventions (e.g., vaccines for pandemic influenza or medications to prevent or treat illnesses caused by acts of terrorism).

Seasonal Influenza Vaccine and Avian or Swine Influenza

Human infection with novel or nonhuman influenza A virus strains, including influenza A viruses of animal origin, is a nationally notifiable disease (*386*). Human infections with nonhuman or novel human influenza A virus should be identified quickly and investigated to determine possible sources of exposure, identify additional cases, and evaluate the possibility of human-to-human transmission because transmission patterns could change over time with variations in these influenza A viruses.

Sporadic severe and fatal human cases of infection with highly pathogenic avian influenza A(H5N1) viruses have been identified in Asia, Africa, Europe and the Middle East, primarily among persons who have had direct or close unprotected contact with sick or dead birds associated with the ongoing H5N1 panzootic among birds (*387–392*). Limited, nonsustained human-to-human transmission of H5N1 viruses has likely occurred in some case clusters (*393,394*). To date, no evidence exists of genetic reassortment between human influenza A and H5N1 viruses. However, influenza viruses derived from strains circulating among poultry (e.g., the H5N1 viruses that have caused outbreaks of avian influenza and occasionally have infected humans) have the potential to recombine with human influenza A viruses (*395,396*). To date, highly pathogenic H5N1 viruses have not been identified in wild or domestic birds or in humans in the United States.

Human illness from infection with different avian influenza A subtype viruses also have been documented, including infections with low pathogenic and highly pathogenic viruses. A range of clinical illness has been reported for human infection with low pathogenic avian influenza viruses, including conjunctivitis with influenza A(H7N7) virus in the U.K., lower respiratory tract disease and conjunctivitis with influenza A(H7N2) virus in the U.K., and uncomplicated influenza-like illness with influenza A(H9N2) virus in Hong Kong and China (*397–402*). Two human cases of infection with low pathogenic influenza A(H7N2) were reported in the United States (*400*). Although human infections with highly pathogenic A(H7N7) virus infections typically have influenza-like illness or conjunctivitis, severe infections, including one fatal case in the Netherlands, have been reported (*403,404*). Conjunctivitis has also been reported because of human infection with highly pathogenic influenza A(H7N3) virus in Canada and low pathogenic A(H7N3) in the U.K (*397,404*). In contrast, sporadic infections with highly pathogenic avian influenza A(H5N1) viruses have caused severe illness in many countries, with an overall case-fatality ratio of >60% (*394,405*).

Swine influenza A(H1N1), A(H1N2), and A(H3N2) viruses are endemic among pig populations in the United States (*406*), including reassortant viruses. Two clusters of influenza A(H2N3) virus infections among pigs have been recently reported (*407*). Outbreaks among pigs normally occur in colder weather months (late fall and winter) and sometimes with the introduction of new pigs into susceptible herds. An estimated 30% of the pig population in the United States has serologic evidence of having had swine influenza A(H1N1) virus infection. Sporadic human infections with swine influenza A viruses occur in the United States, but the frequency of these human infections is unknown. Persons infected with swine influenza A viruses typically report direct contact with ill pigs or places where pigs have been present (e.g., agricultural fairs or farms), and have symptoms that are clinically indistinguishable from infection with other respiratory viruses (*408*). Clinicians should consider swine influenza A virus infection in the differential diagnosis of patients with ILI who have had recent contact with pigs. The sporadic cases identi-

fied in recent years have not resulted in sustained human-to-human transmission of swine influenza A viruses or community outbreaks. Although immunity to swine influenza A viruses appears to be low in the overall human population (<2%), 10%–20% of persons occupationally exposed to pigs (e.g., pig farmers or pig veterinarians) have been documented in certain studies to have antibody evidence of prior swine influenza A(H1N1) virus infection (*409,410*).

Current seasonal influenza vaccines are not expected to provide protection against human infection with avian influenza A viruses, including H5N1 viruses, or to provide protection against currently circulating swine influenza A viruses. However, reducing seasonal influenza risk through influenza vaccination of persons who might be exposed to nonhuman influenza viruses (e.g., H5N1 viruses) might reduce the theoretical risk for recombination of influenza A viruses of animal origin and human influenza A viruses by preventing seasonal influenza A virus infection within a human host.

CDC has recommended that persons who are charged with responding to avian influenza outbreaks among poultry receive seasonal influenza vaccination (*411*). As part of preparedness activities, the Occupational Safety and Health Administration (OSHA) has issued an advisory notice regarding poultry worker safety that is intended for implementation in the event of a suspected or confirmed avian influenza outbreak at a poultry facility in the United States. OSHA guidelines recommend that poultry workers in an involved facility receive vaccination against seasonal influenza; OSHA also has recommended that HCP involved in the care of patients with documented or suspected avian influenza should be vaccinated with the most recent seasonal human influenza vaccine to reduce the risk for co-infection with human influenza A viruses (*412*).

Recommendations for Using Antiviral Agents for Seasonal Influenza

Annual vaccination is the primary strategy for preventing complications of influenza virus infections. Antiviral medications with activity against influenza viruses are useful adjuncts in the prevention of influenza, and effective when used early in the course of illness for treatment. Four influenza antiviral agents are licensed in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Influenza A virus resistance to amantadine and rimantadine can emerge rapidly during treatment. Because antiviral testing results indicated high levels of resistance (*413–416*), neither amantadine nor rimantadine should be used for the treatment or chemoprophylaxis of influenza A in the United States during the 2007–08 influenza season. Surveillance demonstrating that susceptibility to these antiviral medications has been reestablished among circulating influenza A viruses will be needed before amantadine or rimantadine can be used for the treatment or chemoprophylaxis of influenza A. Oseltamivir or zanamivir can be prescribed if antiviral chemoprophylaxis or treatment of influenza is indicated. Oseltamivir is licensed for treatment of influenza in persons aged ≥1 year, and zanamivir is licensed for treating influenza in persons aged ≥7 years. Oseltamivir and zanamivir can be used for chemoprophylaxis of influenza; oseltamivir is licensed for use as chemoprophylaxis in persons aged ≥1 year, and zanamivir is licensed for use in persons aged ≥5 years.

During the 2007–08 influenza season, influenza A (H1N1) viruses with a mutation that confers resistance to oseltamivir were identified in the United States and other countries. As of June 27, 2008, in the United States, 111 (7.6%) of 1,464 influenza A viruses tested, and none of 305 influenza B viruses tested have been found to be resistant to oseltamivir. All of the resistant viruses identified in the United States and elsewhere are influenza A (H1N1) viruses. Of 1020 influenza A (H1N1) viruses isolated from patients in the United States, 111 (10.9%) exhibited a specific genetic mutation that confers oseltamivir resistance (*417*). Influenza A (H1N1) virus strains that are resistant to oseltamivir remain sensitive to zanamivir. Neuraminidase inhibitor medications continue to be the recommended agents for treatment and chemoprophylaxis of influenza in the United States. However, clinicians should be alert to changes in antiviral recommendations that might occur as additional antiviral resistance data becomes available during the 2008–09 influenza season (http://www.cdc.gov/flu/professionals/antivirals/index.htm).

Role of Laboratory Diagnosis

Influenza surveillance information and diagnostic testing can aid clinical judgment and help guide treatment decisions. However, only 69% of practitioners in one recent survey indicated that they test patients for influenza during the influenza season (*418*). 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 (*26,39,40*) (see Clinical Signs and Symptoms of Influenza).

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, reverse transcriptase-polymerase chain reaction (RT-PCR), and immunofluorescence assays (*419*). As with any diagnostic test, results should be evaluated in the context of other clinical and epidemiologic informa-

tion available to health-care providers. Sensitivity and specificity of any test for influenza can vary by the laboratory that performs the test, the type of test used, the type of specimen tested, 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 have higher yields than throat swab specimens (*420*). In addition, positive influenza tests have been reported up to 7 days after receipt of LAIV (*421*).

Commercial rapid diagnostic tests are available that can detect influenza viruses within 30 minutes (*422,423*). Certain tests are licensed for use in any outpatient setting, whereas others must be used in a moderately complex clinical laboratory. These rapid tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Different tests can detect 1) only influenza A viruses; 2) both influenza A and B viruses, but not distinguish between the two types; or 3) both influenza A and B and distinguish between the two. None of the rapid influenza diagnostic tests specifically identifies any influenza A virus subtypes.

The types of specimens acceptable for use (i.e., throat, nasopharyngeal, or nasal aspirates, swabs, or washes) also vary by test, but all perform best when collected as close to illness onset as possible. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test (*419,422–424*). Rapid tests for influenza have high specificity (>90%), but are only moderately sensitive (<70%). A recent study found sensitivity to be as low as 42% in clinical practice (*425*). Rapid tests 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 (*426*). Since RT-PCR has high sensitivity to detect influenza virus infection compared to viral culture, rapid tests have lower sensitivity than viral culture when compared to RT-PCR.

The limitations of rapid diagnostic tests must be understood in order to properly interpret results. Positive rapid influenza test results are generally reliable when community influenza activity is high and are useful in deciding whether to initiate antiviral treatment. Negative rapid test results are less helpful in making treatment decisions for individual patients when influenza activity in a community is high. Because of the lower sensitivity of the rapid tests, physicians should consider confirming negative tests with viral culture or other means because of the possibility of false-negative rapid test results, especially during periods of peak community influenza activity. The positive predictive value of rapid tests will be lower during periods of low influenza activity, and clinicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community when interpreting results (*424*). 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 should still be considered for influenza antiviral treatment despite a negative rapid influenza test unless illness can be attributed to another cause. However, because certain bacterial infections can produce symptoms similar to influenza, if bacterial infections are suspected, they should be considered and treated appropriately. 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 diagnostic tests. Additional updated information concerning diagnostic testing is available at http://www.cdc.gov/flu/professionals/lab diagnosis.htm.

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

Antiviral Agents for Influenza

Zanamivir and oseltamivir are chemically related antiviral medications known as neuraminidase inhibitors that have activity against both influenza A and B viruses. The two medications differ in pharmacokinetics, adverse events, routes of administration, approved age groups, dosages, and costs. An overview of the indications, use, administration, and known primary adverse events of these medications is presented in the following sections. Package inserts should be consulted for additional information. Detailed information about amantadine and rimantadine (adamantanes) is available in previous ACIP influenza recommendations (*427*).

Indications for Use of Antivirals

Treatment

Initiation of antiviral treatment within 2 days of illness onset is recommended, although the benefit of treatment is greater as the time after illness onset is reduced. Certain persons have a high priority for treatment (Box 3); however, treatment does not need to be limited to these persons. In clinical trials conducted in outpatient settings, the benefit of antiviral treatment for uncomplicated influenza was minimal unless treatment was initiated within 48 hours after illness onset. However, no data are available on the benefit for severe influenza when antiviral treatment is initiated >2 days after illness onset. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

Evidence for the efficacy of these antiviral drugs is based primarily on studies of outpatients with uncomplicated influenza. When administered within 2 days of illness onset to otherwise healthy children or adults, zanamivir or oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day compared with placebo (*143,428–442*). Minimal or no benefit was reported when antiviral treatment is initiated >2 days after onset of uncomplicated influenza. Data on whether viral shedding is reduced are inconsistent. The duration of viral shedding was reduced in one study that employed experimental infection; however, other studies have not demonstrated reduction in the duration of viral shedding. A recent review that examined neuraminidase inhibitor effect on reducing ILI concluded that neuraminidase inhibitors were not effective in the control of seasonal influenza (*443*). However, lower or no effectiveness using a nonspecific (compared with laboratory-confirmed influenza) clinical endpoint such as ILI would be expected (*444*).

Data are limited about the effectiveness of zanamivir and oseltamivir in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases), or for preventing influenza among persons at high risk for serious complications of influenza. In a study that combined data from 10 clinical trials, the risk for pneumonia among those participants with laboratory-confirmed influenza receiving oseltamivir 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) (*445*). 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. One randomized controlled trial documented a decreased incidence of otitis media among children treated with oseltamivir (*437*). Another randomized controlled study conducted among influenza-infected children with asthma demonstrated significantly 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 (*446*). Inadequate data exist regarding the efficacy of any of the influenza antiviral drugs for use among children aged <1 year, and none are FDA-licensed for use in this age group.

Two observational studies suggest 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 to untreated influenza patients. The average age of adults in this study was 77 years, and 71% began treatment >48 hours after illness onset. In the multivariate analysis, oseltamivir treatment was associated with a significantly decreased risk for death within 15 days of hospitalization (odds ratio = 0.21; CI = 0.06–0.80). Benefit was observed even among those starting treatment >48

BOX 3. Persons for whom antiviral treatment should be considered

If possible, antiviral treatment should be started within 48 hours of influenza illness onset. The effectiveness of initiating antiviral treatment >48 hours after illness onset has not been established. Persons for whom antiviral treatment should be considered include:

- persons hospitalized with laboratory-confirmed influenza (limited data suggests benefit even for persons whose antiviral treatment is initiated >48 hours after illness onset);
- persons with laboratory-confirmed influenza pneumonia;
- persons with laboratory-confirmed influenza and bacterial coinfection;
- persons with laboratory-confirmed influenza infection who are at higher risk for influenza complications; and
- persons presenting to medical care with laboratory-confirmed influenza within 48 hours of influenza illness onset who want to decrease the duration or severity of their symptoms and transmission of influenza to others at higher risk for complications.

Note: Recommended antiviral medications (neuraminidase inhibitors) are not licensed for treatment of children aged <1 year (oseltamivir) or aged <7 years (zanamivir). Updates or supplements to these recommendations (e.g., expanded age or risk group indications for licensed vaccines) might be required. Health-care providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information.

When determining the timing and duration for administering influenza antiviral medications for chemoprophylaxis, factors related to cost, compliance, and potential adverse events should be considered. To be maximally effective as chemoprophylaxis, the drug must be taken each day for the duration of influenza activity in the community. Additional clinical guidelines on the use of antiviral medications to prevent influenza are available (*453*,*454*).

Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun

Development of antibodies in adults after vaccination takes approximately 2 weeks (*369*,*370*). Therefore, when influenza vaccine is administered after influenza activity in a community has begun, chemoprophylaxis should be considered for persons at higher risk for influenza complications during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccination for the first time might require as much as 6 weeks of chemoprophylaxis (i.e., chemoprophylaxis until 2 weeks after the second dose when immunity after vaccination would be expected). Persons at higher risk for complications of influenza still can benefit from vaccination after community influenza activity has begun because influenza viruses might still be circulating at the time vaccine-induced immunity is achieved.

Persons Who Provide Care to Those at High Risk

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

Persons Who Have Immune Deficiencies

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

Other Persons

Chemoprophylaxis throughout the influenza season or during increases in influenza activity within the community might be appropriate for persons at high risk for whom vaccination is contraindicated, or for whom vaccination is likely to be ineffective. Health-care providers and patients should make decisions regarding whether to begin chemoprophylaxis and how long to continue it on an individual basis.

Antiviral Drug-Resistant Strains of Influenza

Oseltamivir and Zanamivir (Neuraminidase Inhibitors)

Among 2,287 isolates obtained from multiple countries during 1999–2002 as part of a global viral surveillance system, eight (0.3%) had a more than ten fold decrease in susceptibility to oseltamivir, and two (25%) of these eight also were resistant to zanamivir (*467*). In Japan, where more oseltamivir is used than in any other country, resistance to oseltamivir was identified in three (0.4%) A (H3N2) viruses in 2003–04, no A (H3N2) viruses in 2004–05, and no A (H3N2) viruses in 2005–06 influenza seasons. In 2005–06, four (2.2%) A (H1N1) viruses were identified to have oseltamivir resistance with a specific genetic marker (*468*). Neuraminidase inhibitor resistance remained low in the United States through the 2006–07 influenza season (CDC, unpublished data, 2007).

In 2007–08, increased resistance to oseltamivir was reported among A (H1N1) viruses in many countries (*469*,*470*). Persons infected with oseltamivir resistant A (H1N1) viruses had not previously received oseltamivir treatment and were not known to have been exposed to a person undergoing oseltamivir treatment (*469*,*470*). In the United States, approximately 10% of influenza A (H1N1) viruses, no A (H3N2) viruses, and no influenza B viruses were resistant to oseltamivir during the 2007–08 influenza season, and the overall percentage of influenza A and B viruses resistant to oseltamivir in the United States was <5%. No viruses resistant to zanamivir were identified (*417*). Oseltamivir or zanamivir continue to be the antiviral agents recommended for the prevention and treatment of influenza (*418*). Although recommendations for use of antiviral medications have not changed, enhanced surveillance for detection of oseltamivir-resistant viruses is ongoing and will enable continued monitoring of changing trends over time.

Development of viral resistance to zanamivir or oseltamivir during treatment has also been identified but does not appear to be frequent (*450*,*471*–*474*). One limited study reported

that oseltamivir-resistant influenza A viruses were isolated from nine (18%) of 50 Japanese children during treatment with oseltamivir (*475*). Transmission of neuraminidase inhibitor-resistant influenza B viruses acquired from persons treated with oseltamivir is rare but has been documented (*476*). No isolates with reduced susceptibility to zanamivir have been reported from clinical trials, although the number of post-treatment isolates tested is limited (*451,477*). Only one clinical isolate with reduced susceptibility to zanamivir, obtained from an immunocompromised child on prolonged therapy, has been reported (*451*). Prolonged shedding of oseltamivir- or zanamivir-resistant virus by severely immunocompromised patients, even after cessation of oseltamivir treatment, has been reported (*478,479*).

Amantadine and Rimantadine (Adamantanes)

Adamantane resistance among circulating influenza A viruses increased rapidly worldwide over the past several years, and these medications are no longer recommended for influenza prevention or treatment, although in some limited circumstances use of adamantanes in combination with a neuraminidase inhibitor medication might be considered (see Prevention and Treatment of Influenza when Oseltamivir Resistance is Suspected). The proportion of influenza A viral 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 (*480*). 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 (*413,414*). Preliminary data from the 2007–08 influenza season indicates that resistance to adamantanes remains high among influenza A isolates, with approximately 99% of tested influenza A(H3N2) isolates and approximately 10% of influenza A(H1N1) isolates resistant to adamantanes (CDC, unpublished data, 2008). Amantadine or rimantidine should not be used alone for the treatment or prevention of influenza in the United States until evidence of susceptibility to these antiviral medications has been reestablished among circulating influenza A viruses. Adamantanes are not effective in the prevention or treatment of influenza B virus infections.

Prevention and Treatment of Influenza when Oseltamivir Resistance is Suspected

Testing for antiviral resistance in influenza viruses is not available in clinical settings. Because the proportion of influenza viruses that are resistant to oseltamivir remains <5% in the United States, oseltamivir or zanamivir remain the medications recommended for prevention and treatment of influenza. Influenza caused by oseltamivir-resistant viruses appears to be indistinguishable from illness caused by oseltamivir-sensitive viruses (*469*). When local viral surveillance data indicates that oseltamivir-resistant viruses are widespread in the community, clinicians have several options. Consultation with local health authorities to aid in decision-making is recommended as a first step. Persons who are candidates for receiving chemoprophylaxis as part of an outbreak known to be caused by oseltamivir-resistant viruses or who are being treated for influenza illness in communities where oseltamivir-resistant viruses are known to be circulating widely can receive zanamivir. However, zanamivir is not licensed for chemoprophylaxis indications in children aged <5 years, and is not licensed for treatment in children aged <7 years (*451*). In addition, zanamivir is not recommended for use in persons with chronic cardiopulmonary conditions, and can be difficult to administer to critically ill patients because of the inhalation mechanism of delivery. In these circumstances, a combination of oseltamivir and either rimantadine or amantadine can be considered, because influenza A (H1N1) viruses characterized to date that were resistant to oseltamivir have usually been susceptible to adamantane medications (CDC, unpublished data, 2008). However, adamantanes should not be used for chemoprophylaxis or treatment of influenza A unless they are part of a regimen that also includes a neuraminidase inhibitor, because viral surveillance data has documented that adamantane resistance among influenza A viruses is common. Influenza B viruses are not sensitive to adamantane drugs.

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. In addition to antiviral medications, other outbreak-control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, re-offering influenza vaccinations to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients (*481–483*). Both adamantanes and neuraminidase inhibitors have been successfully used to control outbreaks caused by antiviral susceptible strains when antivirals are combined with other infection control measures. (*460,462,464,484–488*).

When confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis with a neuraminidase inhibitor medication should be

started as early as possible to reduce the spread of the virus (*489,490*). 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 cases for viral culture to assess antiviral resistance and provide data on the outbreak viruses. Chemoprophylaxis should be administered to all eligible residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 7–10 days after illness onset in the last patient (*489*). Chemoprophylaxis also can be offered to unvaccinated staff members who provide care to persons at high risk. Chemoprophylaxis should be considered for all employees, regardless of their vaccination status, if 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, studies indicating low vaccine effectiveness, or circulation in the surrounding community of suspected index case(s) of strains not contained in the vaccine.

In addition to use in nursing homes, chemoprophylaxis also can be considered for controlling influenza outbreaks in other closed or semiclosed settings (e.g., dormitories, correctional facilities, or other settings in which persons live in close proximity). To limit the potential transmission of drug-resistant virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis.

Dosage

Dosage recommendations vary by age group and medical conditions (Table 4).

Adults

Zanamivir is licensed 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).

Oseltamivir is licensed for treatment of adults with uncomplicated acute illness caused by influenza A or B virus and for chemoprophylaxis of influenza among adults. Dosages and schedules for adults are listed (Table 4).

Children

Zanamivir is licensed for treatment of influenza among children aged ≥7 years. The recommended dosage of zanamivir for treatment of influenza is 2 inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart). Zanamivir is licensed for chemoprophylaxis of influenza among children aged ≥5 years; the chemoprophylaxis dosage of zanamivir for children aged ≥5 years is 10 mg (2 inhalations) once a day.

Oseltamivir is licensed for treatment and chemoprophylaxis among children aged ≥1 year. 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 >15–23 kg, 60 mg twice a day for those who weigh >23–40 kg, and 75 mg twice a day for those who weigh >40 kg. Dosages for chemoprophylaxis are the same for each weight group, but doses are administered only once per day rather than twice.

Persons Aged ≥65 Years

No reduction in dosage for oseltamivir or zanamivir is recommended on the basis of age alone.

Persons with Impaired Renal Function

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 (*450*). 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 (*491,492*). 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 (*451*).

Serum concentrations of oseltamivir carboxylate, the active metabolite of oseltamivir, increase with declining renal function (*450*). For patients with creatinine clearance of 10–30 mL per minute (*450*), a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the chemoprophylaxis dosage to 75 mg every other day is recommended. No treatment or chemoprophylaxis dosing recommendations are available for patients undergoing routine renal dialysis treatment.

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 4); 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 (*497*). 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 B2-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a >20% decline in forced expiratory volume in 1 second (FEV1) after treatment (*451,498*). 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 (*451*). 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 airway disease (*451*). Allergic reactions, including oropharyngeal or facial edema, also have been reported during postmarketing surveillance (*451,498*).

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and for those receiving placebo (i.e., inhaled lactose vehicle alone) (*428–432,498*). 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 (*451*). Zanamivir does not impair the immunologic response to TIV (*499*).

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%) (*434,435,450,500*). 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 (*437*), and a limited number of adults who were enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (*450*). Similar types and rates of adverse events were reported in studies of oseltamivir chemoprophylaxis (*450*). Nausea and vomiting might be less severe if oseltamivir is taken with food (*450*). No published studies have assessed whether oseltamivir impairs the immunologic response to TIV.

Transient neuropsychiatric events (self-injury or delirium) have been reported postmarketing among persons taking oseltamivir; the majority of reports were among adolescents and adults living in Japan (*501*). FDA advises that persons receiving oseltamivir be monitored closely for abnormal behavior (*450*).

Use During Pregnancy

Oseltamivir and zanamivir are both "Pregnancy Category C" medications, indicating that no clinical studies have been conducted to assess the safety of these medications for pregnant women. Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these two drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus; the manufacturers' package inserts should be consulted (*450,451*). However, no adverse effects have been reported among women who received oseltamivir or zanamivir during pregnancy or among infants born to such women.

Drug Interactions

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of in vitro and animal study data (*450,451,502*).

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 (*468*).

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☆U.S. Government Printing Office: 2008-723-026/41109 Region IV ISSN: 1057-5987