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Prevention and Control of Influenza with Vaccines

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CONTENTS

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Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010

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Summary

This report updates the 2009 recommendations by CDC's Advisory Committee on Immunization Practices (ACIP) regarding the use of influenza vaccine for the prevention and control of influenza (CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2009;58[No. RR-8] and CDC. Use of influenza A (H1N1) 2009 monovalent vaccine—recommendations of the Advisory Committee on Immunization Practices [ACIP], 2009. MMWR 2009;58:[No. RR-10]). The 2010 influenza recommendations include new and updated information. Highlights of the 2010 recommendations include 1) a recommendation that annual vaccination be administered to all persons aged ≥6 months for the 2010–11 influenza season; 2) a recommendation that children aged 6 months–8 years whose vaccination status is unknown or who have never received seasonal influenza vaccine before (or who received seasonal vaccine for the first time in 2009–10 but received only 1 dose in their first year of vaccination) as well as children who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine regardless of previous influenza vaccine history should receive 2 doses of a 2010–11 seasonal influenza vaccine (minimum interval: 4 weeks) during the 2010–11 season; 3) a recommendation that vaccines containing the 2010–11 trivalent vaccine virus strains A/California/7/2009 (H1N1)-like (the same strain as was used for 2009 H1N1 monovalent vaccines), A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens be used; 4) information about Fluzone High-Dose, a newly approved vaccine for persons aged ≥65 years; and 5) information about other standard-dose newly approved influenza vaccines and previously approved vaccines with expanded age indications. Vaccination efforts should begin as soon as the 2010–11 seasonal influenza vaccine is available and continue through the influenza season. These recommendations also include a summary of safety data for U.S.-licensed influenza vaccines. These recommendations and other information are available at CDC's influenza website (http://www.cdc.gov/flu); any updates or supplements that might be required during the 2010–11 influenza season also will be available at this website. Recommendations for influenza diagnosis and antiviral use will be published before the start of the 2010–11 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.

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Introduction

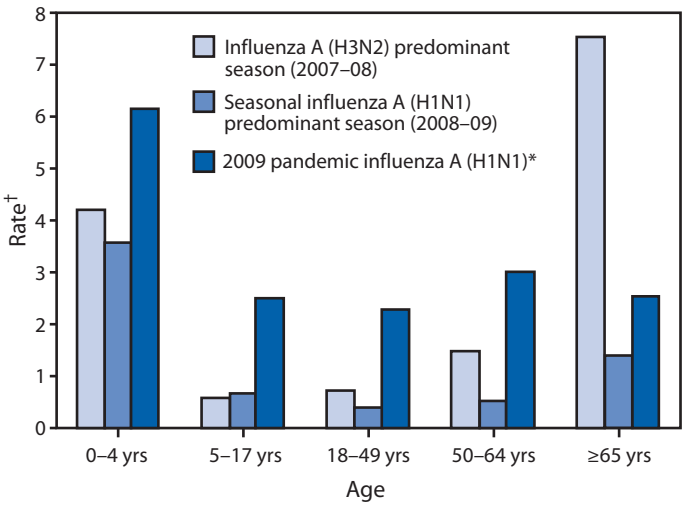
In the United States, annual epidemics of influenza occur typically during the late fall through early spring. Influenza viruses can cause disease among persons in any age group, but rates of infection are highest among children (*1–3*). During these annual epidemics, rates of serious illness and death 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*). Influenza epidemics were associated with estimated annual averages of approximately 36,000 deaths during 1990–1999 and approximately 226,000 hospitalizations during 1979–2001 (*6,7*).

Influenza A subtypes that are generated by a major genetic reassortment (i.e., antigenic shift) or that are substantially different from viruses that have caused infections over the previous several decades have the potential to cause a pandemic (*8*). In April 2009, a novel influenza A (H1N1) virus, 2009 influenza A (H1N1), that is similar to but genetically and antigenically distinct from influenza A (H1N1) viruses previously identified in swine, was determined to be the cause of respiratory illnesses that spread across North America and were identified in many areas of the world by May 2009 (*9,10*). Influenza morbidity caused by 2009 pandemic influenza A (H1N1) remained above seasonal baselines throughout spring and summer 2009 and was the cause of the first pandemic since 1968. In the United States, the pandemic was characterized by a substantial increase in influenza activity, as measured by multiple influenza surveillance systems, that was well beyond historical norms in September 2009, peaking in late October 2009, and returning to seasonal baseline by January 2010 (Figures 1 and 2). During this time, >99% of viruses characterized were the 2009 pandemic influenza A (H1N1) virus (*11*). Data from epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicate that the risk for influenza complications among adults aged 19–64 years who had 2009 pandemic influenza A (H1N1) was greater than typically occurs for seasonal influenza (*12*). Influenza caused by 2009 pandemic influenza A (H1N1) virus is expected to continue to occur during future winter influenza seasons in the Northern and Southern Hemispheres, but whether 2009 pandemic influenza A (H1N1) viruses will replace or co-circulate with one or more of the two seasonal influenza A virus subtypes (seasonal H1N1 and H3N2) that have co-circulated since 1977 is unknown. Influenza viruses undergo frequent antigenic change as a result of point mutations and recombination events that occur during viral replication (i.e., antigenic drift). The extent of antigenic drift and evolution of 2009 pandemic influenza A (H1N1) virus strains in the future cannot be predicted.

Annual influenza vaccination is the most effective method for preventing influenza virus infection and its complications (*8*). Annual vaccination with the most up-to-date strains predicted on the basis of viral surveillance data is recommended. Influenza vaccine is recommended for all persons aged ≥6 months who do not have contraindications to vaccination.

FIGURE 1. Cumulative rate of hospitalizations during three influenza seasons, by age group — Emerging Infections Program, United States, 2007–2010

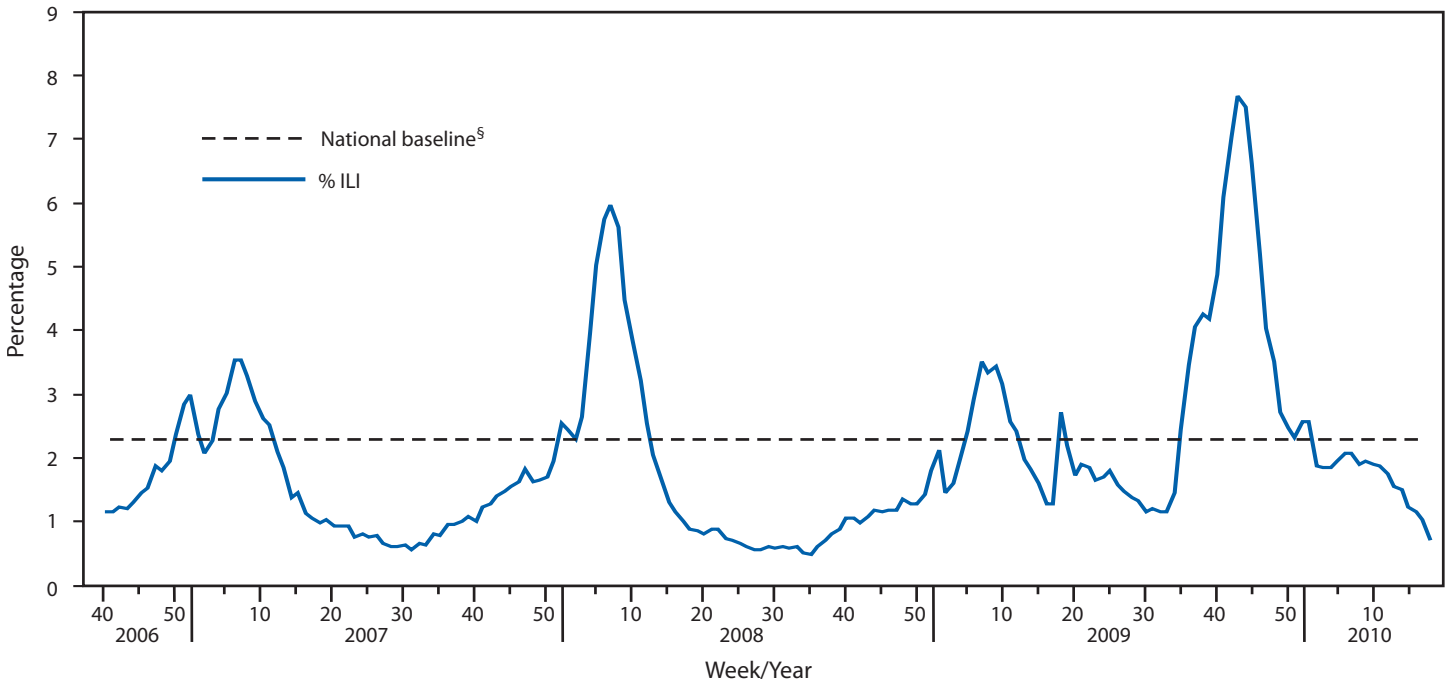


* 2009 Pandemic Influenza A(H1N1) hospitalization data from September 1, 2009–January 21, 2010.
† Per 10,000 population.

Trivalent inactivated influenza vaccine (TIV) can be used for any person aged ≥6 months, including those with high-risk conditions (Box). Live, attenuated influenza vaccine (LAIV) may be used for healthy nonpregnant persons aged 2–49 years. No preference is indicated for LAIV or TIV when considering vaccination of healthy nonpregnant persons aged 2–49 years. 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 be vaccinated only with TIV. Although vaccination coverage has increased in recent years for many groups recommended for routine vaccination, considerable room for improvement remains (*13*), and strategies to improve vaccination coverage in the medical home and in nonmedical settings should be implemented or expanded (*14*).

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. However, the emergence since 2005 of resistance to one or more of the four licensed antiviral agents (oseltamivir, zanamivir, amantadine, and rimantadine) among circulating strains has complicated antiviral treatment and chemoprophylaxis recommendations. CDC has revised recommendations for antiviral treatment and chemoprophylaxis of influenza periodically in response to new data on antiviral resistance patterns among circulating strains and risk factors for influenza complications (*15*). With few exceptions, 2009 pandemic influenza A (H1N1) virus strains that began circulating in April 2009 remained sensitive to oseltamivir (*16*).

FIGURE 2. Percentage of visits for influenza-like Illness (ILI)* reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet),† by surveillance week — United States, October 1, 2006–May 1, 2010



* ILI is defined as fever (temperature of ≥100°F [≥37.8°C) and a cough and/or a sore throat in the absence of a known cause other than influenza.
† ILINet consists of approximately 2,400 health-care providers in 50 states reporting approximately 16 million patient visits each year.
§ The mean percentage of visits for ILI during noninfluenza weeks for the previous three seasons plus two standard deviations. A noninfluenza week is a week during which <10% of specimens tested positive for influenza.

Methods

CDC's Advisory Committee on Immunization Practices (ACIP) provides annual recommendations for the prevention and control of influenza. The ACIP Influenza Work Group (the Work Group)* meets every 2–4 weeks throughout the year to discuss newly published studies, review current guidelines, and consider revisions to the recommendations. As the Work Group reviews the annual recommendations for consideration by the full ACIP, its members discuss a variety of issues, including the burden of influenza illness; vaccine effectiveness, vaccine safety, and coverage in groups recommended for vaccination; feasibility; cost-effectiveness; and anticipated vaccine supply. Work 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. CDC's Influenza Division (available at http://www.cdc.gov/flu) provides influenza surveillance and antiviral resistance data. 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 are considered. Among studies discussed or cited, those of greatest scientific quality and those that measure influenza-specific outcomes are the most influential. For example, population-based estimates of influenza disease burden supported by laboratory-confirmed influenza virus infection outcomes contribute the most specific data. The best evidence for vaccine or antiviral efficacy 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 viruses' circulation and degree of match between vaccine strains and wild circulating strains (*17,18*). However, randomized controlled trials cannot be performed ethically in populations for which vaccination already is recommended, and in this context, observational studies that assess outcomes associated with laboratory-confirmed influenza infection also can provide important vaccine or antiviral safety and effectiveness data. Evidence for vaccine or antiviral safety also is provided

* A list of the members appears on page 62 of this report.

BOX. Summary of influenza vaccination recommendations, 2010

- All persons aged ≥6 months should be vaccinated annually.
- Protection of persons at higher risk for influenza-related complications should continue to be a focus of vaccination efforts as providers and programs transition to routine vaccination of all persons aged ≥6 months.
- When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to persons who:
  - are aged 6 months–4 years (59 months);
  - are aged ≥50 years;
  - have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
  - are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus);
  - are or will be pregnant during the influenza season;
  - are aged 6 months–18 years and receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection;
  - are residents of nursing homes and other chronic-care facilities;
  - are American Indians/Alaska Natives;
  - are morbidly obese (body-mass index ≥40);
  - are health-care personnel;
  - are 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
  - are household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

by randomized controlled studies; however, the number of subjects in these studies often is inadequate to detect associations between vaccine and rare adverse events. The best way to assess the frequency of rare adverse events after vaccination is by controlled studies after vaccines are used widely in the population. These studies often use electronic medical records from large linked clinical databases and medical charts of persons who are identified as having a vaccine adverse event (*19–21*). Vaccine coverage data from a nationally representative, randomly selected population that include verification of vaccination through health-care record review are superior to coverage data derived from limited population samples or from self-reported vaccination status; however, the former rarely is obtained in vaccination coverage data for children aged ≥5 years (*22*). 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 around an estimate of effect allowed rejection of the null hypothesis (i.e., no effect).

Data presented in this report were current as of June 29, 2010, and represent recommendations presented to the full ACIP and approved on February 24, 2010, and June 24, 2010. Modifications were made to the ACIP statement during the subsequent review process at CDC to update and clarify wording in the document. Vaccine recommendations apply only to persons who do not have contraindications to vaccine use (see Contraindications and Precautions for Use of TIV and Contraindications and Precautions for Use of LAIV). 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 2010 recommendations include five principal changes or updates:

- Routine influenza vaccination is recommended for all persons aged ≥6 months. This represents an expansion of the previous recommendations for annual vaccination of all adults aged 19—49 years and is supported by evidence that annual influenza vaccination is a safe and effective preventive health action with potential benefit in all age groups. By 2009, annual vaccination was already recommended for an estimated 85% of the U.S. population, on the basis of risk factors for influenza-related complications or having close contact with a person at higher risk for influenza-related complications. The only group remaining that was not recommended for routine vaccination was healthy nonpregnant adults aged 18–49 years who did not have an occupational risk for infection and who were not close contacts of persons at higher risk for influenza-related complications. However, some adults who have influenza-related complications have no previously identified risk factors for influenza complications. In addition, some adults who have medical conditions

or age-related increases in their risk for influenza-related complications or another indication for vaccination are unaware that they should be vaccinated. Further support for expansion of annual vaccination recommendations to include all adults is based on concerns that 2009 pandemic influenza A (H1N1)-like viruses will continue to circulate during the 2010–11 influenza season and that a substantial proportion of young adults might remain susceptible to infection with this virus. Data from epidemiologic studies conducted during the 2009 pandemic indicate that the risk for influenza complications among adults aged 19–49 years is greater than is seen typically for seasonal influenza (*12,23,27*).

- As in previous recommendations, all children aged 6 months–8 years who receive a seasonal influenza vaccine for the first time should receive 2 doses. Children who received only 1 dose of a seasonal influenza vaccine in the first influenza season that they received vaccine should receive 2 doses, rather than 1, in the following influenza season. In addition, for the 2010–11 influenza season, children aged 6 months–8 years who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010–11 seasonal influenza vaccine, regardless of previous influenza vaccination history. Children aged 6 months–8 years for whom the previous 2009–10 seasonal or influenza A (H1N1) 2009 monovalent vaccine history cannot be determined should receive 2 doses of a 2010–11 seasonal influenza vaccine.
- The 2010–11 trivalent vaccines will contain A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The influenza A (H1N1) vaccine virus is derived from a 2009 pandemic influenza A (H1N1) virus.
- A newly approved inactivated trivalent vaccine containing 60 mcg of hemagglutinin antigen per influenza vaccine virus strain (Fluzone High-Dose [sanofi pasteur]) is an alternative inactivated vaccine for persons aged ≥65 years. Persons aged ≥65 years can be administered any of the standard-dose TIV preparations or Fluzone High-Dose. Persons aged <65 years who receive inactivated influenza vaccine should be administered a standard-dose TIV preparation.
- Previously approved inactivated influenza vaccines that were approved for expanded age indications in 2009 include Fluarix (GlaxoSmithKline), which is now approved for use in persons aged ≥3 years, and Afluria (CSL Biotherapies), which is now approved for use in persons aged ≥6 months. A new inactivated influenza vaccine, Agriflu (Novartis), has been approved for persons aged ≥18 years.

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. During 1977–2010, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have circulated globally. Influenza A subtypes and B viruses are separated further into groups on the basis of antigenic similarities. New influenza virus variants result from frequent antigenic change (i.e., antigenic drift) caused by point mutations and recombination events that occur during viral replication (*8*). Recent studies have explored the complex molecular evolution and epidemiologic dynamics of influenza A viruses (*28–30*).

New or substantially different 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 when little or no previously existing immunity has been identified among humans (*8*). In April 2009, human infections with a novel influenza A (H1N1) virus were identified, and this virus subsequently caused a worldwide pandemic (*9*). The 2009 pandemic influenza A (H1N1) virus is derived from influenza A viruses that have circulated in swine during the past several decades and is antigenically distinct from human influenza A (H1N1) viruses in circulation since 1977. The 2009 pandemic influenza A (H1N) virus contains a combination of gene segments that had not been reported previously in animals or humans. The hemagglutination (HA) gene, which codes for the surface protein most important for immune response, is related most closely to the HA found in contemporary influenza viruses circulating among pigs. This HA gene apparently evolved from the avian-origin 1918 pandemic influenza H1N1 virus, which is thought to have entered human and swine populations at about the same time (*28*).

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 (*31*).

Immunity to surface antigens, particularly hemagglutinin, reduces the likelihood of infection (*32*). 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 (*33*). 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. The 2009 pandemic influenza A (H1N1) virus is not a new subtype, but because most humans had no pre-existing antibody to key pandemic 2009 influenza A (H1N1) virus hemagglutinin epitopes, widespread transmission was possible (*28*).

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. 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 (*34–36*). However, increases in health-care provider visits for acute febrile respiratory illness occur each year during the time when influenza viruses circulate. Data from the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet) demonstrate the annual increase in physician visits for influenza-like illness (ILI)[†] and for each influenza season; for 2009, these data also indicated the increase in respiratory illness associated with circulation of 2009 pandemic influenza A (H1N1) virus during Spring 2009 and the resurgence of cases in Fall 2009 (Figure 2) (*37,38*).

In typical winter influenza seasons, an increase in deaths and hospitalizations is observed during periods when influenza viruses are circulating. Some persons whose hospitalization is attributed to invasive pneumococcal pneumonia are likely to have influenza as a co-pathogen, based on correlation between influenza activity and seasonal variations in pneumococcal pneumonia (*39*). The number of deaths or hospitalizations attributable at least partly to influenza can be estimated by applying modeling techniques to viral surveillance and national mortality or hospitalizations data and includes deaths and hospitalizations for which influenza infection is likely a contributor to mortality but not necessarily the sole cause of death (*6,7,40,41*).

Excess deaths and hospitalizations during influenza season that are likely to be caused at least partly by influenza are derived from the broad category of pulmonary and circulatory deaths or hospitalizations. Estimates that include only outcomes attributed to pneumonia and influenza underestimate the proportion of severe illnesses that are attributable at least partly to influenza because such estimates exclude deaths caused by exacerbations of underlying cardiac and pulmonary conditions that are associated with influenza infection (*6,7,40–42*).

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*). 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, including many who were at higher risk for death from influenza complications (*6*). When mortality data that included deaths attributable to both the pneumonia and influenza as well as the respiratory and circulatory categories were used as a basis for estimating the influenza burden, an average of approximately 19,000 influenza-associated deaths per influenza season occurred during 1976–1990 compared with an average of approximately 36,000 deaths per season during 1990–1999 (*6*). On the basis of data from the pneumonia and influenza category alone, an estimated annual average of 8,000 influenza-related deaths occurred. In addition, influenza A (H3N2) viruses, which have been associated with higher mortality (*43*), predominated in 90% of influenza seasons during 1990–1999 compared with 57% of seasons during 1976–1990 (*6*). From the 1990–91 influenza season through the 1998–99 season, the estimated annual number of deaths attributed to influenza ranged from 17,000 to 51,000 per epidemic (*6*). Estimates of mortality using a variety of different modeling techniques generally have been similar, although estimates for more recent years, when influenza A (H1N1) viruses have predominated more often, have been somewhat lower (*40*).

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 seasonal influenza are higher among adults aged ≥65 years, children aged <5 years, and persons of any age who

[†] ILI is defined as fever (temperature of ≥100°F [≥37.8°C) and a cough and/or a sore throat in the absence of a known cause other than influenza.

have medical conditions that place them at increased risk for complications from influenza (*1,4,5,44–47*). Estimated rates of influenza-associated hospitalizations and deaths varied substantially by age group in studies conducted during different seasonal 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*).

During the 2009 influenza A (H1N1) pandemic, epidemiologic studies in multiple countries indicated that hospitalization rates and deaths among children and adults aged <65 years exceeded those observed during typical winter seasonal influenza epidemics (*12,23,25,48,49*). In one analysis, the mean age among persons who died in the United States during May–December 2009 and who had laboratory-confirmed influenza was 37 years. In contrast, the estimated mean age among persons who died from seasonal influenza during 1979–2001 was 76 years (*50*). The estimated number of hospitalizations and deaths among adults aged ≥65 years was below that observed in most seasonal epidemics. This difference was attributed to a lower risk for infection (*51*) associated with a higher prevalence of partial or full immunity among older persons, presumably as a result of exposures to antigenically similar influenza A viruses that circulated in the early-mid 20th century. One indication of some degree of preexisting immunity was the presence of cross-reacting antibody present among approximately one third of older adults (*52*), which has been attributed to similarities in the structure of the hemagglutinin protein among the 2009 H1N1 virus and those that circulated earlier in the 20th century (*53*).

Children

Among children aged <5 years, influenza-related illness is a common cause of visits to medical practices and emergency departments (EDs). 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 ED visits. On the basis of these data, the rate of visits to medical clinics for influenza was estimated to be 50–95 visits per 1,000 children, and the rate of visits to EDs was estimated to be 6–27 visits per 1,000 children (*54*). In a multiyear study in New York City that used viral surveillance data to estimate influenza strain-specific illness rates among ED visits, in addition to the expected variation by season and age group, influenza B epidemics were determined to be an important cause of illness among school-aged children in several seasons, and annual epidemics of both influenza A and B peaked among school-aged children before other age groups (*55*). Retrospective studies using medical records data have demonstrated similar rates of illness among children aged <5 years during other influenza seasons (*45,56,57*). During an influenza season, seven to 12 additional outpatient visits and five to seven additional antibiotic prescriptions per 100 children aged <15 years have been estimated compared with periods when influenza viruses are not circulating, with rates decreasing with increasing age of the child (*57*). During 1993–2004 in the Boston area, the rate of ED visits for respiratory illnesses that were attributed to influenza virus on the basis of viral surveillance data among children aged ≤7 years during the winter respiratory illness season ranged from 22.0 per 1,000 children aged 6–23 months to 5.4 per 1,000 children aged 5–7 years (*58*).

Estimates of rates of influenza-associated hospitalization are substantially higher among infants and children aged <2 years compared with older children and are similar to rates for other groups considered at higher risk for influenza-related complications (*59–64*), including persons aged ≥65 years (*57,61*). During 1979–2001, the estimated rate of influenza-associated hospitalizations among children aged <5 years in the United States was 108 hospitalizations per 100,000 person-years, based on data from a national sample of hospital discharges of influenza-associated hospitalizations (*7*). Recent population-based studies that measured hospitalization rates for laboratory-confirmed influenza in young children have documented hospitalization rates that are similar to or higher than rates derived from studies that analyzed hospital discharge data (*54,56,63,65,66*). 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 (*54*). Hospitalization rates for children aged <5 years with high-risk medical conditions are approximately 250–500 per 100,000 children (*45,47,67*).

Influenza-associated deaths are uncommon among children. An estimated annual average of 92 influenza-associated 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 aged <18 years 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 children with risk factors for influenza complications are at higher risk for death, the majority of pediatric deaths occur among children with no known high-risk conditions.

Since 2004, death associated with laboratory-confirmed influenza virus infection among children (defined as persons aged <18 years) has been a nationally reportable condition. During 2004–2005, the annual number of seasonal influenza-associated deaths among children aged <18 years reported to CDC ranged from 47 during 2004–05 to 88 during 2007–08 (*70*). During April 2009–March 2010, over 300 deaths attributable to laboratory-confirmed 2009 H1N1 influenza among children, the majority of whom had one or more underlying medical conditions, were reported to CDC in the United States, and over 1,000 deaths are estimated to have occurred (*71*; CDC, unpublished data, 2010).

Deaths among children that have been attributed to co-infection with influenza and *Staphylococcus aureus*, particularly methicillin-resistant *S. aureus* (MRSA), have increased (*38,72*), and illness severity of co-infection is increased compared with influenza alone (*73*). The reason for this increase in co-infections has not been established but might reflect an increasing prevalence within the general population of colonization with MRSA strains, some of which carry certain virulence factors (*74,75*).

Adults

Among healthy younger adults, illness caused by seasonal influenza is typically not severe and rarely results in hospitalization, compared with children aged <5 years, adults aged ≥65 years, pregnant women, or persons with chronic medical conditions. However, illness burden among healthy adults aged 19–49 years is an important cause of outpatient medical visits and worker absenteeism. The impact of influenza varies considerably by season, making estimates of the attack rate in healthy younger adults difficult. In most studies, attack rates have varied from 2% to 10% annually, and influenza has been estimated to cause 0.6–2.5 workdays lost per illness (*76–80*). In one economic analysis, the average annual burden of seasonal influenza among adults aged 18–49 years who did not have a medical condition that conferred a higher risk for influenza complications was estimated to include approximately 5 million illnesses, 2.4 million outpatient visits, 32,000 hospitalizations, and 680 deaths (*78*).

Hospitalization rates during typical influenza seasons are substantially increased for persons aged ≥65 years compared with younger age groups. 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 persons aged ≥65 years. Persons aged 50–64 years who have underlying medical conditions also were at substantially increased risk for hospitalizations during influenza season compared with healthy adults aged 50–64 years (*44*).

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

During the 2009 H1N1 pandemic, adults aged <65 years were at higher risk for influenza-related complications (*23,81,82*), particularly those aged 50–64 years who had underlying medical conditions, compared with typical influenza seasons. The distribution of hospitalizations by age group differed from usual seasonal influenza patterns during 2009–10, with more hospitalizations among younger age groups and fewer among adults aged ≥65 years (Figure 1). Hospitalization rates exceeded those seen in any recent influenza season among adults aged ≤65 years (*26*). Pneumonia with evidence of invasive bacterial co-infection has been reported in approximately one third of fatal cases in autopsy studies (*83*). In one study of critically ill adults who required mechanical ventilation, *Streptococcus pneumoniae* pneumonia at admission was an independent risk factor for death (*84*). In addition, obesity (body-mass index [BMI] ≥30) and particularly morbid obesity (BMI ≥40) appeared to be risk factors for hospitalization and death in some studies (*23,24,81,85,86*). Additional studies are needed to determine whether obesity is a risk factor specific to the 2009 H1N1-like influenza viruses or a previously unrecognized risk factor for influenza-related complications caused by other influenza viruses. Other epidemiologic features of the 2009 H1N1 pandemic underscored racial and ethnic disparities in the risk for influenza-related complications among adults, including higher rates of hospitalization for blacks and a disproportionate number of deaths among American Indians/Alaska Natives and indigenous populations in other countries (*87–91*). These disparities might be attributable in part to the higher prevalence of underlying medical conditions or disparities in medical care among these racial/ethnic groups (*92,93*).

The duration of influenza symptoms is prolonged and the severity of influenza illness increased among persons with

human immunodeficiency virus (HIV) infection (*94–98*). A retrospective study of women aged 15–64 years 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 (*99*). Another study estimated that the risk for influenza-related death was 94–146 deaths per 100,000 persons with acquired immune deficiency 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 (*100*).

Influenza-related excess deaths among pregnant women were reported during the pandemics of 1918–1919, 1957–1958, and 2009–2010 (*48,101–106*). Severe infections among postpartum women (those delivered within the previous 2 weeks) also were observed in the 2009–10 pandemic (*48,107,108*). Case reports and several epidemiologic studies also indicate that pregnancy increases the risk for seasonal influenza complications for the mother (*109–114*). 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 (*115*). 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 (*116*). 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 of 68 admissions per 100,000 women without comorbidities was reported (*117*). In one study, pregnant women with hospitalizations for respiratory symptoms did not have an increase in adverse perinatal outcomes or delivery complications (*118*); another study indicated an increase in delivery complications, including fetal distress, preterm labor, and cesarean delivery. However, infants born to women with laboratory-confirmed influenza during pregnancy do not have higher rates of low birth weight, congenital abnormalities, or lower Apgar scores compared with infants born to uninfected women (*109,119*).

In a case series conducted during the 2009 H1N1 pandemic, 56 deaths were reported among 280 women admitted to intensive care units (*120*). Among the deaths, 36 (64%) occurred in the third trimester. Pregnant women who received treatment >4 days after symptom onset were more likely than those treated within 2 days after symptom onset to be admitted to an intensive care unit (57% and 9%, respectively; relative risk [RR]: 6.0; 95% CI = 3.5–10.6) (*120*).

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 health-care personnel [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. However, coverage levels among these persons need to be increased before effects on transmission can be measured reliably. Antiviral medications can be used for chemoprophylaxis and have been demonstrated to prevent influenza illness. When used for treatment, antiviral medications have been demonstrated to reduce the severity and duration of illness, particularly if used within the first 48 hours after illness onset. However, antiviral medications are adjuncts to vaccine in the prevention and control of influenza, and primary prevention through annual vaccination is the most effective and efficient prevention strategy. Despite recommendations to use antiviral medications to treat hospitalized patients with suspected influenza, antiviral drugs are underused (*121*).

Reductions in detectable influenza A viruses on hands after handwashing have been demonstrated, and handwashing has been demonstrated to reduce the overall incidence of respiratory diseases (*122–124*). Nonpharmacologic interventions (e.g., frequent handwashing and improved respiratory hygiene) are reasonable and inexpensive. However, the impact of hygiene interventions such as handwashing on influenza virus transmission is not well understood, and hygiene measures should not be advocated as a replacement or alternative to specific prevention measures such as vaccination. 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 (*125–127*). An interventional trial among university students indicated that students living in dormitories who were asked to use surgical face masks, given an alcohol-based hand sanitizer, and provided with education about mask use and hand hygiene during influenza season had substantially lower rates of ILI compared with students in dormitories for whom no intervention was recommended. However, neither face mask nor hand sanitizer use alone was associated with statistically significant reduction in ILI (*128*). During the 2009 pandemic, one study indicated that having members of households in which an influenza case was identified discuss ways to avoid transmission was associated with a significant reduction in the frequency of additional cases after one household member became ill, suggesting that education measures might be an effective way to reduce secondary transmission (*129*). Limited data suggest that transmission of seasonal influenza or ILI among household members can be reduced if household contacts use a surgical face mask or implement hand washing early in the course of an ill index case patient's illness (*130,131*). However, these interventions might supplement use of vaccine as a means to reduce influenza transmission or provide some protection when vaccine is not available (*130–132*).

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), laboratory-confirmed influenza virus illness, influenza or pneumonia-associated hospitalizations or deaths, or seroconversion. 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 (*133*). 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 (*134,135*). 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 equivalent antigenically 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. The 2010–11 trivalent vaccines will contain A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The A/California/7/2009 (H1N1)-like antigen is derived from a pandemic 2009 influenza A (H1N1) virus and is the same vaccine antigen used in the influenza A (H1N1) 2009 monovalent vaccines. The A/Perth/16/2009 (H3N2)-like antigen is different from the H3N2-like antigen recommended for the 2009–10 northern hemisphere seasonal influenza vaccine. The influenza B vaccine strain will remain B/Brisbane/16/2008 and is not changed compared with the 2009–10 northern hemisphere seasonal influenza vaccine (*136*). Viruses for currently licensed TIV and LAIV preparations are grown in chicken eggs. Either vaccine is 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). None of the influenza vaccines licensed in the United States contains an adjuvant.

Major Differences Between TIV and LAIV

TIV contains inactivated viruses and thus cannot cause influenza. LAIV contains live attenuated influenza viruses that have the potential to cause mild signs or symptoms related to vaccine virus infection (e.g., rhinorrhea, 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

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

Factor	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Killed virus
No. of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration	Annually*	Annually*
Approved age	Persons aged 2–49 yrs†	Persons aged ≥6 mos§
Interval between 2 doses recommended for children aged ≥6 mos–8 yrs who are receiving influenza vaccine for the first time	≥4 wks	≥4 wks
Can be given to persons with medical risk factors for influenza-related complications†	No	Yes
Can be given to children with asthma or children aged 2–4 yrs with wheezing in the past yr¶	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 higher risk including pregnant women, but not severely immunosuppressed	Yes	Yes
Can be administered simultaneously with other vaccines	Yes**	Yes††
If not administered simultaneously, can be administered within 4 weeks of another live vaccine	Prudent to space ≥4 wks apart	Yes
If not administered simultaneously, can be administered within 4 wks of an inactivated vaccine	Yes	Yes

* Children aged ≥6 months–8 years who have never received a seasonal influenza vaccine before or who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses, spaced ≥4 weeks apart. Those children aged 6 months–8 years who were vaccinated for the first time in the 2009–10 season with the seasonal 2009–10 vaccine but who received only 1 dose of seasonal influenza vaccine should receive 2 doses in the following year, spaced ≥4 wks apart.

† Persons at higher risk for complications of influenza infection because of underlying medical conditions should not receive LAIV. Such persons include those who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic (including diabetes mellitus) disorders; those who are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus); those who are or will be pregnant during the influenza season; those aged 6 months–18 years and receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection; and residents of nursing homes and other chronic-care facilities.

§ Approval varies by formulation. Fluzone (sanofi pasteur) and Afluria (CSL Biotherapies) have been approved previously for use in children as young as age 6 months. Fluzone High-Dose is approved for use in persons aged ≥65 years. Immunization providers should check Food and Drug Administration–approved prescribing information for 2010–11 influenza vaccines for the most updated information.

¶ 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 within the preceding 12 months, should not receive LAIV.

** LAIV coadministration has been evaluated systematically only among children aged 12–15 months who received with 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.

2–49 years; safety has not been established in persons with underlying medical conditions that confer a higher risk for 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). During the preparation of TIV, the vaccine viruses are made noninfectious (i.e., inactivated or killed) (*8*). Only subvirion and purified surface antigen preparations of TIV (often referred to as "split" and subunit vaccines, respectively) are available in the United States. Standard-dose TIV preparations contain 7.5 mcg HA antigen per vaccine strain (for children aged <36 months) or 15 mcg of HA antigen (for persons aged ≥36 months) per vaccine strain (i.e., 22.5 mcg or 45 mcg total HA antigen). A newly licensed higher dose TIV (60 mcg per vaccine strain or 180 mcg total HA antigen) was approved recently for persons aged ≥65 years (Fluzone High-Dose, Sanofi pasteur).

Correlates of Protection after Vaccination

Immune correlates of protection against influenza infection after vaccination include serum hemagglutination inhibition antibody and neutralizing antibody (*32,137*). Increased levels of antibody induced by vaccination decrease the risk for illness caused by strains that are similar antigenically to those strains of the same type or subtype included in the vaccine (*138–141*). The majority of healthy children and adults have high titers of antibody after vaccination (*139,142*). 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 (typically defined as a hemagglutination titer of 1:32 or 1:40) 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 (*143,144*). Laboratory measurements that correlate with protective immunity induced by LAIV have been described, including measurement of cell-mediated immunity with ELISPOT assays that measure gamma-interferon (*143*).

Duration of Immunity

The recommended composition of influenza vaccines changes in most seasons, with one or more vaccine strains replaced annually to provide better protection against wild-type viruses that are likely to circulate. However, evidence from clinical trials suggests that protection against viruses that are similar antigenically to those contained in the vaccine extends for at least 6–8 months. Three years after vaccination with the A/Hong Kong/68 vaccine, vaccine effectiveness was 67% for prevention of influenza caused by the A/Hong Kong/68 virus (*145*). In randomized trials conducted among healthy college students, immunization with TIV provided 92% and 100% efficacy against influenza H3N2 and H1N1 illnesses, respectively, during the first year, and a 68% reduction against H1N1 illness during the second year (when the predominant circulating virus was H1N1) without revaccination (*146*). In a similar study of young adults in 1986–1987, TIV reduced influenza A (H1N1) illness 75% in the first year, H3N2 illness 45% in the second year, and H1N1 illness 61% in the third year after immunization (*146*). Serum anti-influenza antibodies and nasal IgA elicited by vaccination remain detectable in children vaccinated with LAIV for more than 1 year (*147*). In one community-based nonrandomized open label trial, continued protection from MAARI during the 2000–01 influenza season was demonstrated in children who received only a single dose of LAIV during the 1999–2000 season (*148*).

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) (*149,150*). However, a review of the published literature concluded that no clear evidence existed that immunity declined more rapidly in the elderly (*151*), and additional vaccine doses during the same season do not increase the antibody response. One study that measured the proportion of persons who retained seroprotective levels of anti-influenza antibody declined in all age groups, including those aged ≥65 years, within 1 year of vaccination. However, the proportion in each age group that retained seroprotective antibody levels remained above standards typically used for vaccine licensure for seasonal influenza A (H1N1) and influenza A (H3N2) in all age groups. In this study, anti-influenza B antibody levels declined more quickly, but remained elevated well above licensure threshold for at least 6 months in all age groups (*152*). The frequency of breakthrough infections is not known to be higher among those who were vaccinated early in the season. Infections among the vaccinated elderly might be more likely related to an age-related reduction in ability to respond to vaccination rather than reduced duration of immunity.

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 seasonal inactivated influenza vaccine (*137,142,153–157).* Immunogenicity studies using the influenza A (H1N1) 2009 monovalent vaccine indicated that >90% of children aged ≥9 years responded to a single dose with anti-influenza antibody levels that are considered to be protective. Young children had inconsistent responses to a single dose of the influenza A (H1N1) 2009 monovalent vaccine across studies, with 20% of children aged 6–35 months responding to a single dose with protective anti-influenza antibody levels. However, in all studies, 80%–95% of vaccinated infants, children, and adolescents developed protective anti-influenza antibody levels to the 2009 H1N1 influenza virus after 2 doses (*158–160*; National Institutes of Health, unpublished data, 2010).

In most seasons, one or more seasonal vaccine antigens are changed compared with 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 (*161–163*).

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 (*164*). 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 (*165*).

The antibody response among children at higher risk for influenza-related complications (e.g., children with chronic

medical conditions) might be lower than those reported typically among healthy children (*166,167*). 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 (*168*).

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 <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 received 2 doses in their first year of being vaccinated. Two 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 (*165,169*). Similar results were reported in a case-control study of children aged 6–59 months in which laboratory-confirmed influenza was the outcome measured (*170*). These results, along with the immunogenicity data indicating that antibody responses are substantially higher when young children are given 2 doses, are the basis for the recommendation that all children aged 6 months–8 years who are being vaccinated for the first time should receive 2 vaccine doses separated by ≥4 weeks.

Estimates of vaccine efficacy or effectiveness among children aged ≥6 months have varied by season and study design. 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%) (*139*). 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 (*171*). 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 the 1999–00 influenza season but did not reduce culture-confirmed influenza illness substantially during the 2000–01 influenza season (*172*).

A case-control study conducted during the 2003–04 season indicated vaccine effectiveness of 49% against laboratory-confirmed influenza (*170*). An observational study among children aged 6–59 months with laboratory-confirmed influenza compared with children who tested negative for influenza reported vaccine effectiveness of 44% in the 2003–04 influenza season and 57% during the 2004–05 season (*173*). Partial vaccination (only 1 dose for children being vaccinated for the first time) was not effective in either study. During an influenza season (2003–04) with a suboptimal vaccine match, a retrospective cohort study conducted among approximately 30,000 children aged 6 months–8 years 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 (*169*). Another retrospective cohort 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 (*165*). Among children, TIV effectiveness might increase with age (*139,174*). A systematic review of published studies estimated vaccine effectiveness at 59% for children aged >2 years but concluded that additional evidence was needed to demonstrate effectiveness among children aged 6 months–2 years (*175*).

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. 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 (*176*). The association between vaccination and prevention of asthma exacerbations is unclear. Vaccination was demonstrated to provide protection against asthma exacerbations in some studies (*177,178*).

TIV has been demonstrated to reduce acute otitis media in some studies. Two studies have reported that TIV decreases the risk for influenza-related otitis media by approximately 30% among children with mean ages of 20 and 27 months, respectively (*179,180*). However, a large study conducted among children with a mean age of 14 months indicated that TIV was not effective against acute otitis media (*172*). Influenza vaccine effectiveness against a nonspecific clinical outcome such as 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.

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 (*181–183*). The influenza A (H1N1) 2009 monovalent vaccines were also highly immunogenic; >90% of adults developed levels of anti-influenza antibody considered to be protective (*160,184*). 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 (*77,80,185–187*). 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 (*77,185,186*). Efficacy or effectiveness against laboratory-confirmed influenza illness was substantially lower in studies conducted during different influenza seasons when the vaccine strains were antigenically dissimilar to the majority of circulating strains (*77,80,180,182,185,186*). However, effectiveness among healthy adults against influenza-related hospitalization, measured in the most recent of these studies, was 90% (*188*).

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 (*189–191*). Vaccine effectiveness among adults aged <65 years who are at higher risk for influenza complications typically is lower than that reported for healthy adults. In a case-control study conducted during the 2003–04 influenza season, 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 (*188*). 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 (*188*). 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 (*192*).

Few randomized controlled trials have studied the effect of influenza vaccination on noninfluenza outcomes. A controlled trial conducted in Argentina among 301 adults hospitalized with myocardial infarction or undergoing angioplasty for cardiovascular disease (56% of whom were aged ≥65 years) who were randomized to receive influenza vaccine or no vaccine indicated that a substantially lower percentage (6%) of cardiovascular deaths occurred among vaccinated persons at 1 year after vaccination compared with unvaccinated persons (17%) (*193*). A randomized, double-blind, placebo-controlled study conducted in Poland among 658 persons with coronary artery disease indicated that significantly fewer vaccinated persons had a cardiac ischemic event during the 9 months of follow up compared with unvaccinated persons ($p<0.05$) (*194*).

Observational studies that have measured clinical endpoints without laboratory confirmation of influenza virus infection typically have demonstrated substantial reductions in hospitalizations or deaths among adults with risk factors for influenza complications. For example, in a case-control study conducted during 1999–2000 in Denmark among adults aged <65 years with underlying medical conditions, vaccination reduced deaths attributable to any cause 78% and reduced hospitalizations attributable to respiratory infections or cardiopulmonary diseases 87% (*195*). A benefit was reported after the first vaccination and increased with subsequent vaccinations in subsequent years (*196*). 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 (*197*). 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 (*134,135*). One meta-analysis of published studies concluded that evidence was insufficient to demonstrate that persons with asthma benefit from vaccination (*198*). However, a meta-analysis that examined effectiveness among persons with chronic obstructive pulmonary disease identified evidence of benefit from vaccination (*199*).

Immunocompromised Persons

TIV produces adequate antibody concentrations against influenza among vaccinated HIV-infected persons who have no or minimal AIDS-related symptoms (*200–202*). Among persons who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, TIV might not induce protective antibody titers (*202,203*); a second dose of vaccine does not improve the immune response in these persons (*203,204*). 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/mm^3; however, a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study (*204*). 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 (*95*).

On the basis of certain limited 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 (*205–207*). However, a study among persons with liver transplants indicated reduced immunologic responses to influenza vaccination (*208–210*), especially if vaccination occurred within the 4 months after the transplant procedure (*208*).

Pregnant Women and Neonates

Pregnant women have protective levels of anti-influenza antibodies after vaccination (*211,212*). Passive transfer of anti-influenza antibodies that might provide protection from vaccinated women to neonates has been reported (*211,213–216*). One randomized controlled trial conducted in Bangladesh that provided vaccination to pregnant women during the third trimester demonstrated a 29% reduction in respiratory illness with fever among the mothers and a 36% reduction in respiratory illness with fever among their infants during the first 6 months of life. In addition, infants born to vaccinated women had a 63% reduction in laboratory-confirmed influenza illness during the first 6 months of life (*217*). All women in this trial breastfed their infants (mean duration: 14 weeks). 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 (*218*). In another study conducted during 1995–2001, medical visits for respiratory illness among infants were not reduced substantially (*219*).

Adults Aged ≥65 Years

One prospective cohort study indicated that immunogenicity among hospitalized persons who either were aged ≥65 years or were aged 18–64 years and had one or more chronic medical conditions was similar compared with outpatients (*220*). Immunogenicity data from three studies among persons aged ≥65 years indicate that higher-dose preparations elicit substantially higher hemagglutinin inhibition (HI) titers compared with the standard dose (*221–223*). In one study, prespecified criteria for superiority (defined as when the lower bound of the two-sided confidence interval of a ratio of geometric mean HI titers is >1.5 and the difference in fourfold rise of HI titers is >10%) were demonstrated for influenza A (H1N1) and influenza A (H3N2) antigens among persons aged ≥65 years who received a TIV formulation (Fluzone High-Dose, sanofi pasteur) that contains four times the standard amount of HA antigen (180 mcg [60 mcg of each strain]) of influenza virus hemagglutinin per dose (*222,224*). Prespecified criteria for noninferiority to a standard-dose vaccine (Fluzone, sanofi pasteur) was demonstrated for the influenza B antigen (*222*).

The only randomized controlled trial among community-dwelling persons aged ≥60 years reported a vaccine efficacy of 58% (95% CI = 26%–77%) against laboratory-confirmed influenza illness during a season when the vaccine strains were considered to be well-matched to circulating strains (*225*). Additional information from this trial published separately indicated that efficacy among those aged ≥70 years was 57% (95% CI = -36%–87%), similar to younger persons. However, few persons aged >75 years participated in this study, and the wide confidence interval for the estimate of efficacy among participants aged ≥70 years could not exclude no effect (i.e., included 0) (*226*). Influenza vaccine effectiveness in preventing MAARI among the elderly in nursing homes has been estimated at 20%–40% (*227,228*), 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 (*229,230*). In contrast, some studies have indicated that vaccination can be up-to-80% effective in preventing influenza-related death (*227,231–233*). Among elderly persons not living in nursing homes or similar long-term–care facilities, influenza vaccine is 27%–70% effective in preventing hospitalization for pneumonia and influenza (*234–236*). 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) (*235–240*). 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 controlled adequately for differences in the propensity for healthier persons to be more likely than less healthy persons to receive vaccination (*134,135,232,241–244*).

Immunogenicity of Inactivated 2009 Pandemic H1N1 Vaccines

The 2010–11 seasonal influenza vaccine will contain an influenza A (H1N1) California/7/2009-like strain, which was also the strain used for the 2009 pandemic H1N1 monovalent vaccines. Clinical studies of the 2009 H1N1 monovalent vaccines indicate that this vaccine antigen is immunogenic and response rates are similar to those observed after immunization with influenza A antigens found in typical seasonal influenza vaccines. Among children aged 6–35 months, 19%–92% responded with an HI titer ≥40 at ≥21 days after 1 dose, and >90% responded with an HI titer ≥40 after 2 doses separated

by ≥21 days (*159,160*; National Institutes of Health, unpublished data, 2010). Among children aged 3 –9 years, 44%–93% responded with an HI titer ≥40 at 21 or more days after 1 dose, and >90% responded with an HI titer ≥40 after 2 doses separated by ≥21 days (*158–160*; National Institutes of Health, unpublished data, 2010). Among older children and adults, response rates after 1 dose exceeded 90% (*160,184*) although geometric mean titers were substantially lower among adults aged ≥50 years in one study (*184*) and among adults aged ≥65 years (*160*). Additional data on 2009 H1N1 pandemic vaccine immunogenicity among persons with chronic medical conditions or pregnant women are not yet available, but results from studies in other groups suggest that immunogenicity is likely to be similar to that observed in studies of seasonal vaccine immunogenicity.

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 (*245*). When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of ⅞–1¼ inches is recommended (*245*).

Infants and young children should be vaccinated in the anterolateral aspect of the thigh. A needle length of ⅞–1 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 251,600 children aged <18 years (including 8,476 vaccinations in children aged 6–23 months) who were enrolled in one of five health maintenance organizations within the Vaccine Safety Datalink (VSD) during 1993–1999. This study indicated no increase in clinically important medically attended events during the 2 weeks after inactivated influenza vaccination compared with control periods 3–4 weeks before and after vaccination (*246*). A retrospective cohort study using VSD medical records data from 45,356 children aged 6–23 months during 1991–2003 provided additional evidence supporting overall safety of TIV in this age group. During the 2 weeks after vaccination, TIV was not associated with statistically significant increases in any clinically important medically attended events other than gastritis/duodenitis, compared with 2-week control time periods before and after vaccination. Analysis also indicated that 13 diagnoses, including acute upper respiratory illness, otitis media, and asthma, were substantially less common during the 2 weeks after influenza vaccine. On chart review, most children with a diagnosis of gastritis/duodenitis had acute episodes of vomiting or diarrhea, which usually are self-limiting symptoms. The positive or negative associations between TIV and any of these diagnoses do not necessarily indicate a causal relationship (*247*). The study identified no increased risk for febrile seizure during the 3 days after vaccination. Similarly, no increased risk for febrile seizure was observed during the 14 days after TIV vaccination, after controlling for simultaneous receipt of measles-mumps-rubella (MMR) vaccine which has a known association with febrile seizures in the second week after MMR vaccination (*247*). Another analysis assessed risk for prespecified adverse events in the VSD, including seizures and Guillan-Barré Syndrome (GBS), after TIV during three influenza seasons (2005–06, 2006–07, and 2007–08). No elevated risk for adverse events was identified among 1,195,552 TIV doses administered to children aged <18 years (*248*).

In a study of 791 healthy children aged 1–15 years, postvaccination fever was noted among 12% of those aged 1–5 years, 5% among those aged 6–10 years, and 5% among those aged 11–15 years (*139*). 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) (*249*). These reactions begin 6–12 hours after vaccination and can persist for 1–2 days (*249*).

Data about potential adverse events among children after influenza vaccination are available from the Vaccine Adverse Event Reporting System (VAERS). Because of the limitations of passive reporting systems, determining causality for specific types of adverse events usually is not possible using VAERS data alone. Published reviews of VAERS reports submitted after administration of TIV to children aged 6–23 months indicated 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

TABLE 2. Influenza vaccines for different age groups — United States, 2010–11 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 prefilled syringe	0.0	6–35 mos	1 or 2§	Intramuscular¶
			0.5 mL prefilled syringe	0.0	≥36 mos	1 or 2§	Intramuscular
			0.5 mL vial	0.0	≥36 mos	1 or 2§	Intramuscular
			5.0 mL multidose vial	25.0	≥6 mos	1 or 2§	Intramuscular
TIV	Fluvirin	Novartis Vaccine	5.0 mL multidose vial	24.5	≥4 yrs	1 or 2§	Intramuscular
			0.5 mL prefilled syringe	<1.0			
TIV	Fluarix	Glaxo SmithKline	0.5 mL prefilled syringe	0.0	≥3 yrs	1	Intramuscular
TIV	FluLaval	Glaxo SmithKline	5.0 mL multidose vial	25.0	≥18 yrs	1	Intramuscular
TIV	Afluria	CSL Biotherapies	0.5 mL prefilled syringe	0.0	≥6 mos	1	Intramuscular
			5.0 mL multidose vial	25.0			
TIV High Dose**	Fluzone High-Dose	sanofi pasteur	0.5 mL prefilled syringe	0.0	≥65 yrs	1	Intramuscular
LAIV††	FluMist§§	MedImmune	0.2 mL sprayer, divided dose	0.0	2–49 yrs	1 or 2§	Intranasal

* Immunization providers should check Food and Drug Administration–approved prescribing information for 2010–11 influenza vaccines for the most updated information.

† Trivalent inactivated vaccine.

§ Children aged 6 months–8 years who have never received a seasonal TIV before or who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses, spaced ≥4 weeks apart. Those children aged 6 months–8 years who were vaccinated for the first time in the 2009–10 season with the seasonal 2009–10 seasonal vaccine but who received only 1 dose should receive 2 doses of the 2010–11 influenza vaccine formula, spaced ≥4 weeks apart.

¶ 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.

** Trivalent inactivated vaccine high dose. A 0.5-mL dose contains 60 mcg each of A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens.

†† Live attenuated influenza vaccine.

§§ FluMist is shipped refrigerated and stored in the refrigerator at 36°F–46°F (2°C–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 within the past 12 months should not receive FluMist.

to be febrile (*250,251*). Seizure and fever were the leading serious adverse events (SAEs) reported to VAERS in these studies (*250,2511*); analysis of VSD data did not confirm an association with febrile seizures and influenza vaccination as observed in VAERS (*247*).

In April 2010, Australia's Therapeutic Goods Administration reported preliminary data indicating an elevated risk for febrile reactions, including febrile seizures, among young children in Australia who received the 2010 trivalent vaccine Fluvax Jr., the southern hemisphere inactivated trivalent vaccine for children manufactured by CSL Biotherapies. The risk for febrile seizures was estimated to be as high as five to nine cases per 1,000 vaccinated children aged <5 years, and most seizures occurred among children aged <3 years. Other influenza vaccines, including previous seasonal and pandemic influenza vaccines manufactured by CSL Biotherapies, have not been associated with an increased risk for febrile seizures among children in the United States or Australia. As of July 2010, no cause for the increased frequency of febrile reactions among young children who received the southern hemisphere CSL Biotherapies vaccine had been identified (*252*). ACIP will continue to monitor safety studies being conducted in Australia and might provide further guidance on use of Afluria, the northern hemisphere trivalent vaccine manufactured by CSL Biotherapies later in 2010. Immunization providers should consult updated information on use of the CSL vaccine from CDC (http://www.cdc.gov/flu) and FDA (http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/default.htm).

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 (*253,254*). These local reactions typically were mild and rarely interfered with the recipients' ability to conduct usual daily activities. Placebo-controlled trials demonstrated 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 (*77,198,253–255*). One prospective cohort study indicated that the rate of adverse events was similar among hospitalized persons who either were aged ≥65 years or were aged 18–64 years and had one or more chronic medical conditions compared with outpatients (*220*). Among adults vaccinated in consecutive years, reaction frequencies declined in the second year of vaccination (*256*). In clinical trials, SAEs were reported to occur after vaccination with TIV at a rate of <1%. Adverse events in adults aged ≥18 years reported to VAERS during 1990–2005 were analyzed. The most common adverse events reported to VAERS in adults included injection-site reactions, pain, fever, myalgia, and headache. The VAERS review identified no new safety concerns. Fourteen percent of the TIV VAERS reports in adults were classified as SAEs, similar to proportions seen overall in VAERS. The most common SAE reported after receipt of TIV in VAERS in adults was GBS (*257*). The potential association between TIV and GBS has been an area of ongoing research (see Guillain-Barré Syndrome and TIV). No elevated risk for prespecified events after TIV was identified among 4,773,956 adults in a VSD analysis (*249*).

Solicited injection-site reactions and systemic adverse events among persons aged ≥65 years were more frequent after vaccination with a vaccine containing 180 mcg of HA antigen (Fluzone High-Dose, sanofi pasteur) compared with a standard dose (45 mcg) (Fluzone, Sanofi pasteur vaccines) but were typically mild and transient. In the largest study, 915 (36%) of 2,572 persons who received Fluzone High-Dose reported injection-site pain, compared with 306 (24%) of the 1,260 subjects who received Fluzone. The pain was of mild intensity and resolved within 3 days in the majority of subjects. Among Fluzone High Dose recipients, 1.1% reported moderate to severe fever; this was substantially higher than the 0.3% of Fluzone recipients who reported this systemic adverse event (*222*). During the 6-month follow-up period, SAEs were reported in 6% of the High-Dose recipients and 7% of the Fluzone recipients (*222*).

Pregnant Women and Neonates

FDA has classified TIV as a "Pregnancy Category C" medication, indicating that adequate animal reproduction studies have not been conducted. Available data do not indicate that influenza vaccine causes fetal harm when administered to a pregnant woman. 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 (*258*). 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 (*212*). 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 related causally to vaccination (*259*). Similar results have been reported in certain smaller studies (*211,213,260*), and a recent international review of data on the safety of TIV concluded that no evidence exists to suggest harm to the fetus (*261*). The rate of adverse events associated with TIV was similar to the rate of adverse events among pregnant women who received pneumococcal polysaccharide vaccine in one small randomized controlled trial in Bangladesh, and no severe adverse events were reported in any study group (*217*).

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 (*262*), and two additional studies also have indicated no increase in wheezing among vaccinated asthmatic children (*177*) or adults (*195*). One study reported that 20%–28% of children aged 9 months–18 years with asthma had injection-site pain and swelling at the site of influenza vaccination (*167*), and another study reported that 23% of children aged 6 months–4 years with chronic heart or lung disease had injection-site reactions (*153*). 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 receipt of TIV (25%) than placebo-injection (21%) (*262*). However, a placebo-controlled trial of TIV indicated no difference in injection-site reactions among 53 children aged 6 months–6 years with high-risk medical conditions or among 305 healthy children aged 3–12 years (*157*).

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% (*153*), 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 (*263*). 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 (*264*). 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 (*202,265*). However, more recent and better-designed studies have not documented a substantial increase in the replication of HIV (*266–269*). CD4+ T-lymphocyte cell counts or progression of HIV disease have not been reduced after influenza vaccination among HIV-infected persons compared with unvaccinated HIV-infected persons (*202,270*). 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 (*94,271*).

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 (*205,206*), heart transplants (*207*), or liver transplants (*208*).

Immediate Hypersensitivity Reactions After Receipt of Influenza Vaccines

Vaccine components rarely can cause allergic reactions, also called immediate hypersensitivity reactions, among certain recipients. Immediate hypersensitivity reactions are mediated by preformed immunoglobulin E (IgE) antibodies against a vaccine component and usually occur within minutes to hours of exposure (*272*). Symptoms of immediate hypersensitivity range from mild urticaria (hives) and angioedema to anaphylaxis. Anaphylaxis is a severe life-threatening reaction that involves multiple organ systems and can progress rapidly. Symptoms and signs of anaphylaxis can include but are not limited to generalized urticaria, wheezing, swelling of the mouth and throat, difficulty breathing, vomiting, hypotension, decreased level of consciousness, and shock. Minor symptoms such as red eyes or hoarse voice also might be present *(246,272–275)*.

Allergic reactions might be caused by the vaccine antigen, residual animal protein, antimicrobial agents, preservatives, stabilizers, or other vaccine components (*276*). Manufacturers use a variety of compounds to inactivate influenza viruses and add antibiotics to prevent bacterial growth. Package inserts for specific vaccines of interest should be consulted for additional information. ACIP has recommended that all vaccine providers should be familiar with the office emergency plan and be certified in cardiopulmonary resuscitation (*246*). The Clinical Immunization Safety Assessment (95% CISA) network, a collaboration between CDC and six medical research centers with expertise in vaccination safety, has developed an algorithm to guide evaluation and revaccination decisions for persons with suspected immediate hypersensitivity after vaccination (*272*).

Immediate hypersensitivity reaction after receipt of TIV and LAIV are rare. A VSD study of children aged <18 years in four health maintenance organizations during 1991–1997 estimated the overall risk for postvaccination anaphylaxis after childhood vaccine to be approximately 1.5 cases per 1 million doses administered, and in this study, no cases were identified in TIV recipients (*277*). Anaphylaxis occurring after receipt of TIV and LAIV in adults has been reported rarely to VAERS (*257*).

Some immediate hypersensitivity reactions after receipt of TIV or LAIV are caused by the presence of residual egg protein in the vaccines (*278*). 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. Asking persons if they can eat eggs without adverse effects is a reasonable way to determine who might be at risk for allergic reactions from receiving influenza vaccines (*246*). Persons who have had symptoms such as hives or swelling of the lips or tongue or who have experienced acute respiratory distress after eating eggs should consult a physician for appropriate evaluation to help determine if future influenza vaccine should be administered. Persons who have documented 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 (*279–281*). A regimen has been developed for administering influenza vaccine to asthmatic children with severe disease and egg hypersensitivity (*280*).

Hypersensitivity reactions to other vaccine components also can occur rarely. Although exposure to vaccines containing thimerosal can lead to delayed-type (Type IV) hypersensitivity (*282*), 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 (*283,284*). When reported, hypersensitivity to thimerosal typically has consisted of local delayed hypersensitivity reactions (*283*).

Ocular and Respiratory Symptoms After Receipt of TIV

Ocular or respiratory symptoms have been reported occasionally within 24 hours after TIV administration, but these symptoms typically are mild and resolve quickly without specific treatment. In some trials conducted in the United States,

ocular or respiratory symptoms included red eyes (<1%–6%), cough (1%–7%), wheezing (1%), and chest tightness (1%–3%) (*274,275,285–287*). However, most of these trials were not placebo-controlled, and causality cannot be determined. In addition, ocular and respiratory symptoms are features of a variety of respiratory illnesses and seasonal allergies that would be expected to occur coincidentally among vaccine recipients unrelated to vaccination. A placebo-controlled vaccine effectiveness study among young adults indicated that 2% of persons who received the 2006–07 formulation of Fluzone (sanofi pasteur) reported red eyes compared with none of the controls (p=0.03) (*288*). A similar trial conducted during the 2005–06 influenza season indicated that 3% of Fluzone recipients reported red eyes compared with 1% of placebo recipients; however the difference was not statistically significant (*289*).

Oculorespiratory syndrome (ORS), an acute, self-limited reaction to TIV with prominent ocular and respiratory symptoms, was first described during the 2000–01 influenza season in Canada. The initial case-definition for ORS was the onset of one or more of the following within 2–24 hours after receiving TIV: bilateral red eyes and/or facial edema and/or respiratory symptoms (coughing, wheezing, chest tightness, difficulty breathing, sore throat, hoarseness or difficulty swallowing, cough, wheeze, chest tightness, difficulty breathing, sore throat, or facial swelling) (*290*). ORS was first described in Canada and strongly associated with one vaccine preparation (Fluviral S/F, Shire Biologics, Quebec, Canada) not available in the United States during the 2000–01 influenza season (*291*). Subsequent investigations identified persons with ocular or respiratory symptoms meeting an ORS case-definition in safety monitoring systems and trials that had been conducted before 2000 in Canada, the United States, and several European countries (*292–294*).

The cause of ORS has not been established; however, studies suggest that the reaction is not IgE-mediated (*295*). After changes in the manufacturing process of the vaccine preparation associated with ORS during 2000–01, the incidence of ORS in Canada was reduced greatly (*293*). In one placebo-controlled study, only hoarseness, cough, and itchy or sore eyes (but not red eyes) were strongly associated with a reformulated Fluviral preparation. These findings indicated that ORS symptoms following use of the reformulated vaccine were mild, resolved within 24 hours, and might not typically be of sufficient concern to cause vaccine recipients to seek medical care (*296*).

Ocular and respiratory symptoms reported after TIV administration, including ORS, have some similarities with immediate hypersensitivity reactions. One study indicated that the risk for ORS recurrence with subsequent vaccination is low, and persons with ocular or respiratory symptoms (e.g., bilateral red eyes, cough, sore throat, or hoarseness) after receipt of TIV that did not involve the lower respiratory tract have been revaccinated without reports of SAEs after subsequent exposure to TIV (*297*).

Revaccination in Persons Who Experienced Ocular or Respiratory Symptoms After Receipt of TIV

When assessing whether a patient who experienced ocular and respiratory symptoms should be revaccinated, providers should determine if concerning signs and symptoms of Ig-E mediated immediate hypersensitivity are present (see Immediate Hypersensitivity after Influenza Vaccines). Healthcare providers who are unsure whether symptoms reported or observed after receipt of TIV represent an IgE-mediated hypersensitivity immune response should seek advice from an allergist/immunologist. Persons with symptoms of possible IgE-mediated hypersensitivity after receipt of TIV should not receive influenza vaccination unless hypersensitivity is ruled out or revaccination is administered under close medical supervision (*272*).

Ocular or respiratory symptoms observed after receipt of TIV often are coincidental and unrelated to TIV administration, as observed among placebo recipients in some randomized controlled studies. Determining whether ocular or respiratory symptoms are coincidental or related to possible ORS might not be possible. Persons who have had red eyes, mild upper facial swelling, or mild respiratory symptoms (e.g., sore throat, cough, or hoarseness) after receipt of TIV without other concerning signs or symptoms of hypersensitivity can receive TIV in subsequent seasons without further evaluation. Two studies indicated that persons who had symptoms of ORS after receipt of TIV were at a higher risk for ORS after subsequent TIV administration; however, these events usually were milder than the first episode (*297,298*).

Contraindications and Precautions for Use of TIV

TIV is contraindicated and should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine unless the recipient has been desensitized. 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. Moderate or severe acute illness with or without fever is a precaution for TIV. GBS within 6

weeks following a previous dose of influenza vaccine is considered to be a precaution for use of influenza vaccines.

Guillain-Barré Syndrome and TIV

The annual incidence of GBS is 10–20 cases per 1 million adults (*299*). Substantial evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni* gastrointestinal infections and upper respiratory tract infections, are associated with GBS (*300–302*). A recent study identified serologically confirmed influenza virus infection as a trigger of GBS, with time from onset of influenza illness to GBS of 3–30 days. The estimated frequency of influenza-related GBS was four to seven times higher than the frequency that has been estimated for influenza-vaccine–associated GBS (*303*).

The 1976 swine influenza vaccine was associated with an increased frequency of GBS, estimated at one additional case of GBS per 100,000 persons vaccinated (*304,305*). The risk for influenza-vaccine–associated GBS was higher among persons aged ≥25 years than among persons aged <25 years (*306*). However, obtaining epidemiologic evidence for a small increase in risk for a rare condition with multiple causes is difficult, and no evidence consistently exists for a 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 has demonstrated an increase in GBS associated with influenza vaccines on the order of magnitude seen in 1976–77. 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 (*307–309*). However, in a study of the 1992–93 and 1993–94 seasons, the overall relative risk for GBS was 1.7 (95% 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 (*305*). 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 (*310*). 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 (*304*). Published data from the United Kingdom's General Practice Research Database (GPRD) indicated that influenza vaccine was associated with a decreased risk for GBS, although whether this was associated with protection against influenza or confounding because of a "healthy vaccinee" effect (e.g., healthier persons might be more likely to be vaccinated and also be at lower risk for GBS) (*311*) is unclear. A separate GPRD analysis identified no association between vaccination and GBS for a 9-year period; only three cases of GBS occurred within 6 weeks after administration of influenza vaccine (*312*). A third GPRD analysis indicated that GBS was associated with recent ILI, but not influenza vaccination (*313,314*).

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. Preliminary data from the systems monitoring influenza A (H1N1) 2009 monovalent vaccines suggest that if a risk exists for GBS after receiving inactivated vaccines, it is not substantially higher than that reported in some seasons for TIV (*315*); analyses are ongoing to quantify any potential GBS risk (*316*).

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 (*299*). 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. Among 311 patients with GBS who responded to a survey, 11 (4%) reported some worsening of symptoms after influenza vaccination; however, some of these patients had received other vaccines at the same time, and recurring symptoms were generally mild (*317*). However, as a precaution, persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks of receipt of an influenza vaccine generally should not be vaccinated. 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 also are at high risk for severe complications from influenza.

Vaccine Preservative (Thimerosal) in Multidose Vials of TIV

Thimerosal, a mercury-containing antibacterial compound, has been used as a preservative in vaccines and other medications since the 1930s (*318*) and is used in multidose vial preparations of TIV to reduce the likelihood of bacterial growth. No scientific evidence indicates that thimerosal in vaccines, including influenza vaccines, is a cause of adverse events other than occasional local hypersensitivity reactions in vaccine recipients. In addition, no scientific evidence indicates that thimerosal-containing vaccines are a cause of adverse events among children born to women who received vaccine during pregnancy. The weight of accumulating evidence does not suggest an increased risk for neurodevelopment disorders from exposure to thimerosal-containing vaccines (*319–328*). The U.S. Public Health Service and other organizations have 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 (*319,320,329*). Also, continuing public concerns about exposure to mercury in vaccines has been viewed as a potential barrier to achieving higher vaccine coverage levels and reducing the burden of vaccine-preventable diseases, including influenza. 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 (*246*). ACIP and other federal agencies and professional medical organizations continue to support efforts to provide thimerosal-preservative–free vaccine options.

The U.S. vaccine supply for infants and pregnant women is in a period of transition as manufacturers expand the availability of thimerosal-reduced or thimerosal-free vaccine to reduce the cumulative exposure of infants to mercury. Other environmental sources of mercury exposure are more difficult or impossible to avoid or eliminate (*319*). The benefits of influenza vaccination for all recommended groups, including pregnant women and young children, outweigh concerns on the basis of a theoretic 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 harm from exposure to vaccine containing thimerosal preservative has been demonstrated. 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 identified no difference in the safety profile of preservative-containing compared with preservative-free TIV vaccines in infants aged 6–23 months (*251*).

Nonetheless, some states have enacted legislation banning the administration of vaccines containing mercury; the provisions defining mercury content vary (*330*). 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 routinely available in those states.

Dosage, Administration, and Storage of LAIV

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. Providers should refer to the package insert, which contains additional information about the formulation of this vaccine and other vaccine components. LAIV does not contain thimerosal. LAIV is made from attenuated viruses that are able to replicate efficiently only at temperatures present in the nasal mucosa. LAIV recipients might experience nasal congestion or mild fever, which is probably a result of effects of intranasal vaccine administration or local viral replication. However, LAIV does not typically cause the more prominent systemic symptoms of influenza such as high fever, myalgia, and severe fatigue (*331*).

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 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 (*331*). Vaccine prepared for a previous influenza season should not be administered to provide protection for any subsequent season.

Shedding, Transmission, and Stability of LAIV 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 197 children aged 8–36 months in a child care center assessed transmissibility of vaccine viruses from 98 vaccinated children to the other 99 unvaccinated children; 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 1%–2% (*332*).

Studies assessing whether vaccine viruses are shed have been based on viral cultures or polymerase chain reaction (PCR) detection of vaccine viruses in nasal aspirates from persons who have received LAIV. Among 345 subjects aged 5–49 years, 30% had detectable virus in nasal secretions obtained by nasal swabbing after receiving LAIV. The duration of virus shedding and the amount of virus shed was correlated inversely with age, and maximal shedding occurred within 2 days of vaccination. Symptoms reported after vaccination, including runny nose, headache, and sore throat, did not correlate with virus shedding (*333*). Other smaller studies have reported similar findings (*334,335*). 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 (*336*), and three (13%) of 23 HIV-infected children compared with seven (28%) of 25 children who were not HIV-infected (*337*). 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 (*334–337*).

In clinical trials, viruses isolated from vaccine recipients have retained attenuated phenotypes. In one study, nasal and throat swab specimens were collected from 17 study participants for 2 weeks after vaccine receipt (*338*). 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 (*339*).

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 (*147,340–345*).

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 (*346,347*). This trial included a subset of children aged 60–71 months who received 2 doses in the first season. During the first season (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. During the second season (1997–98), 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 for 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 (*346,348*). 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 (*349*) 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 (*350*). 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 (*148*). LAIV efficacy in preventing laboratory-confirmed influenza also has 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). In clinical trials, an increased risk for wheezing postvaccination was observed in LAIV recipients aged <24 months. An increase in hospitalizations also was observed in children aged <24 months after vaccination with LAIV (*331*).

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. 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 substantially decreased among LAIV recipients compared with those who received placebo. However, vaccine recipients had substantially fewer severe febrile illnesses (19% reduction) and febrile upper respiratory tract illnesses (24% reduction), and substantial 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 (*351,352*). Efficacy against culture-confirmed influenza in a randomized, placebo-controlled study among young adults was 57% in the 2004–05 influenza season, 43% in the 2005–06 influenza season, and 51% in the 2007–08 influenza season, although efficacy in 2004–05 and 2005–06 was not demonstrated to be substantially greater than placebo (*187,288,289*).

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, 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) (*346*). 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%) (*340,342,343,349,353–356*). These symptoms were associated more often with the first dose and were self-limited. A placebo-controlled trial in 9,689 children aged 1–17 years assessed prespecified medically attended outcomes during the 42 days after vaccination (*355*). Following >1,500 statistical analyses in the 42 days after LAIV, elevated risks that were assessed to be biologically plausible were observed for asthma, upper respiratory infection, musculoskeletal pain, otitis media with effusion, and adenitis/adenopathy. The increased risk for wheezing events after LAIV was observed among children aged 18–35 months (RR: 4.06; 90% CI = 1.3–17.9). 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 (*355*). In this study, the rate of SAEs was 0.2% in LAIV and placebo recipients; none of the SAEs was judged to be related to the vaccine by the study investigators (*355*).

In a randomized trial, LAIV and TIV were compared among children aged 6–59 months (*357*). Children with medically diagnosed or treated wheezing within 42 days before enrollment or with a history of severe asthma were excluded from this prelicensure study. Among children aged 24–59 months who received LAIV, the rate of medically significant wheezing, using a prespecified definition, was not greater compared with those who received TIV (*357*). Wheezing was observed more frequently among younger LAIV recipients aged 6–23 months in this study; LAIV is not licensed for this age group.

Another study was conducted among >11,000 children aged 18 months–18 years in which 18,780 doses of vaccine were administered over 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 (*358*). A 4-year, open-label field trial study assessed LAIV safety of >2,000 doses administered to children aged 18 months–18 years with a history of intermittent wheeze who were otherwise healthy. Among these children, no increased risk was reported for medically attended acute respiratory illnesses, including acute asthma exacerbation, during the 0–14 or 0–42 days after LAIV compared with the pre- and postvaccination reference periods (*359*).

Initial data from VAERS during 2007–2008 and 2008–2009, following ACIP's recommendation for use of LAIV in healthy children aged 2–4 years, did not demonstrate an increased frequency of wheezing after administration of LAIV. However, data also indicate that uptake of LAIV among children aged 2–4 years was limited (CDC, unpublished data, 2010). Safety monitoring for wheezing events after LAIV is ongoing.

Adults Aged <50 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 (*346,360*). In one clinical trial among a subset of

healthy adults aged 18–49 years, signs and symptoms reported significantly more often ($p<0.05$) 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) (*144*). A review of 460 reports to VAERS after distribution of approximately 2.5 million doses during the 2003–04 and 2004–05 influenza seasons did not indicate any new safety concerns (*361*). Few of the LAIV VAERS reports (9%) were SAEs; respiratory events (47%) were the most common conditions reported (*361*).

The 2010–11 seasonal live attenuated influenza vaccine will contain an influenza A (H1N1) California/7/2009-like strain, which was also the strain used for the 2009 pandemic H1N1 monovalent live attenuated vaccine. (See Safety Monitoring of Pandemic 2009 H1N1 Monovalent Vaccines for additional information about 2009 H1N1 monovalent vaccine safety data among children and adults.)

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 with CD4+ counts ≥200 cells/mm^3 who received LAIV, no SAEs were reported during a 1-month follow-up period (*336*). 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 (*337*). LAIV was well-tolerated among adults aged ≥65 years with chronic medical conditions (*362*). 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.

Safety Monitoring of Pandemic 2009 H1N1 Monovalent Vaccines

The 2010–11 seasonal influenza vaccine will contain an influenza A (H1N1) California/7/2009-like strain, which was also the strain used for the 2009 pandemic H1N1 monovalent vaccines. Clinical immunogenicity and safety studies of the 2009 H1N1 monovalent vaccines indicate that the reactogenicity profile in children and adults is similar to seasonal influenza vaccines (*158–160,184*). Ongoing comprehensive safety monitoring of the pandemic 2009 H1N1 vaccine was implemented as part of the pandemic immunization program (*363*). A nongovernment working group was established by the National Vaccine Advisory Committee to provide an independent review of safety data, with members representing other federal advisory committees as well as experts in internal medicine, pediatrics, immunology, and vaccine safety (*314*). Data from the first 2 months of implementation of H1N1 vaccination from VAERS and VSD suggested a similar safety profile for influenza A (H1N1) 2009 monovalent vaccines and seasonal influenza vaccines. As of July 2010, analysis and review of vaccine safety data from numerous systems were underway (*314,316*).

Comparisons of LAIV and TIV Efficacy or Effectiveness

Both TIV and LAIV have been demonstrated to be effective in children and adults. However, data directly comparing the efficacy or effectiveness of these two types of influenza vaccines are limited and insufficient to identify whether one vaccine might offer a clear advantage over the other in certain settings or populations. 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 that was conducted 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 (*364*). 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 were conducted to assess efficacy at time points later than 28 days (*364*). In a randomized, double-blind, placebo-controlled trial that was conducted among young adults during the 2004–05 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 attributable primarily to a difference in efficacy against influenza B (*289*). Similar studies conducted during the 2005–06 and 2007–08 influenza seasons identified no significant difference in vaccine efficacy in 2005–06 (*288*), but a 50% relative efficacy or TIV compared with LAIV in the 2007–08 season (*187*).

A randomized controlled clinical trial conducted among children aged 6–59 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 (*357*). In this study, LAIV efficacy was higher compared with TIV against antigenically drifted viruses and well-matched viruses (*357*). 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%) (*365*). An observational study conducted among military personnel aged 17–49 years over three influenza seasons indicated that persons who received TIV had a substantially lower incidence of health-care encounters resulting in diagnostic coding for pneumonia and influenza compared with those who received LAIV. However, among new recruits being vaccinated for the first time, the incidence of pneumonia- and influenza-coded health-care encounters among those received LAIV was similar to those receiving TIV (*366*).

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 (*367*) and 52% increased protection compared with TIV among children aged 6–71 months with recurrent respiratory tract infections (*368*).

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 (*369–371*). Influenza outbreaks have been attributed to low vaccination rates among HCP in hospitals and long-term–care facilities (*372–374*). 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 (*369*). Observational studies have demonstrated that vaccination of HCP is associated with decreased deaths among nursing home patients (*375,376*). 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%) (*377*). Another trial demonstrated substantially lower rates of ILI among residents and staff absences in nursing homes where staff were specifically targeted for vaccination (coverage rate: 70%) compared with nursing homes where no intervention was attempted (coverage rate: 32%) (*378*). A review concluded that vaccination of HCP in settings in which patients also were vaccinated provided significant reductions in deaths among elderly patients from all causes and deaths from pneumonia (*379*).

Epidemiologic studies of community outbreaks of influenza demonstrate that school-aged 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 most studies have not used laboratory-confirmed influenza as an outcome measure. A single-blinded, randomized controlled study conducted 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 (*380*). A randomized, placebo-controlled trial among children with recurrent respiratory tract infections demonstrated that members of families with children who had received a live attenuated virosomal vaccine formulation (not currently available in the United States) were substantially less likely to have respiratory tract infections and reported substantially fewer workdays lost compared with families with children who received placebo (*381*). One cluster randomized trial conducted among rural Hutterite communities in Canada compared laboratory confirmed influenza among unvaccinated persons in communities where children were administered influenza vaccine (coverage: 83%) among children aged 3–15 years with communities where children received hepatitis A vaccine. Influenza vaccine effectiveness for prevention of influenza among unvaccinated persons was 61% (95% CI = 8%–81%) (*382*)

In nonrandomized community-based studies, administration of LAIV has been demonstrated to reduce MAARI (*383,384*) and ILI-related economic and medical consequences (e.g., workdays lost and number of health-care provider visits) among contacts of vaccine recipients (*384*). Households with children attending schools in which school-based LAIV vac-

cination 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 (*384*). During an influenza outbreak during the 2005–06 influenza season, countywide school-based influenza vaccination was associated with reduced absenteeism among elementary and high school students in one county that implemented a school-based vaccination program compared with another county without such a program (*385*). These community-based studies have not used laboratory-confirmed influenza as an outcome.

Some studies also have 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 (*386*). An observational 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) (*387*). 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 that did not provide routine influenza vaccination programs for all children (*383*). 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. 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 (*365*).

The largest study to examine the community effects of increasing overall vaccine coverage was an ecologic study that described the experience in Ontario, Canada, which is the only province to implement a universal influenza vaccination program beginning in 2000. On the basis of models developed from administrative and viral surveillance data, influenza-related mortality, hospitalizations, ED use, and physicians' office visits decreased substantially more in Ontario after program introduction than in other provinces, with the largest reductions observed in younger age groups (*388*). In addition, influenza-associated antibiotic prescriptions were substantially reduced compared with other provinces (*389*).

Efficacy and Effectiveness of Influenza Vaccination When Circulating Influenza Virus Strains Differ from Vaccine Strains

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. In addition, two distinct lineages of influenza B viruses have co-circulated in recent years, and limited cross-protection is observed against the lineage not represented in the vaccine (*70*). 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 reductions in vaccine effectiveness sometimes are observed compared with seasons when vaccine and circulating strains are well-matched (*77,170,188,239,289,390*). However, even during years when vaccine strains were not antigenically well-matched to circulating strains (the result of antigenic drift), substantial protection has been observed against severe outcomes, presumably because of vaccine-induced cross-reacting antibodies (*77,188,289,352*). For example, in one study conducted during the 2003–04 influenza season, when the predominant circulating strain was an influenza A (H3N2) virus that was antigenically different from that season's vaccine strain, effectiveness against laboratory-confirmed influenza illness among persons aged 50–64 years was 60% among healthy persons and 48% among persons with medical conditions that increased the risk for influenza complications (*188*). 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 an influenza B strain from a different lineage compared with vaccine strains (*391*). 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 (*165,169*). However, the 2009–10 seasonal influenza vaccines provided no protection against medically attended illness caused by the pandemic 2009 influenza A (H1N1) virus, because of substantial changes in key viral antigens compared with recently circulating strains (*392*).

Continued improvements in collecting representative circulating viruses and use of surveillance data to forecast antigenic drift are needed. Manufacturing trivalent influenza virus vaccines is a challenging process that takes 6–8 months to complete. 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 that are 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 measures). However, most studies indicate that vaccination reduces or minimizes health care, societal, and individual costs and 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 (*78*).

Studies of influenza vaccination in the United States among persons aged ≥65 years have estimated substantial reductions in hospitalizations and deaths and overall societal cost savings (*234,235*). 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 (*393*).

Economic analyses among adults aged <65 years have reported mixed results regarding influenza vaccination. Two studies in the United States indicated that vaccination can reduce both direct medical costs and indirect costs from work absenteeism and reduced productivity (*79,394*). However, another U.S. study indicated no productivity and absentee savings in a strategy to vaccinate healthy working adults, although vaccination still was estimated to be cost-effective (*395*). In Ontario, Canada, where a universal influenza vaccination program was implemented beginning in 2000, costs were estimated to be approximately twice as much as a targeted vaccination program; however, the number of cases of influenza was reduced 61%, and influenza-related mortality declined 28%, saving an estimated 1,134 QALYs per season overall from a health-care payer perspective. Most cost savings were attributed to the avoidance of hospitalizations. The incremental cost-effectiveness ratio was estimated to be $10,797 Canadian per QALY gained (*396*).

Cost analyses have documented the considerable financial burden of illness among children. In a study of 727 children conducted 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 in the general wards) (*397*). A strategy that focuses 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 (*395*). 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, respectively, using LAIV (*398*). 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 (*399–402*).

Economic analyses most influenced by 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) (*403*). 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 (*403*). Medicare and Vaccines for Children program reimbursement rates in recent years have been less than the costs associated with providing vaccination in a medical practice (*404,405*).

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. One of the *Healthy People 2010* objectives (objective no. 14-29a) includes achieving an influenza vaccination coverage level of 90% for persons aged ≥65 years and among nursing home residents (*406,407*); new strategies to improve coverage are needed to achieve this objective (*408,409*).

On the basis of 2009 final data and 2010 early release data from the National Health Interview Survey (NHIS), estimated national influenza vaccine coverage during the 2007–08 and 2008–09 influenza seasons did not increase substantially among persons aged ≥65 years and those aged 50–64 years (Table 3) and are only slightly higher than coverage levels observed before the 2004–05 vaccine shortage year (*410–412*). In the 2007–08 and 2008–09 influenza seasons, estimated vaccination coverage levels (based on NHIS data) among adults with high-risk conditions aged 18–49 years were 30.4% and 33%, respectively, substantially lower than the *Healthy People 2000* and *Healthy People 2010* objectives of 60% (Table 3) (*406,407*). Among adults with asthma aged 18–49 years and 50–64 years, estimated coverage during the 2006–07 influenza season was 24% and 55% respectively; the national objective for coverage among adults with asthma is 60% (*413*). Epidemiologic studies conducted during the 2009 pandemic indicated that more hospitalizations and deaths were occurring among adults aged <65 years with high-risk conditions than among any other group, and these adults were among the initial target groups to receive the 2009 H1N1 vaccination while vaccine supply was limited (*414*). However, coverage among adults aged <65 years with medical conditions that confer a higher risk for influenza complications was <40% for the 2009 H1N1 monovalent vaccine (*415*).

During the 2009 influenza A (H1N1) pandemic, state-level estimates of seasonal vaccine coverage data for both seasonal influenza and the monovalent 2009 H1N1 vaccines were obtained via telephone surveys conducted by the Behavioral Risk Factor Surveillance System (BRFSS) and the National 2009 H1N1 Flu Survey. By January 31, 2010 estimated state seasonal influenza vaccination coverage among persons aged ≥6 months ranged from 30.3% to 54.5% (median: 40.6%). Median coverage was 41.2% for children aged 6 months–17 years, 38.3% for adults aged 18–49 years with high-risk conditions, 28.8% for adults aged 18–49 years without high-risk conditions, 45.5% for adults aged 50–64 years, and 69.3% for adults aged ≥65 years. These results, compared with the previous season, suggest large increases in coverage for children and a moderate increase for adults aged 18–49 years without high-risk compared with seasonal influenza vaccine coverage estimates in previous seasons (*415,416*). However, vaccine coverage estimates using BRFSS data typically have been higher than estimates derived from NHIS data (*416*).

Studies conducted among children and adults indicate that opportunities to vaccinate persons at risk for influenza complications (e.g., during hospitalizations for other causes) often are missed. In one study, 23% of children hospitalized with influenza and a comorbidity had a previous hospitalization during the preceding influenza vaccination season (*417*). In a study of hospitalized Medicare patients, only 31.6% were vaccinated before admission, 1.9% during admission, and 10.6% after admission (*418*). A study in New York City conducted during 2001–2005 among 7,063 children aged 6–23 months indicated that 2-dose vaccine coverage increased from 1.6% to 23.7% over time; however, 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 (*419*). Using standing orders in hospitals increases vaccination rates among hospitalized persons (*420*), and vaccination of hospitalized patients is safe and stimulates an appropriate immune response (*220*). In one survey, the strongest predictor of receiving vaccination was the survey respondent's belief that he or she was in a high-risk group, based on data from one survey; however, many persons in high-risk groups did not know that they were in a group recommended for vaccination (*421,422*). In one study, over half of adults who did not receive influenza vaccination reported that they would have received vaccine if this had been recommended by their health-care provider (*422*).

Reducing racial/ethnic health disparities, including disparities in influenza vaccination coverage, is an overarching national goal that is not being met (*407*). Estimated vaccination coverage levels in 2008 among persons aged ≥65 years were 70% for non-Hispanic whites, 52% for non-Hispanic blacks, and 52% for Hispanics (*423*). 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 (*424,425*). 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 (*426*). Differences in coverage by race or ethnicity might be partly attributable to differences in beliefs about vaccine effectiveness and safety (*422*). Among nursing home patients, fewer blacks and Hispanics are offered vaccine or receive it compared with whites, and blacks refuse vaccination more frequently (*427*). Disparities in seasonal influenza vaccine coverage among adult whites (43%), blacks (31%), and Hispanics (31%) also were observed during 2009–2010 (*416*).

TABLE 3. Influenza vaccination* coverage levels for the 2006–07, 2007–08, and 2008–09 influenza seasons, among population groups — National Health Interview Survey (NHIS), United States, 2007–2009, and National Immunization Survey (NIS), 2006–2008.

Population Group	2006–07 season			2007–08 season			2008–09 season		
	Crude sample size†	Influenza vaccination level		Crude sample size	Influenza vaccination level		Crude sample size	Influenza vaccination level	
		%	(95% CI§)		%	(95% CI)		%	(95% CI)
Persons with an age indication									
Aged 6–23 mos (NIS¶)	9,710	31.8	(30.2–33.4)	11964	40.7	(39.1–42.2)	NA**	NA	NA
Aged 2–4 yrs	853	37.9	(34.2–41.7)	674	40.3	(35.8–45.0)	652	41.8)	(36.5–47.4)
Aged 50–64 yrs	3,746	36.0	(34.0–38.0)	3,258	38.4	(36.4–40.4)	3,136	40.1	(37.9–42.3)
Aged ≥65 yrs	3,086	65.6	(63.3–67.9)	2,658	66.3	(64.2–68.3)	2,455	65.5	(63.2–67.8)
Persons with high-risk conditions††									
Aged 5–17 yrs	387	33.0	(26.2–40.7)	262	36.2	(29.3–43.6)	273	34.7	(27.8–42.3)
Aged 18–49 yrs	1,186	25.5	(22.4–28.9)	1,049	30.4	(27.1–34.0)	1,087	33.0	(29.7–36.4)
Aged 50–64 yrs	1,117	46.1	(42.8–49.4)	1,001	48.4	(44.7–52.2)	1,048	51.3	(47.2–55.3)
Aged 18–64 yrs	2,303	35.3	(33.0–37.7)	2,050	38.8	(36.2–41.4)	2,135	42.0	(39.3–44.6)
Persons without high–risk conditions									
Aged 5–17 yrs	3,307	17.5	(15.9–19.2)	2,925	21.1	(19.3–23.1)	2,906	24.6	(22.4–26.9)
Aged 18–49 yrs	7,905	15.3	(14.2–16.4)	6,467	17.0	(15.7–18.3)	6,083	19.3	(18.1–20.7)
Aged 50–64 yrs	2,619	31.8	(29.5–34.1)	2,248	34.1	(31.7-36.6)	2,083	34.3	(31.8–36.9)
Pregnant women§§	177	13.4	(8.5–20.5)	113	24.2	(15.1–36.6)	177	11.3	(6.4–19.0)
Health-care workers¶¶	850	44.4	(40.2–48.7)	1,037	49.0	(45.1–52.8)	NA	NA	NA
Household contacts of persons at high risk, including children aged <5 years* **									
Aged 5–17 yrs	741	26.0	(21.5–31.1)	968	24.8	(21.4–28.6)	997	26.0	(23.6–30.3)
Aged 18–49 yrs	1,349	17.0	(15.0–19.4)	1,753	19.5	(17.1–22.1)	1,775	23.7	(21.4–26.2)

* 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 through August.

† Population sizes by subgroups are available at http://www.cdc.gov/flu/professionals/vaccination/pdf/influenza_vaccine_target_populations.pdf.

§ 95% confidence interval.

¶ NIS uses provider-verified vaccination status to improve the accuracy of the estimate. The NIS estimate for the 2008–09 season will be available summer or fall 2010.

** Data not yet available.

†† 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 preaceding 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 (postcoding for a cancer diagnosis was not yet completed at the time of this publication so this diagnosis was not included 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.

*** 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 (as defined in previous footnote for adults at high risk). 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; therefore, certain adults aged 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 children aged 2–4 years was not in place during the 2005–06 season, children aged 2–4 years were included in these calculations as if the recommendation already was in place to facilitate comparison of coverage data for subsequent years.

Reported vaccination levels are low among children at increased risk for influenza complications. Coverage among children aged 2–17 years with asthma was estimated to be 29% for the 2004–05 influenza season (*428*). During the 2007–08 influenza season, the fourth season for which ACIP recommended that all children aged 6–23 months receive vaccination, National Immunization Survey data demonstrated that 41% of children aged 6–23 months received at least 1 dose of influenza vaccine, and 23% were fully vaccinated (i.e., received 1 or 2 doses depending on previous vaccination history); however, results varied substantially among states (*429*). Data from the eight Immunization Information System sentinel sites during 2008–09 indicated that 48% of children aged 6–23 months had received at least 1 dose, and 29% were fully vaccinated (*430*). Coverage levels in these sites for older children were lower and declined with increasing age, ranging from 22% fully vaccinated among children aged 2–4 years to 9% among children aged 13–18 years (*430*). 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 (*431*). 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 (*432*). Implementation of a reminder/recall system in a pediatric clinic increased the percentage of children with asthma receiving vaccination from 5% to 32% (*433*). Reminder/recall systems might be particularly useful when limited vaccine availability requires targeted vaccination of children with high-risk conditions (*434*).

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 (*435–437*), NHIS data demonstrated a vaccination coverage level of only 44.4% among HCP during the 2006–07 season, and 49% during the 2007–08 season (Table 3). Coverage levels during the 2009 pandemic were higher for seasonal vaccine, but remained low for the 2009 pandemic vaccine. By mid-January 2010, estimated vaccination coverage among HCP was 37% for 2009 pandemic influenza A (H1N1) and 62% for seasonal influenza, based on a RAND Corporation–conducted telephone survey that used a somewhat different methodology than NHIS (*438*). Overall, 64% received either of these influenza vaccines, higher coverage than any previous season, but only 35% of HCP reported receiving both vaccines (*438*). Vaccination of HCP has been associated with reduced work absenteeism (*370*) and with fewer deaths among nursing home patients (*375,377*) and elderly hospitalized patients (*379*). 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. HCP who decline vaccination frequently express doubts about the risk for influenza and the need for vaccination, are concerned about vaccine effectiveness and side effects, and dislike injections (*439*).

Vaccine coverage among pregnant women increased during the 2007–08 influenza season, with 24% of pregnant women reporting vaccination, excluding pregnant women who reported diabetes, heart disease, lung disease, and other selected high-risk conditions; seasonal vaccine coverage estimates for 2008–09 were only 11%, however, which is closer to pre-2007 estimates and likely reflects variation in estimates caused by the small sample size rather than significant fluctuations in coverage (Table 3). The causes of persistent low coverage among pregnant women are not fully determined. However, in a study of influenza vaccination acceptance by pregnant women, 71% of those who were offered the vaccine chose to be vaccinated (*440*). 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 (*441*). Pregnancy was an important risk factor during the 2009 H1N1 pandemic (*106,120*), and because the 2009 H1N1 influenza virus is expected to continue circulation during 2010–11, improved vaccination coverage among pregnant women is needed.

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 NHIS, for the three most recent influenza seasons for which these data are available, approximately 84% of all influenza vaccinations were administered during September–November. Among persons aged ≥65 years, the percentage of September–November vaccinations was 92% (*442*). 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 seasonal influenza vaccination annually during National Influenza Vaccination Week (December 6–12, 2010) 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 (*443*). Patient self-reports should be accepted as evidence of influenza vaccination in clinical practice (*443*). However, information on the validity of parents' reports of pediatric influenza vaccination is not yet available.

Vaccination coverage estimates for the influenza A (H1N1) 2009 monovalent vaccines indicate that most doses were administered to the initial target groups, and that, by January 2, 2010 (approximately 90 days after vaccine first became available), an estimated 20% of the U.S. population (61 million persons) had been vaccinated, including 28% of persons in the initial target groups. An estimated 30% of U.S. children aged 6 months–18 years had been vaccinated, including 33% of children aged 6 months–4 years. Estimated coverage for specific initial target groups was 38% for pregnant women, 22% for HCP, and 12% for adults aged 25–64 years with medical conditions that confer a higher risk for influenza complications. Estimates of 2009 H1N1 vaccination coverage levels generally were higher among non-Hispanic whites than among non-Hispanic blacks (*438*). These coverage estimates were in the same approximate range as estimates for seasonal vaccination coverage, suggesting that concerns about the pandemic were not sufficient to overcome some barriers to influenza vaccination among persons at higher risk for influenza complications.

Recommendations for Using TIV and LAIV During the 2010–11 Influenza Season

Routine vaccination of all persons aged ≥6 months is recommended. During the 2009–10 influenza season, an estimated 85% of the U.S. population already had an indication for vaccination (*444*). A universal vaccination recommendation for all persons aged ≥6 months eliminates the need to determine whether each person has an indication for vaccination and emphasizes the importance of preventing influenza among person of all ages. The expansion of recommendations for annual vaccination to include all adults is supported by evidence that influenza vaccines are safe and effective. In addition, morbidity and mortality among adults aged <50 years, including adults who were previously healthy, occurs in every influenza season. Although most adults in this age group who develop influenza-related complications have medical risk factors, some have no previously identified risk factors for influenza complications, or have risk factors but are unaware that they should be vaccinated. Expansion of vaccination recommendations to all adults reflects the need to remove potential barriers to receipt of influenza vaccine, including lack of awareness about vaccine indications among persons at higher risk for influenza complications and their close contacts. Although the capacity now exists to produce sufficient influenza vaccines to meet the predicted increase in demand, the annual supply of influenza vaccine and timing of its distribution cannot be guaranteed in any year.

Further support for expansion of recommendations to include all adults is based on data from the 2009 pandemic experience. Data from epidemiologic studies conducted during the 2009 influenza A (H1N1) pandemic indicates that the risk for influenza complications among adults aged <50 years who had 2009 pandemic influenza A (H1N1) is greater than is typically seen for seasonal influenza (*12*). Explosive outbreaks of 2009 H1N1 influenza among young adults in settings such as college campuses (*445*) were part of the basis for prioritizing vaccination of all persons aged 6 months–24 years during the 2009 pandemic influenza response. Pandemic 2009 influenza A (H1N1)-like viruses are expected to continue to circulate during the 2010–11 influenza season, and a substantial proportion of young adults do not yet have immunity as a result of natural infection with this virus (*446*). In addition, severe infections were observed more frequently in some younger adults who did not have previously recognized risk factors for influenza-related complications, including obese persons, persons in certain racial and ethnic minority groups, and postpartum women (*24,48,85,86,90,447*).

Both TIV and LAIV prepared for the 2010–11 season will include A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens. The influenza B virus component of the 2010–11 vaccine is from the Victoria lineage (*448*). These viruses will be used because they are representative of influenza viruses that are predicted to be circulating in the United States during the 2010–11 influenza season and have favorable growth properties in eggs. The H1N1 strain recommended for the 2010–11 trivalent influenza vaccine is the same as the vaccine strain in the 2009 H1N1 monovalent vaccines given during the pandemic. The 2009 pandemic influenza virus-derived vaccine strain has replaced the seasonal influenza H1N1 vaccine strains that were present in the vaccine since 1977.

Healthy nonpregnant persons aged 2–49 years can choose to receive either TIV or LAIV. Some TIV formulations are FDA-licensed for use in persons as young as age 6 months (see Recommended Vaccines for Different Age Groups). Persons aged ≥65 years can be administered either standard-dose TIV 15 mcg per vaccine strain) or the newly licensed TIV containing 60 mcg HA antigen per vaccine strain (Sanofi pasteur). TIV is licensed for use in persons with high-risk conditions (Table 2). 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 (if appropriate) or TIV should receive 2 doses of age-appropriate vaccine in the same season, with a single dose during subsequent seasons. Persons who received a 2009 H1N1 monovalent vaccine should still be vaccinated with the 2010–11 formulation of TIV or LAIV to provide protection against influenza A (H3N2) and influenza B strains that are expected to circulate during the 2010–11 influenza season. In addition, the duration of protection after receipt of the 2009 H1N1 monovalent influenza vaccines is unknown and likely declines over time.

In addition, 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 persons at risk for medical complications from influenza. These persons, their household and close contacts, and all HCP should continue to be a focus of vaccination efforts as providers and programs transition to routinely vaccinating all persons aged ≥6 months (Box). Despite a recommendation for vaccination for approximately 85% of the U.S. population over the past

two seasons, <50% of the U.S. population received a seasonal influenza vaccination in 2008–09 or 2009–10. Estimated vaccine coverage for the 2009 H1N1 monovalent vaccine coverage was <40% (*438*).

Rationale for Vaccination of Specific Populations

Children Aged 6 Months–18 Years

Annual vaccination for all children aged 6 months–18 years is recommended. Healthy children aged 2–18 years can receive either LAIV or TIV. Children aged 6–23 months, and those aged 2–4 years who have evidence of asthma, wheezing, or who have medical conditions that put them at higher risk for influenza complications should receive TIV (see Considerations When Using LAIV).

Recommendations to provide routine influenza vaccination to all children and adolescents aged 6 months–18 years are made on the basis of 1) accumulated evidence that influenza vaccine is effective and safe for children (see Influenza Vaccine Efficacy, Effectiveness, and Safety); 2) increased evidence that influenza has substantial adverse impacts among 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 children and adolescents will improve vaccine coverage levels among children who already have 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, potential benefits include the indirect effect of reducing influenza among persons who have close contact with children and reducing overall transmission within communities (*449*). 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 (*365,386,387*).

All children aged 6 months–8 years who receive a seasonal influenza vaccine for the first time should be administered 2 doses. Children aged 6 months–8 years who received a seasonal vaccine for the first time during 2009–2010 but who received only 1 dose should receive 2 doses, rather than 1, during 2010–2011. In addition, for the 2010–11 influenza season, children aged 6 months–8 years who did not receive at least 1 dose of an influenza A (H1N1) 2009 monovalent vaccine should receive 2 doses of a 2010–11 seasonal influenza vaccine, regardless of previous influenza vaccination history (Figure 3). Children aged 6 months–8 years for whom the previous 2009–10 seasonal or influenza A (H1N1) 2009 monovalent vaccine history cannot be determined should receive 2 doses of a 2010–11 seasonal influenza vaccine. For all children, the second dose of a recommended 2-dose series should be administered ≥4 weeks after the initial dose.

The recommendation to administer 2 doses to children who did not receive an influenza A (H1N1) 2009 monovalent vaccine, regardless of previous seasonal influenza vaccine history, is new. This change in recommendations is made on the basis of data from several immunogenicity studies indicating that children aged <9 years have lower antibody levels and lower rates of protective response after receiving a single dose of vaccines containing the 2009 pandemic H1N1 antigen compared with older children and adults. However, >80% of infants and children aged <3 years and >90% of older children who receive 2 doses of a vaccine that contains the 2009 H1N1 antigen develop protective antibody levels (*158,160*; National Institutes of Health, unpublished data, 2010). Therefore, current immunogonicity data indicate that at least 2 doses of the 2009 H1N1 vaccine antigen are needed to produce protective antibody levels for the majority of young children. This recommendation includes children who have received at least 2 doses of a seasonal influenza vaccine in a previous season and who would normally be scheduled to only receive 1 seasonal vaccine dose in the 2010–11 season.

A second dose is not necessary for children being vaccinated for the first time who were aged 8 years at the time of the first dose but who are seen again after they have reached age 9 years. Children aged 6 months–8 years who had never received a seasonal influenza vaccine previously and who received only the 2009 H1N1 monovalent vaccine should receive 2 doses of the 2010–11 seasonal influenza vaccine, to provide adequate protection against influenza A (H3N2) and influenza B. If possible, children recommended for 2 doses of seasonal influenza

FIGURE 3. Number of 2010–2011 seasonal influenza vaccine doses recommended for children

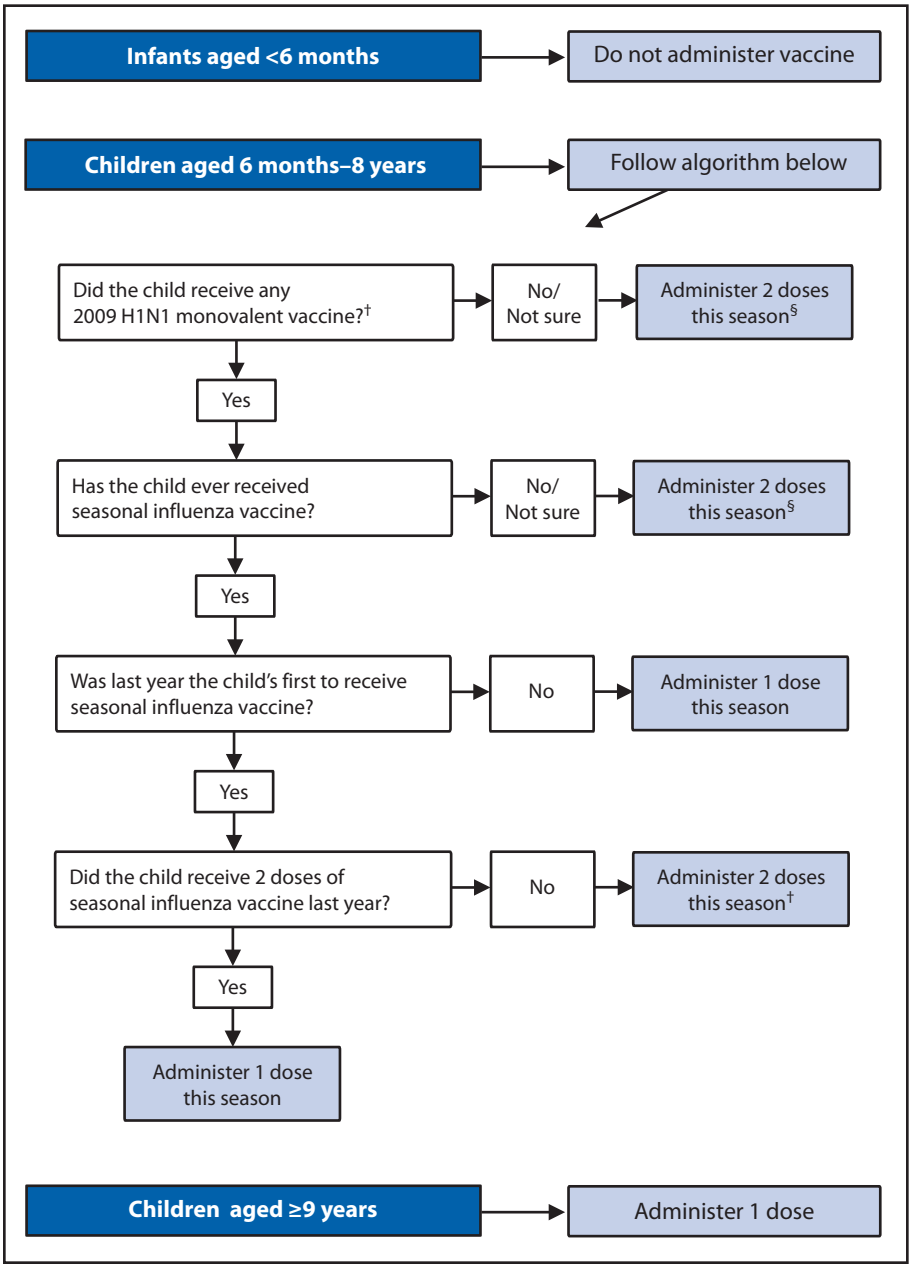


*Figure developed by CDC with the American Academy of Pediatrics, Committee on Infectious Diseases.

† Children who had a laboratory-confirmed 2009 pandemic H1N1 virus infection (e.g., reverse transcription–polymerase chain reaction or virus culture specific for 2009 pandemic influenza A(H1N1) virus) are likely to be immune to this virus. At provider discretion, these children can have a "Yes" entered at this box, and proceed down the path to the next box to determine whether two doses are indicated based on seasonal vaccine history. However, if no test result is available and no influenza A(H1N1) 2009 monovalent vaccine was administered, enter "no" here.

§ Interval between 2 doses is ≥4 weeks.

vaccine should receive them both before onset of influenza season. However, vaccination, including the second dose, is recommended even after influenza virus begins to circulate in a community.

Children who had a laboratory-confirmed 2009 pandemic influenza A (H1N1) virus infection (e.g., reverse transcription–PCR or virus culture specific for 2009 pandemic influenza A (H1N1) virus) are likely to be immune to this virus. There is no known harm in providing 2 doses of 2010–11 seasonal influenza vaccine to a child who has been infected previously with the 2009 pandemic influenza A (H1N1) virus. However, at immunization provider discretion, these children can receive the appropriate number of seasonal vaccine doses (1 or 2) without regard to previous receipt of the influenza A (H1N1) 2009 monovalent vaccine. However, most children did not receive specific diagnostic testing (i.e., were untested or received a rapid antigen test), and for others, evidence of laboratory confirmation using a diagnostic test specific for the 2009 H1N1 antigen is unavailable to immunization providers. If no test results are available and no influenza A (H1N1) 2009 monovalent vaccine had been administered, children who had a febrile respiratory illness during 2009–2010 cannot be assumed to have had influenza A (H1N1) virus infection, and these children should receive 2 doses of the 2010–11 seasonal vaccine. Providers who are determining the number of vaccine doses recommended for children with laboratory-confirmed 2009 pandemic influenza A (H1N1) virus infection (Figure 3) should also determine whether 2 doses are indicated on the basis of seasonal vaccine history.

Persons at Risk for Medical Complications

Vaccination to prevent influenza is particularly important for persons who are at increased risk for severe complications from influenza or at higher risk for influenza-related outpatient, ED, or hospital visits. When vaccine supply is limited, vaccination

efforts should focus on delivering vaccination to the following persons:

- all children aged 6 months–4 years (59 months);
- all persons aged ≥50 years;
- adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurological, hematologic, or metabolic disorders (including diabetes mellitus);
- persons who have immunosuppression (including immunosuppression caused by medications or by HIV);
- women who are or will be pregnant during the influenza season;
- 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;
- residents of nursing homes and other long-term–care facilities;
- American Indians/Alaska Natives;
- persons who are morbidly obese (BMI ≥40);
- HCP;
- 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 higher risk for severe complications from influenza.

For children, the risk for severe complications from influenza is highest among those aged <2 years, who have much higher rates of hospitalization for influenza-related complications compared with older children (*7,54,61*). Medical care and ED visits attributable to influenza are increased among children aged <5 years compared with older children (*54*). Chronic neurologic conditions are thought to place persons at higher risk for influenza complications on the basis of the potential for compromised respiratory function or the handling of respiratory secretions, both of which can increase the risk for aspiration; such conditions include cognitive dysfunction, spinal cord injuries, seizure disorders, or neuromuscular disorders (*46*).

An observational study conducted during the 2009 H1N1 pandemic indicated that morbid obesity, and possibly obesity, might be a new or previously unrecognized risk factor for influenza-related complications (*85*). In another study, American Indians/Alaska Natives were demonstrated to have a higher risk for death from 2009 H1N1 influenza (*90*). These medical and race/ethnicity risk factors might reflect a higher prevalence of underlying chronic medical conditions, including conditions that are not known by the patient or provider. Other minority groups, including blacks, have been demonstrated to have higher incidence of hospitalizations as a result of laboratory-confirmed influenza compared with whites (CDC, unpublished data, 2010); additional study is needed to determine the reasons. Persons who have chronic medical conditions, who are pregnant, or who are at higher risk for 2009 H1N1 influenza-related complications should be encouraged to begin receiving a routine annual influenza vaccination as programs and practitioners transition to providing vaccination for all persons aged ≥6 months (Box).

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

All persons aged ≥6 months should be vaccinated annually. As providers and programs transition to providing annual vaccination to all persons, continued emphasis should be placed on vaccination of persons who live with or care for persons at higher risk for influenza-relate complications. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to persons at higher risk for influenza-related complications as well as these persons:

- HCP;
- household contacts (including children) and caregivers of children aged ≤59 months (i.e., aged <5 years) and adults aged ≥50 years; and
- household contacts (including children) and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza.

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 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 of persons in groups at high risk, including contacts such as children or mothers of newborns.

In addition, because children aged <5 years are at increased risk for influenza-related hospitalization (*7,47,61,450,451*) 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 these children.

Healthy HCP and persons aged 2–49 years who are contacts of persons in these groups and who are not contacts of severely immunocompromised persons living in a protected

environment (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 and persons 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 long-term–care facilities who have contact with patients or residents, and students in these professions who will have contact with patients (*436,437,452*).

Facilities that employ HCP should provide vaccine to workers by using approaches that have been demonstrated to be effective in increasing vaccination coverage. The HCP influenza coverage goal should be vaccination of 100% of employees who do not have medical contraindications. 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 (*437,453,454*). Influenza vaccination rates among HCP within facilities should be measured regularly and reported, and ward-, unit-, and specialty-specific coverage rates should be provided to staff and administration (*437*).

Policies that work best to achieve this coverage goal might vary among facilities. 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 (*435,437,455,456*). A mandatory influenza vaccination policy for HCP, exempting only those with a medical contraindication, has been demonstrated to be a highly effective approach to achieving high vaccine coverage among HCP (*456–458*). Hospitals and health-care systems that have mandated vaccination of HCP often have achieved coverage rates of >90%, and persons refusing vaccination who do not have a medical contraindication have been required to wear a surgical mask during influenza season in some programs (*458*). Efforts to increase vaccination coverage among HCP using mandatory vaccination policies are supported by various national accrediting and professional organizations, including the Infectious Diseases Society of America, and in certain states by statute (*457,459,460*). Worker objections, including legal challenges, are an important consideration for facilities considering mandates (*459,461*). Studies to assess the impact of mandatory HCP vaccination on patient outcomes are needed.

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 (*462*). Some states have regulations regarding vaccination of HCP in long-term–care facilities (*463*), require that health-care facilities offer influenza vaccination to HCP, or require that HCP either receive influenza vaccination or indicate a religious, medical, or philosophic reason for not being vaccinated (*464,465*).

Children aged <6 months are not recommended for vaccination, and antivirals are not licensed for use among infants. Protection of young infants, who have hospitalization rates similar to those observed among the elderly, depends on vaccination of the infants' close contacts. A recent study conducted in Bangladesh demonstrated that infants born to vaccinated women have significant protection from laboratory-confirmed influenza, either through transfer of influenza-specific maternal antibodies or by reducing the risk for exposure to influenza that might occur through vaccination of the mother (*217*). All household contacts, health-care and day care providers, and other close contacts of young infants should be vaccinated.

Immunocompromised persons are at risk for influenza complications but might have inadequate protection after vaccination. Vaccination of close contacts of immunocompromised persons, including HCP, might reduce the risk for influenza transmission. In 2006, a joint recommendation from ACIP and the Hospital Infection Control Practices Advisory Committee (HICPAC) recommended that TIV be used 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) (*437,466*). To reduce the theoretic risk for vaccine virus transmission, ACIP/HICPAC recommended that HCP who receive LAIV should avoid providing care for severely immunosuppressed patients requiring a protected environment for 7 days after vaccination, and 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. Healthy nonpregnant persons aged 2–49 years, including HCP, who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with chronic immunocompromising conditions such as HIV infection, corticosteroid or chemotherapeutic medication use, or who are cared for in other hospital areas such as neonatal intensive care units) can receive TIV or LAIV.

The rationale for avoiding use of LAIV among HCP or other close contacts of severely immunocompromised patients is the theoretic risk that a live attenuated vaccine virus could be transmitted to the severely immunosuppressed person. However, instances of LAIV transmission from a recently vaccinated person to an immunocompromised contact in health-care settings have not been reported. In addition, the temperature-sensitive and attenuated viruses present in LAIV do not cause illness when administered to immunocompromised persons with HIV infection (*336*), children undergoing cancer treatment (*467*), or immunocompromised ferrets given dexamethasone and cytarabine (*468*). Concerns about the theoretic risk posed by transmission of live attenuated vaccine viruses contained in LAIV to patients should not be used to justify preferential use of TIV in health-care settings other than inpatient units that house severely immunocompromised patients requiring protected environments. Some health-care facilities might choose to not restrict use of LAIV in close contacts of severely immunocompromised persons, based on the lack of evidence for transmission in health-care settings since licensure in 2004.

Pregnant and Postpartum Women

Vaccination of pregnant women protects women and newborns. The American College of Obstetricians and Gynecologists and the American Academy of Family Physicians also have previously recommended routine vaccination of all pregnant women (*469*). Women who are postpartum are also at risk for influenza complications and should be vaccinated (*108*). 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 and postpartum women. LAIV is not licensed for use in pregnant women, but postpartum women can receive LAIV or TIV. Pregnant and postpartum women do not need to avoid contact with persons recently vaccinated with LAIV.

Breastfeeding Mothers

Breastfeeding does not affect the immune response adversely and is not a contraindication for vaccination (*246*). Unless contraindicated because of other medical conditions, women who are breastfeeding can receive either TIV or LAIV. In one randomized controlled trial conducted in Bangladesh, infants born to women vaccinated during pregnancy had a lower risk for laboratory-confirmed influenza. However, the contribution to protection from influenza of breastfeeding compared with passive transfer of maternal antibodies during pregnancy was not determined (*217*).

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 (*470,471*). 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 (*472*).

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,
- with organized tourist groups at any time of year, or
- 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, and revaccination is not recommended. Persons at high risk who receive the previous season's vaccine before travel should be receive 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.

Recommended Vaccines for Different Age Groups

Each season, vaccination providers should check the latest information on FDA approval of the 2010–11 seasonal influenza vaccines and CDC recommendations for use of these vaccines to determine which vaccines are licensed for use in any particular age. Immunization providers should consult updated information on use of influenza vaccines from CDC (available at http://www.cdc.gov/flu) and FDA (available at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/vaccinesafety/default.htm). The following information is based on approvals for the 2009–10 seasonal influenza vaccines.

When vaccinating children aged 6–35 months with TIV, health-care providers should use TIV that has been licensed by FDA for this age group (i.e., TIV manufactured by sanofi pasteur [FluZone] or CSL Biotherapies (Afluria) (*286*). TIV

from Novartis (Fluvirin) is FDA-approved in the United States for use among persons aged ≥4 years (*287*). One TIV preparation from GlaxoSmithKline (Fluarix) is licensed for use in children aged ≥3 years, and another preparation (FluLaval) is labeled for use in persons aged ≥18 years (*274,275,285*). LAIV from MedImmune (FluMist) is recommended for use by healthy nonpregnant persons aged 2–49 years (Table 2) (*360*). If a pediatric vaccine dose (0.25mL) is administered inadvertently to an adult, an additional pediatric dose (0.25 mL) should be given to provide a full adult dose (0.5mL). If the error is discovered later (after the patient has left the vaccination setting), an adult dose should be administered as soon as the patient can return. Vaccination with a formulation approved for adult use should be counted as a dose if inadvertently administered to a child.

An inactivated trivalent influenza vaccine (Fluzone High-Dose, sanofi pasteur.) that contains an increased amount of influenza virus antigen compared with other inactivated influenza vaccines was licensed in 2009. Fluzone High-Dose is available as single dose prefilled syringe formulation distinguished from Fluzone by a gray syringe plunger rod (*224*). As with other 2010–11 influenza vaccines, Fluzone High-Dose will contain the three recommended virus strains (A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens) (*136*). ACIP recommends that all persons aged ≥65 years receive an inactivated 2010–11 seasonal influenza vaccination but has not expressed a preference for Fluzone High-Dose or any other inactivated influenza vaccine for use in persons aged ≥65 years (*473*). Whether or not the higher postvaccination immune responses observed among Fluzone High-Dose vaccine recipients (*221–223*) will result in greater protection against influenza illness is not known. High-dose vaccine should not be administered to persons aged <65 years. Several other 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. Providers should review the formulation and packaging before administering influenza vaccine to ensure the product used is appropriate for the age of the patient.

Influenza Vaccines and Use of Influenza Antiviral Medications

Administration of TIV to persons receiving influenza antivirals for treatment or chemoprophylaxis 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. If influenza antiviral medications are administered within 2 weeks after receipt of LAIV, the vaccine dose should be repeated 48 or more hours after the last dose of antiviral medication. Persons receiving antivirals within the period 2 days before to 14 days after vaccination with LAIV should be revaccinated at a later date with any approved vaccine formulation (*246,331*).

Considerations When Using LAIV

LAIV is an option for vaccination of healthy nonpregnant persons aged 2–49 years without contraindications, including HCP and other close contacts of high-risk persons (excepting severely immunocompromised hospitalized persons who require care in a protected environment). The precaution regarding use of LAIV in protected environments is based upon a theoretic concern that the live attenuated vaccine virus could be transmitted to severely immunocompromised persons. However, no transmission of LAIV in health-care settings ever has been reported, and because these viruses are also cold-adapted (and cannot effectively replicate at normal body temperature) the risk for transmitting a vaccine virus to a severely immunocompromised person and causing severe infection appears to be extremely low. HCP working in environments such as neonatal intensive care, oncology, or labor and delivery units can receive LAIV without any restrictions.

No preference is indicated for LAIV or TIV when considering vaccination of healthy nonpregnant persons aged 2–49 years. 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 immediately 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 (*331*).

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.

Clinicians and vaccination programs should screen for asthma or wheezing illness (or history of wheezing illness) when considering use of LAIV for children aged 2–4 years, and should avoid use of this vaccine in children with asthma or a wheezing episode within the previous 12 months. 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 wheezing (*474*). 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, use of TIV, or deferral of administration should be considered until resolution of the illness, is recommended.LAIV is approved for use in persons aged 2–49 years. However, the effectiveness or safety of LAIV is not known or is of potential concern for certain persons, and LAIV is not recommended for these persons. Do not administer LAIV to the following groups:

- persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or to eggs;
- children aged <2 years, because of an increased risk for hospitalization and wheezing observed in clinical trials;
- 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;
- persons with asthma;
- persons aged ≥50 years;
- adults and children who have chronic pulmonary, cardiovascular (except isolated hypertension), renal, hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders;
- adults and children who have immunosuppression (including immunosuppression caused by medications or by HIV);
- children or adolescents aged 6 months–18 years receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza virus infection); or
- pregnant women.

A moderate or severe illness with or without fever is a precaution for use of LAIV. Development of GBS within 6 weeks following a previous dose of influenza vaccine is considered to be a precaution for use of influenza vaccines. LAIV should not be administered to close contacts of immunosuppressed persons who require a protected environment.

Personnel Who Can Administer LAIV

Low-level introduction of vaccine viruses into the environment probably is unavoidable when administering LAIV, but no instances have been reported of illness or attenuated vaccine virus infections among inadvertently exposed HCP or immunocompromised patients. The risk for acquiring vaccine viruses from the environment is unknown but is probably low; in addition, vaccine viruses are cold-adapted and attenuated, and unlikely to cause symptomatic influenza. 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 (*331,475*). Among adults aged ≥50 years, the safety and immunogenicity of zoster vaccine and TIV was similar whether administered simultaneously or spaced 4 weeks apart (*476*). In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent (*246*). 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

Influenza vaccination levels increased substantially over the past 20 years, and a record proportion of children received seasonal or pandemic influenza A (H1N1) vaccines in 2009–10. However, a majority of persons in most groups recommended for vaccination do not receive an annual vaccine. Strategies to improve vaccination levels, including using reminder/recall systems and standing orders programs (*408,409,423*), should be implemented whenever feasible. Vaccination efforts should begin as soon as vaccine is available and continue through the influenza season, which typically extends through April. 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., schools, 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 6–12, 2010) provide opportunities to refocus public attention on the benefits, safety, and availability of influenza vaccination throughout the influenza season. The 2009 pandemic provided opportunities for innovative programs to administer vaccine in a variety of settings, and lessons learned from this experience should be applied when developing routine influenza immunization programs.

Discussing Risk for Adverse Events after Vaccination

Concern about vaccine safety is often cited by persons who refuse vaccination, including health-care workers. When educating patients about adverse events, clinicians should provide Vaccine Information Statements (available at http://www.cdc.gov/vaccines/pubs/vis), and emphasize the risks and benefits of vaccination. Providers should inform patients or parents 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; 3) many patients will experience no side effects and most known side effects are mild, transient, and manageable, such as injection-site pain after receipt of TIV or rhinorrhea after LAIV; and 4) concomitant symptoms or respiratory disease unrelated to vaccination with either TIV or LAIV can occur after vaccination.

Patients concerned about more severe adverse events might be reassured by discussing the many safety studies available, the safety monitoring systems currently in use, and the immunization provider or program's previous experience with influenza vaccines. Providers concerned about the risk for severe adverse events or who observe or report a severe adverse event after vaccination should keep in mind that relatively common events will occur by chance after vaccination. For example, one study used the background rate of spontaneous abortion to estimate that 397 per 1 million vaccinated pregnant women would be predicted to have a spontaneous abortion within 1 day of vaccination (*477*). Even rare events will be observed by chance after vaccination if large numbers of persons are vaccinated, as occurs with annual influenza immunization campaigns. For example, if a cohort of 10 million individuals was vaccinated, approximately 22 cases of GBS and six cases of sudden death would be expected to occur within 6 weeks of vaccination as coincident background cases unrelated to vaccination (*477*).

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, vaccination will not be denied to parents who cannot pay an 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 2009–10 influenza season, 114 million doses of seasonal influenza vaccine were distributed in the United States. However, influenza vaccine distribution delays or vaccine shortages remain possible. One factor that affects production is the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains. Multiple manufacturing and regulatory issues also might affect the production schedule.

If supplies of seasonal influenza vaccine 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. National guidance for tiered use of influenza vaccine during prolonged distribution delays or supply shortfalls will be based primarily on epidemiologic studies indicating that certain persons are at higher risk for influenza infection or influenza-related complications, as well as which vaccine formulations have limited supplies. When epidemiologic studies or other data that would guide tiered use are unavailable, persons previously demonstrated to be at higher risk for influenza or influenza-related complications should be among those targeted by immunization programs for receipt of limited supplies. Even if vaccine use is not restricted to certain persons known to be at higher risk for influenza complications, strategies employed by immunization programs and providers during periods of limited vaccine availability should emphasize outreach to persons at higher risk for influenza or influenza-related complications (Box), or who are part of populations that have limited access to medical care. 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 determined precisely 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 often is 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. 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 (*478,479*).

All children aged 6 months–8 years who are recommended for 2 doses should receive their first dose as soon after vaccine becomes available as is feasible and should receive the second dose ≥4 weeks later. This practice increases the opportunity for both doses to be administered before or shortly after the onset of influenza activity.

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, including school-based clinics, are available at http://www.cdc.gov/flu/professionals/vaccination/vax_clinic.htm, http://www.cdc.gov/h1n1flu/vaccination/statelocal/settingupclinics.htm, and http://www.cdc.gov/h1n1flu/vaccination/slv.

During a vaccine shortage or delay, substantial proportions of TIV or LAIV doses might not be released and distributed until November and December or later. When the vaccines are 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.

Strategies for Implementing Vaccination Recommendations

The expansion of the recommendations to all persons aged ≥6 months highlights the importance of making influenza vaccine readily accessible in a variety of settings. Many of the persons at highest risk for complications will likely continue to be vaccinated in health-care settings. However, vaccination in health-care settings must increasingly be complemented by vaccination in nonmedical settings that increase convenience and access. During the 2009–2010 H1N1 Vaccination Program, substantial efforts were made at the state and local level to direct vaccine to locations such as schools, pharmacies, workplaces, and health departments.

Health-Care Settings

Health-care settings remain a central component of an overall influenza vaccination strategy. Studies consistently show that provider recommendation is the strongest predictor of

vaccination (*425,480,481*). While nonmedical settings play an important role for those motivated to seek vaccination, health-care settings are critical for facilitating vaccination of all those who come into contact with the setting, including those who might not seek out vaccination.

Successful vaccination programs combine publicity and education for HCP and other potential vaccine recipients, 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 (*409,482,483*). 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 and report adverse events. The Centers for Medicare and Medicaid Services (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 (*484*). 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 (*485,486*). 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 (*487*). In addition, physician reminders (e.g., flagging charts) and patient reminders are recognized strategies for increasing rates of influenza vaccination (*483*).

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 offer vaccine to all patients during visits throughout the influenza season. The offer of vaccination and its receipt or refusal should be documented in the medical record or immunization information system. Patients 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., EDs and walk-in clinics) should offer vaccinations throughout the influenza season or provide written information regarding why, where, and how to obtain the vaccine. This written information should be provided in languages at literacy levels appropriate for the populations served by the facility.

Acute-Care Hospitals

Hospitals should serve as a key setting for identifying persons at increased risk for influenza complications. Unvaccinated persons without contraindications 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.

Nursing Homes and Other Long-Term–Care Facilities

Vaccination should be provided routinely to all residents of long-term–care facilities. If possible, all residents should be vaccinated 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 (*488*). Informed consent is required, but this does not necessarily mean a signed consent must be present in order to implement a standing order for vaccination (*489*). Residents admitted after completion of the vaccination program at the facility should be vaccinated at the time of admission.

Lower rates of severe illness among older persons were observed during the 2009 pandemic, but outbreaks among residents of nursing homes and other long-term–care facilities still occurred (*490*). Although the influenza viruses that will circulate during the 2010–11 season are unknown, multiple influenza types and subtypes that often infect and cause severe infections among older adults (e.g., H3N2) circulate each winter influenza season. The 2010–11 influenza vaccine formulation should be administered to all residents and staff.

Since October 2005, 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 (*486,491*).

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

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.

Vaccination for 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 (*437,455,462*).

Other Settings

Influenza vaccination has increasingly become available in nonmedical settings. In the 2009–2010 vaccination season, 33% of seasonal influenza vaccinations occurred in health departments, pharmacies or drug stores, workplaces, schools, or other nonmedical locations (CDC, unpublished data, 2009). The proportion of 2009 H1N1 vaccine administered in these settings was 45% (CDC, unpublished data, 2010). Availability of vaccine in a range of settings such as pharmacies and the workplace is especially important for persons who do not regularly accesss the health-care system. In addition, with the recent expansion of the influenza recommendations to include all persons aged ≥6 months, implementation of strategies that are sustainable beyond vaccination in provider offices are necessary. School-located vaccination provides an opportunity to address the challenges associated with large numbers of children to vaccinate, a short window of time for vaccination, and the need for annual revaccination. A number of states and immunization programs have effectively conducted school-located vaccination both for seasonal vaccination (*492,493*) and 2009 H1N1 vaccination (*494*). School-located vaccination does, however, present challenges from a resource perspective both for vaccine costs and program costs (*493*), because reimbursement practices might be different compared with those used in medical settings. In addition, documentation of vaccination must be provided to the vaccinated person's primary care provider and where appropriate state or local vaccine registries.

Nonmedical settings that should be considered to reach the elderly include assisted living housing, retirement communities, and recreation centers. Such facilities 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 benefits for self, staff and patients of protection from influenza through vaccination.

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 severe morbidity and mortality during typical influenza seasons occurs among persons aged ≥65 years of those who have chronic medical conditions (*6,7,24*). More immunogenic influenza vaccines are needed for persons at higher risk for influenza-related complications. Additional research also is needed to understand potential biases in estimating the benefits of vaccination among older adults in reducing hospitalizations and deaths (*134,241,495*). 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 (*496*). Additional data on indirect effects of vaccination also are needed to quantify the benefits of influenza vaccination of HCP in protecting their patients (*379*) and the impact of a universal vaccination recommendation on influenza epidemiology, particularly the impact on persons at higher risk for influenza complications. In addition, a better understanding is needed of how to motivate persons, particularly those at risk for influenza-related complications and their close contacts, to seek or accept annual influenza vaccination.

The expansion of annual vaccination recommendations to include all persons aged ≥6 months 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. In Canada, a universal vac-

cination recommendation implemented in Ontario in 2000 has been compared with typical practice in other Canadian provinces. These studies have been challenging to conduct, but have indicated that a universal recommendation for annual vaccination is associated with overall reductions in influenza-related mortality, hospitalizations, ED use, physicians' office visits, and antibiotic use (*388,389,396*). However, differences between health-care systems in Canada and the United States limit the ability to generalize the findings in Ontario to the United States, and measures of the impact of a universal recommendation in the United States will likely require many years to evaluate. Additional planning to improve surveillance systems capable of monitoring effectiveness, safety and vaccine coverage, and further development of implementation strategies will be necessary. 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 future influenza pandemics or medical countermeasures to prevent or treat illnesses caused by acts of terrorism).

Seasonal Influenza Vaccine and Influenza Viruses of Animal Origin

Human infection with novel or nonhuman influenza A virus strains, including influenza A viruses of animal origin, is a nationally notifiable disease in the United States (*497*). 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) virus 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 (*498–506*). Severe lower respiratory illness with multiorgan failure has been reported in fatal H5N1 cases, and asymptomatic infection and clinically mild cases also have been reported (*507–510*). Limited, nonsustained human-to-human transmission of H5N1 virus has likely occurred in some case clusters (*508,511*). To date, there is no evidence of genetic reassortment between human influenza A and H5N1 viruses. However, influenza viruses derived from strains circulating among poultry (e.g., the H5N1 virus, which has caused outbreaks of avian influenza and occasionally have infected humans) have the potential to recombine with human influenza A viruses (*512,513*). To date, highly pathogenic H5N1 virus has not been identified in wild or domestic birds or in humans in the United States. Guidance for testing suspected cases of H5N1 virus infection among persons in the United States and follow-up of contacts is available (*514,515*). Human H5N1 cases have continued to occur in 2009 and 2010, including in the Middle East and Southeast Asia (*516*).

Human illness from infection with different avian influenza A subtype viruses also has 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 United Kingdom, lower respiratory tract disease and conjunctivitis with influenza A (H7N2) virus in the United Kingdom, and uncomplicated ILI with influenza A (H9N2) virus in Hong Kong and China (*517–523*). Two human cases of infection with low pathogenic influenza A (H7N2) have been reported in the United States (*520*). Although human infections with highly pathogenic A (H7N7) virus infections typically have ILI or conjunctivitis, severe infections, including one fatal case in the Netherlands, have been reported following exposure to poultry (*524–526*). Conjunctivitis also has been reported because of human infection with highly pathogenic influenza A (H7N3) virus in Canada and low pathogenic A (H7N3) in the United Kingdom (*517,525*). In contrast, sporadic infections with highly pathogenic avian influenza A (H5N1) virus have caused severe illness in many countries, with an overall case-fatality proportion of approximately 60% (*508,526*).

Swine influenza A (H1N1), A (H1N2), and A (H3N2) viruses, including reassortant viruses, are endemic among pig populations in the United States (*527*). Two clusters of influenza A (H2N3) virus infections among pigs have been reported recently (*528*). 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 a variety of swine influenza A viruses occur in the United States, but the incidence of these human infections is unknown (*529–534*). 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 (*531,532,535,536*). Swine influenza virus infection has not been associated with household exposure to pork products or consumption of pork. Clinicians should consider

swine influenza A virus infection in the differential diagnosis of patients with ILI who have had recent contact with pigs. Sporadic cases among persons whose infections were linked to swine exposure have not resulted in sustained human-to-human transmission of swine influenza A viruses or community outbreaks (*9,536*). The 2009 pandemic influenza A (H1N1) virus contains some genes previously found in viruses currently circulating among swine, but the origin of the pandemic has not been definitively linked to swine exposures among humans. Although immunity to swine influenza A viruses appears to be low (<2%) in the overall human population, 10%–20% of persons with occupational exposure 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 (*529,537*).

Current seasonal influenza vaccines are not expected to provide protection against human infection with avian influenza A viruses, including influenza A (H5N1) viruses, or to provide protection against influenza A viruses currently circulating exclusively in swine (*318,448*). However, reducing seasonal influenza risk through influenza vaccination of persons who might be exposed to nonhuman influenza viruses (e.g., H5N1 virus) might reduce the theoretic 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 (*538,539*). 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 (*539*).

Recommendations for Using Antiviral Agents

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. Investigational antiviral medications, such as peramivir and intravenous formulations of zanamivir, might be available under investigational new drug protocols (*540*).

During the 2007–08 influenza season, influenza A (H1N1) viruses with a mutation that confers resistance to oseltamivir became more common in the United States and other countries (*541–543*). As of June 2010, in the United States, approximately 99% of seasonal influenza A (H1N1) viruses (i.e., H1N1 viruses not associated with the 2009 pandemic) tested have been resistant to oseltamivir. None of the influenza A (H3N2) or influenza B viruses tested were resistant to oseltamivir. However, few seasonal influenza viruses isolated after May 2009 are available for testing. As of June 2010, with few exceptions, 2009 pandemic influenza A (H1N1) virus strains that began circulating in April 2009 remained sensitive to oseltamivir, and all were sensitive to zanamivir (*16*). Sporadic cases of 2009 pandemic influenza A (H1N1) virus infection with an H275Y mutation in neuraminidase associated with oseltamivir resistance have been reported worldwide, but as of June 2010, no sustained community-wide transmission has been identified (*544*). Such oseltamivir-resistant virus infections have been identified in severely immunosuppressed patients, persons receiving oseltamivir chemoprophylaxis, and in some persons without oseltamivir exposure, including some influenza illness clusters (*544–549*). CDC's recommendations for use of influenza antiviral medications should be consulted for guidance on antiviral use (*15*). New guidance on clinical management of influenza, including use of antivirals, also is available from the Infectious Diseases Society of America and the World Health Organization (*550–552*). ACIP recommendations for antiviral use will be published separately later in 2010.

Sources of Information Regarding Influenza and its Surveillance

Information regarding influenza surveillance, prevention, detection, and control is available at http://www.cdc.gov/flu. During October–May, surveillance information is updated weekly. In addition, periodic updates regarding influenza are published in *MMWR* (http://www.cdc.gov/mmwr). Additional information regarding influenza vaccine can be obtained by calling 1-800-CDC-INFO (1-800-232-4636). State and local health departments should be consulted about availability of influenza vaccine, access to vaccination programs, information related to state or local influenza activity, reporting of influenza outbreaks and influenza-related pediatric deaths, and advice concerning outbreak control.

Vaccine Adverse Event Reporting System (VAERS)

Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) at http://vaers.hhs.gov/esub/index. Reports can be filed securely online, by mail, or by fax. A VAERS form can be downloaded from the VAERS website or requested by sending an e-mail message to info@vaers.org, by calling telephone 1-800-822-7967, or by sending a faxed request to 1-877-721-0366. Additional information on VAERS or vaccine safety is available at http://vaers.hhs.gov/about/index or by calling telephone 1-800-822-7967.

Reporting of Adverse Events that Occur After Administering Antiviral Medications (MedWatch)

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

National Vaccine Injury Compensation Program

The National Vaccine Injury Compensation Program (VICP), established by the National Childhood Vaccine Injury Act of 1986, as amended, provides a mechanism through which compensation can be paid on behalf of a person determined to have been injured or to have died as a result of receiving a vaccine covered by VICP. The Vaccine Injury Table lists the vaccines covered by VICP and the injuries and conditions (including death) for which compensation might be paid. If the injury or condition is not on the Table, or does not occur within the specified time period on the Table, persons must prove that the vaccine caused the injury or condition.

For a person to be eligible for compensation, the general filing deadlines for injuries require claims to be filed within 3 years after the first symptom of the vaccine injury; for a death, claims must be filed within 2 years of the vaccine-related death and not more than 4 years after the start of the first symptom of the vaccine-related injury from which the death occurred. When a new vaccine is covered by VICP or when a new injury/condition is added to the Table, claims that do not meet the general filing deadlines must be filed within 2 years from the date the vaccine or injury/condition is added to the Table for injuries or deaths that occurred up to 8 years before the Table change. Persons of all ages who receive a VICP-covered vaccine might be eligible to file a claim. Both the intranasal (LAIV) and injectable (TIV) trivalent influenza vaccines are covered under VICP. Additional information about VICP is available at http//www.hrsa.gov/vaccinecompensation or by calling 1-800-338-2382.

Additional Information Regarding Influenza Virus Infection Control Among Specific Populations

Each year, ACIP provides general, annually updated information regarding control and prevention of influenza. Other reports related to controlling and preventing influenza among specific populations (e.g., immunocompromised persons, HCP, hospital patients, pregnant women, children, and travelers) also are available in the following publications:

- CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2006;55(No. RR-15).
- CDC. Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-2).
- CDC. Recommended immunization schedules for persons aged 0 through 18 years—United States, 2010. MMWR 2010;58:Q1–4.
- CDC. Guidelines for preventing health-care–associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR 2004;53(No. RR-3).
- CDC. Respiratory hygiene/cough etiquette in health-care settings. Atlanta, GA: US Department of Health and Human Services, CDC; 2003. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm.
- CDC. Prevention and control of vaccine-preventable diseases in long-term–care facilities. Atlanta, GA: US Department of Health and Human Services, CDC; 2006. Available at http://www.cdc.gov/flu/professionals/infectioncontrol/longtermcare.htm.
- CDC. Vaccine safety. Atlanta, GA: US Department of Health and Human Services, CDC; 2009. Available at http://www.cdc.gov/vaccinesafety/index.htm.

- American College of Obstetricians and Gynecologists. Influenza vaccination and treatment during pregnancy. ACOG committee opinion no. 305. Obstet Gynecol 2004;104:1125–6.
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